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Author(s): Wang, Jinxia; Sun, Xiaoying; Becker, Benjamin; Lei, Yi

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

Jinxia Wang^{1,2}, Xiaoying Sun³, Benjamin Becker^{4*}, Yi Lei^{1*}

¹Institute for Brain and Psychological Sciences, Sichuan Normal University, Chengdu 610066, China

²Faculty of Education and Psychology, University of Jyvaskyla, Finland

³Ningxia College of Construction, Ningxia 750021, China

⁴Clinical Hospital of Chengdu Brain Science Institute, MOE Key Laboratory for Neuroinformation,
University of Electronic Science and Technology of China, Chengdu, China

Corresponding author: Yi Lei; Benjamin Becker

Email: leiyi821@vip.sina.com; ben_becker@uestc.edu.cn

28 **Abstract**

29 Generalization represents the transfer of a conditioned responses to stimuli that
30 resemble the conditioned stimulus (CS). Previous studies on generalization of defensive
31 avoidance responses have primarily focused on fear and have neglected disgust
32 generalization, which represents a key pathological mechanism in some anxiety
33 disorders. In the present study we examined common and distinct mechanisms of fear
34 and disgust generalization by means of a fear or disgust multi-CS conditioning and
35 generalization paradigm with concomitant event-related potential (ERPs) acquisition in
36 $n = 62$ subjects. We demonstrate that compared to fear, disgust-relevant generalized
37 stimuli (GS) elicited larger expectancy ratings and longer reaction times (RTs)
38 reflecting stronger ratings of 'risk'. On the electrophysiological level, increased P2
39 amplitudes were found in response to conditioned CS+ versus CS- across both
40 domains, possibly reflecting higher motivational and attentional salience of aversive
41 conditioned stimuli per se. Contingent negative variation (CNV) amplitude was
42 significantly larger for disgust-CS+ than disgust-CS-, showing stronger preparation of
43 the disgust US. Additionally, we found that the contingent negative variation (CNV)
44 fear generalization gradient, and CNV amplitude were increased with similarity to CS+.
45 In contrast the CNV to disgust-GS did not differ and did not reflect disgust
46 generalization. Together this may indicate that the CNV represents a highly fear-
47 specific index for generalization learning. This study provides the first neurobiological
48 evidence for common and distinct generalization learning in fear versus disgust
49 suggesting that dysregulations in separable defensive avoidance mechanisms may
50 underly different anxiety disorder subtypes.

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

53 1. Introduction

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

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

78 While a large body of research has investigated the important role of fear in
79 anxiety disorders, accumulating evidence suggests that disgust-related mechanisms
80 may also contribute to psychopathological dysregulations (e.g., Armstrong & Olatunji,
81 2017; Cisler et al., 2009; Ludvik et al., 2015). Both, fear and disgust represent adaptive
82 defensive-avoidance mechanisms which have evolved to avoid potential threats in
83 terms of predators or contaminations, respectively (Woody & Teachman, 2000).
84 Individuals with high disgust proneness are more susceptible to developing
85 dysregulated avoidance responses in terms of contamination-associated obsessive-
86 compulsive disorder (OCD), blood-injection-injury phobia, and small animal phobias
87 (e.g., Bhikram et al., 2017; Cogle et al., 2016; Hirai et al., 2018; Olatunji et al., 2017).
88 Woody et al. (2005) moreover demonstrated that disgust plays an important role in
89 avoidance symptoms in spider phobias such that individuals with high fear experienced
90 both, stronger anxiety and disgust as compared to individuals with low fear. [Although](#)
91 [OCD and post-traumatic stress disorders \(PTSD\) were removed from anxiety disorder](#)
92 [category in the DSM-5, both conditions are closely linked to exaggerated fear and](#)
93 [disgust reactivity \(McGuire et al., 2016\). In parallel to studies examining dysregulations](#)
94 [in fear learning, Pavlovian disgust conditioning models have been successfully applied](#)
95 [to determine disgust-associated pathomechanisms in contamination-based OCD \(Stein](#)
96 [et al., 2001\) as well as PTSD \(Badour et al., 2013\).](#) Furthermore, accumulating
97 evidence suggests a direct association between symptoms of contamination-based OCD
98 and disgust sensitivity (Olatunji et al., 2010), and – in contrast to fear – acquired disgust
99 responses are highly resistant to extinction as indexed by subjective experience as well
100 as behavioral indices (Mason, & Richardson, 2010).

101 Further evidence for distinct yet also interacting mechanisms underlying fear and
102 disgust learning comes is provided by developmental studies reporting that children

103 experienced increased disgust after vicarious fear learning by presenting novel animals
104 (CSs) with adult faces expressing fear (USs) as well as increased fear experience after
105 vicarious disgust learning (Askew et al., 2014). Klucken et al. (2012) investigated the
106 neural basis of fear- and disgust-conditioning and demonstrated that both aversive
107 learning mechanisms involved common neural circuits encompassing the occipital
108 cortex, the nucleus accumbens, the orbitofrontal cortex, and the dorsal anterior
109 cingulate cortex, with higher disgust sensitivity being associated with increased insula
110 activation. However, common and distinct generalization gradients and underlying
111 differentiable electrophysiological responses during fear- and disgust-generalization
112 have not been systematically examined.

113 An increasing number of recent studies examined the temporal dynamics of fear
114 conditioning by means of electrophysiological approaches such as event-related
115 potentials and demonstrated that early attention components, including P2 and P3,
116 showed enhanced amplitude in response to CS+ compared to CS- (Junghöfer et al.,
117 2015; Junghöfer et al., 2017; Sperl et al, 2021). Further, studies focusing on the late
118 positive potential (LPP) component suggest a sustained attention to CS+ probably
119 representing the newly acquired fear (Pavlov & Kotchoubey, 2019; Ventura-Bort et al.,
120 2016). Krusemark and Li (2011), employed visual fear and disgusting stimuli of natural
121 objects in a visual search paradigm with concomitant event-related potential (P1)
122 acquisition, contrasting the effects of the two defensive responses on early neural
123 indices of sensory perception and attention. The results showed that, compared to
124 neutral stimuli, fear images elicited a larger P1 (96 ms) amplitude whereas disgust
125 images evoked an attenuated P1 amplitude, demonstrating an opposite pattern of early
126 sensory discrimination. Despite these initial findings on differential early perceptual
127 discrimination the common and separable ERP-responses underlying generalization

128 may further allow to determine the process-specific contribution of neurobiological
129 separable fear and disgust mechanisms to segregate separable psychopathological
130 markers for fear and disgust-related anxiety disorders.

131 Against this background the present study aimed to determine common and
132 distinct behavioral and neural signatures of fear and disgust generalization during
133 associative learning. Particularly, to ensure a sufficient signal-to-noise ratio, we
134 adopted the MultiCS conditioning learning paradigm. In MultiCS conditioning, many
135 similar stimuli were paired with the aversive US (CSs-US association), whereas the
136 same number of similar CS was presented alone (CSs-no US association) (Rehbein et
137 al., 2018). MultiCS conditioning paradigms use a series of similar and complex stimuli
138 to comprise an affective category, making the associative learning process more
139 complex and avoiding rapid extinction in the generalization test (Steinberg et al., 2012;
140 Steinberg et al., 2013). To avoid carry over effects, habituation and expectations in the
141 experimental design participants were divided into two groups in this study, with one
142 group completing the fear generalization paradigm, and the other group completing the
143 disgust learning paradigm. Thus, we analyzed the acquisition and the generalization
144 phase of these two aversive conditioning processes. We hypothesized that the US
145 expectancy of CS+/GS+ would be significantly higher than that of CS-/GS-. Based on
146 the different evolutionary functions of disgust (avoidance of contamination from a
147 class of stimuli) and fear (anticipation of physical attack e.g. in a highly specific
148 context) (e.g. Curtis, de Barra., & Aunger, 2011) we expected enhanced generalization
149 for the conditioned disgusting-CS+ as compared to the fearful-CS+. On the ERP
150 activation level, we hypothesized that (1) fear-conditioned and disgust-conditioned
151 CS+ and GS+ would evoke an early attentional bias reflected by P2; (2) LPP amplitude
152 would be modulated by both stimuli types reflecting that both stimuli types capture

153 strong sustained attention possible suggesting threat monitoring; and (3) differential
154 electrophysiological modulation of disgust-relevant CS/GS versus the fear-related
155 CS/GS, in particular larger LPP amplitudes response to conditioned disgust-CS+ than
156 to fear-CS+ given that previous studies reported a larger attentional bias for disgusting
157 than fear stimuli (Charash & McKay, 2002; Carretié et al., 2011) and stronger
158 interference by disgusting stimuli (Cisler et al., 2009; van Hooff et al., 2013).

159

160 **2. Materials and Methods**

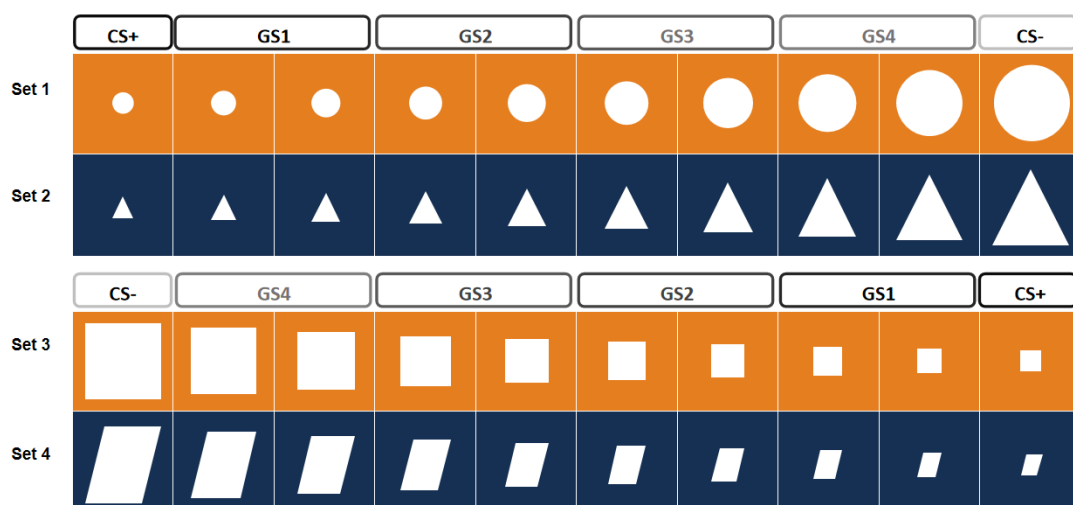
161 **2.1 Participants**

162 A priori sample size calculation (G*Power) indicated that 52 participants in total
163 would be sufficient to achieve a medium effect size of 0.20, an alpha level of 0.05, and
164 a 1-beta level of 0.80 (Erfelder, Faul, & Buchner, 1996; Faul et al., 2007; Hendrikx et
165 al., 2021). We recruited 62 healthy college participants (27 women; $M_{age} = 20.87$; SD_{age}
166 $= 2.51$) who were randomly assigned to either fear- or disgust-associative learning
167 ($n = 31$ per group; $Age_{fear} = 21.07 \pm 2.92$; $Age_{disgust} = 20.68 \pm 2.09$). Five participants
168 (three in fear group: $N_{fear} = 28$ and two in disgust group: $N_{disgust} = 29$) were excluded
169 from the final data analysis because they rated the US expectancy of the CS- larger
170 than that of the CS+. All participants had normal or corrected vision and had no history
171 of psychiatric or neurological diseases (according to self-report). All subjects had a BDI
172 score < 13 and STAI < 50 which is in the normal range and thus indirectly confirm the
173 absence of mood, anxiety disorders. Participants provided written informed consent and
174 received monetary compensation. The research was approved by the Medicine Ethics
175 Committee of Shenzhen University and the experimental protocol was established,
176 according to the ethical guidelines of the Helsinki Declaration.

177 **2.2 Stimuli**

178 2.2.1 CS and GS

179 The generalized stimuli used in this study were a modified version of those used
 180 in a previous study to maximize signal to noise ratio (Lissek et al., 2008). The
 181 conditioned and generalized stimuli were a series of shapes including a circle, triangle,
 182 square, and parallelogram, and each shape was presented in a separate block.
 183 Specifically, each shape was designed with 10 stimuli, continuously increasing in size
 184 (5.08–14.22 cm in diameter, 20% increments) (Figure 1). The assignment of CS+ was
 185 counter-balanced between blocks. For two of the four blocks, the smallest stimuli (5.08
 186 cm) served as CS+ paired with the US (75% reinforcement), and the largest stimuli
 187 served as CS- (14.22 cm). In the remaining two blocks, the largest stimuli were used
 188 as CS+, and the smallest stimuli were used as CS-. The remaining stimuli in the middle
 189 served as GS.



190

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

196 2.2.2 US

197 The USs were chosen from the Threat Picture System, including 36 different fear-
198 evoking pictures (e.g., a spider) and 36 different disgust-evoking pictures (e.g., vomit).
199 The arousal of the fear-eliciting set ($M = 6.16$; $SD = .58$) was significantly higher than
200 that of the disgust-related set ($M = 5.54$; $SD = 0.47$, $t(80) = 7.329$, $p < .001$, Cohen's d
201 $= 1.17$). Importantly, the ratings of fear in the fear set ($M = 4.80$; $SD = 1.06$) were larger
202 than those in the disgust set ($M = 3.32$; $SD = .86$; $t(80) = 12.715$, $p < .001$, Cohen's d
203 $= .87$), and the ratings of disgust in the disgust category ($M = 5.84$; $SD = 1.21$) were
204 higher than those for the fear category ($M = 4.05$; $SD = .97$; $t(83) = 22.737$, $p < .001$,
205 Cohen's $d = 2.40$). The Threat Picture System has been validated in previous studies
206 (Wang, J. et al., 2021).

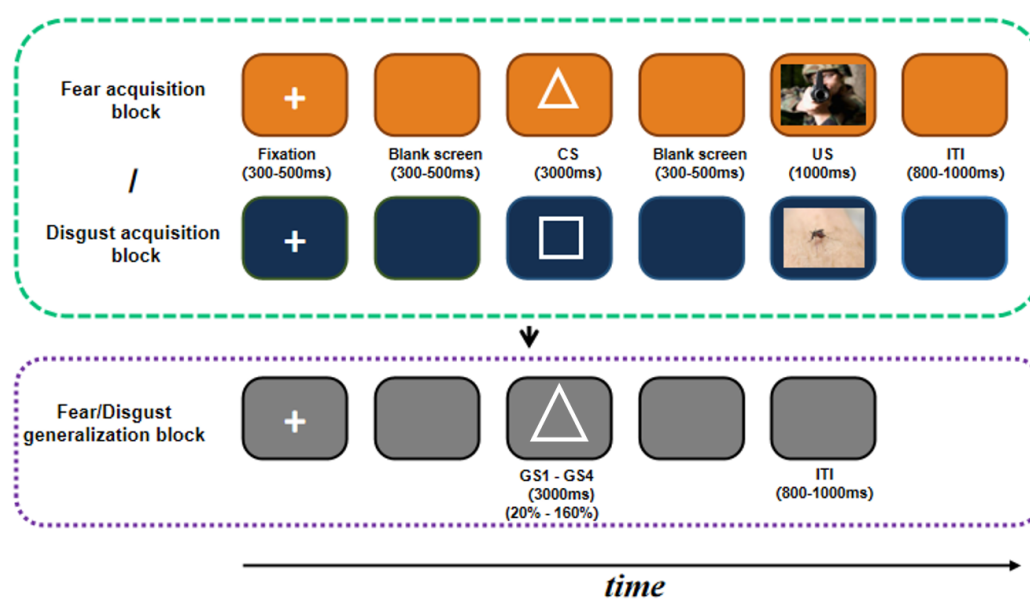
207 2.3 Procedure

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

216 Each of the four CS/GS types was presented in a separate block (10 stimuli per
217 block) and four blocks (circle, triangle, square, and parallelogram) were displayed in a
218 randomized order. During the acquisition phase, two pictures (those of the smallest and
219 the largest size) were employed as as conditioned stimuli, one paired with fear US or
220 disgust US (CS+) with a 75% reinforcement schedule (9/12), and the other used as a

221 safety cue (CS⁻) presented with a blank picture. Each block included 12 repetitions of
 222 each CS (48 trials in total). In the generalization test phase, each of the eight generalized
 223 stimuli, varying in size, were displayed six times (24 trials in total). Furthermore, we
 224 divided all generalized stimuli into four groups: every two neighboring intermediaries
 225 were averaged to form a level of similarity with CS⁺ (e.g., [Ring 2 + Ring 3] / 2 = GS1)
 226 (Lissek et al., 2008). Thus, the test phase included four types of GS: GS1; GS2; GS3,
 227 and GS4; each condition including 48 trials. To prevent extinction, the CS⁺ and CS⁻
 228 were presented six times in each block, and the CS⁺ was followed by the US with a
 229 50% reinforcement rate (Dunsmoor & Murphy, 2014).

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



236

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

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

245 **2.3.1 ERP recordings and data pre-processing**

246 Continuous electroencephalogram (EEG) data were collected by using a standard
247 10–20 acquisition EEG cap with a 64-channel Brain Products system (Brain Products
248 GmbH, Munich, Germany; passband: 0.05–100 Hz, sampling rate: 500 Hz). The
249 reference electrodes were placed on the mastoids, with ground electrodes located on the
250 medial frontal line. Electro-oculogram data were collected via facial electrodes located
251 above and below the left eye and the outer canthi of each eye. The impedance was
252 maintained below 10 k Ω during the recordings. ERP data were obtained using the
253 EEGLAB Matlab toolbox (Delorme & Makeig, 2004) and were band pass filtered from
254 0.1 to 20 Hz. Blinking and eye movements were corrected by using independent
255 component analysis and trials with activities exceeding 80 or below -80 μ V were
256 removed. The EEG data were segmented from 100 ms before stimulus onset to 800 ms
257 after onset.

258 **2.4 Statistics**

259 US expectancy ratings and RTs for CSs/GS were computed separately for
260 acquisition and generalization phases. Data of US expectancy ratings and reaction times
261 in the acquisition phase were analyzed by using a two-way repeated measures ANOVA
262 model with Conditioned Stimulus Type (CS+, CS-) as the within-subject factor and,

263 Emotion Type (fear, disgust) as the between-subject factor. A repeated measures 2×6
264 ANOVA was performed with the within-subject factor Conditioned Type (CS+, GS1,
265 GS2, GS3, GS4, CS-) and between-subject factor Emotion Type (fear, disgust). In
266 order to estimate the level of confidence in online ratings, we plotted the participants'
267 reaction times (RTs) during the acquisition phase. RTs was examined using a 2
268 (Emotion Type: fear, disgust) \times 2 (Conditioned Stimulus Type: CS+, CS-) \times 4 (Block:
269 Acq1, Acq2, Acq3, Acq4) repeated measures ANOVA. Conditioned Stimulus Type,
270 Block were included as within-subjects factors and Emotion Type was included as a
271 between-subjects factor.

272 To better describe the generalization gradients, we modeled the responses of US
273 expectancy ratings as Gaussian curve (Ghirlanda and Enquist, 2003). First, we
274 standardized the response data (i.e. CS+, GS1, GS2, GS3, GS4, CS-) by subtracting
275 the CS- value. Then we fitted the response data with a Gaussian function, $f(x) = a \cdot \exp(-$
276 $(b-x)^2/2c^2)$ by using non-linear least squares (Tuominen et al., 2019), where a
277 corresponds to the height of the curve and c (the standard deviation) responds to the
278 width, and b (fixed at bound, i.e., the CS+) is the location of the peak. The parameter c
279 represents the generalization gradients, indexing the extent of fear generalization.

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

288 were reported. Effects were considered significant when $p < .05$.

289 3. Results

290 3.1 Demographics data

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

294 **Table 1. Demographic data**

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

295 $M =$ mean; $SD =$ standard deviation

296 Standardized questionnaires were obtained to characterize the sample according to
 297 gender, age, their levels of state anxiety (State Trait Anxiety Inventory: STAI-S) and
 298 depression (Beck Depression Inventory: BDI), as these factors were previously shown
 299 to influence the acquisition and generalization of fear (Peyrot et al., 2020; Glenn et al.,
 300 2012; Vriends et al., 2011; Waters et al., 2014).

301 3.2 Conditioning phase

302 3.2.1 Subjective expectancy ratings

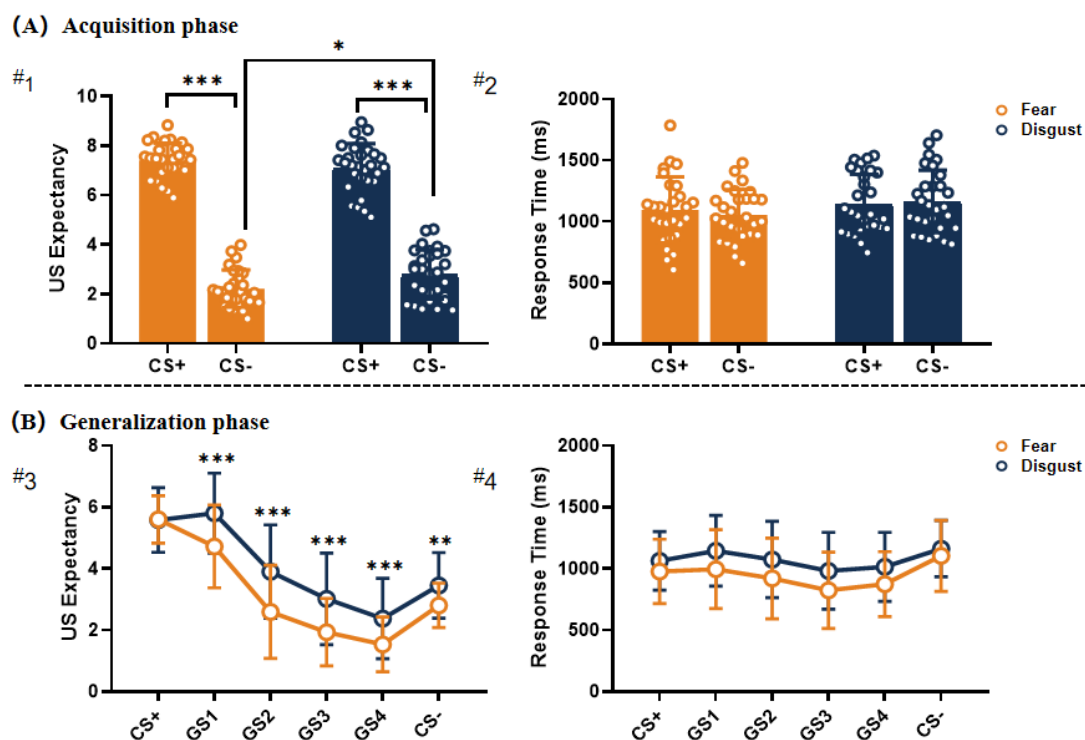
303 The results yielded a significant main effect for Conditioned Type ($F_{(1,55)} =$
 304 699.192 ; $p < .001$, $\eta^2 = .927$), however, no differences were observed between the
 305 fear and disgust groups (Emotion Type) ($F_{(1,55)} = .843$; $p = .363$, $\eta^2 = .015$).
 306 Interestingly, the interaction between these two factors was significant ($F_{(1,55)} = 5.876$;

307 $p = .019$, $\eta p^2 = .097$). Bonferroni corrected post-hoc analysis revealed that participants
 308 reported higher expectancy ratings of CS+ than those of CS- in both groups (Fear: [The
 309 difference of Means (DiffM) was 5.190, 95%CI (4.676; 5.70); $p < .001$]; Disgust:
 310 [DiffM 4.318, 95%CI (3.813; 4.823), $p < .001$]). and the expectancy ratings of disgust-
 311 related CS- were higher than those of fear-related CS- [DiffM -0.570, 95%CI (-1.042;
 312 -.097); $p = .019$] (Figure 3 #1).

313 The extent between disgust generalization ($c = 2.487 \pm 0.224$ (M \pm SEM)) and fear
 314 generalization ($c = 2.981 \pm 0.201$) was not statistically significant ($t = -1.635$, $p =$
 315 0.108).

3.2.2. Reaction times

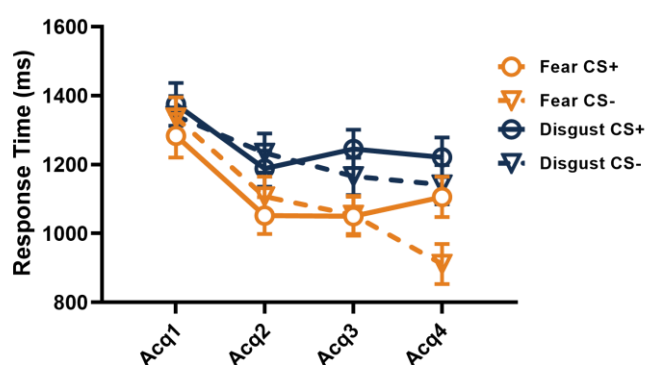
317 The main effect of Condition Type, $F_{(1,55)} = .338$; $p = .563$, $\eta p^2 = .006$, the main
 318 effect of emotion type, $F_{(1,55)} = 1.626$; $p = .208$, $\eta p^2 = .029$, and Condition Type \times
 319 emotion type interaction, $F_{(1,55)} = 2.133$; $p = .150$, $\eta p^2 = .037$, were all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



321

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

326 On the other hand, a main effect of Block was found, $F_{(2.039, 112.118)} = 33.043$; p
 327 $< .001$, $\eta^2 = 0.375$. Additionally, the Block \times Conditioned Stimulus Type interaction
 328 was significant, $F_{(2.505, 137.750)} = 5.489$, $p = 0.003$, $\eta^2 = 0.091$. Simple effect analysis
 329 showed that, for CS+, the RTs of Acq1 was longer than that of Acq2 ([DiffM 209.170,
 330 $p < .001$; 95%CI (103.405; 314.935)], Acq3 ([DiffM 181.251, $p < .001$; 95%CI
 331 (72.953; 289.548)]) and Acq4 ([DiffM 165.572, $p < .001$; 95%CI (60.999; 270.145)]).
 332 For CS-, the RTs of Acq1 was larger than that of Acq2 ([DiffM 168.373, $p = .001$;
 333 95%CI (57.986; 278.761)]), Acq3 ([DiffM 228.738, $p < .001$; 95%CI (110.017;
 334 347.459)]) and Acq4 ([DiffM 312.096, $p < .001$; 95%CI (178.267; 445.924)]); Further,
 335 the RTs of Acq2 ([DiffM 143.722, $p < .001$; 95%CI (43.904; 243.541)]) and Acq3
 336 ([DiffM 83.358, $p = .004$; 95%CI (19.993; 146.722)]) were longer than that of Acq4
 337 (Figure 4).



338
 339 **Figure 4.** The time course of response time during the fear acquisition (means \pm SEMs).

340 3.3 Generalization phase

341 3.3.1 Subjective expectancy ratings

342 The US ratings in both groups in the generalization phase exhibited a significant
 343 main effect of Conditioned Type ($F_{(2,279,125.359)} = 230.779; p < .001, \eta p^2 = .808$).
 344 Bonferroni corrected post-hoc analysis revealed that US ratings significantly differed
 345 across generalized stimuli ($p < .001$) except CS+ with GS1 and CS- with GS2 (p
 346 $> .05$), exhibiting a gradient of generalization. Furthermore, the US ratings during
 347 generalization were characterized by a main effect of Emotion Type ($F_{(1,55)} = 9.699; p$
 348 $= .003, \eta p^2 = .150$) and their interaction ($F_{(2,279,125.359)} = 5.808; p = .003, \eta p^2 = .096$).
 349 Simple effect analysis showed that the five types of disgust-related GS (GS1
 350 [DiffM .649, $p = .010$; 95%CI (.165; 1.134)], GS2 ([DiffM 1.084, $p = .003$; 95%CI
 351 (0.381; 1.787)]), GS3 ([DiffM 1.311, $p = .002$; 95%CI (.505; 2.116)]), GS4 ([DiffM
 352 1.085, $p = .003$; 95%CI (.388; 1.782)]) and CS- ([DiffM .840, $p = .007$; 95%CI (0.243;
 353 1.437)]) were larger than those of fear-related GS (Figure 3 #3).

354 3.3.2 Reaction times

355 The main effects for Conditioned Type ($F_{(2,326,127.911)} = 31.704; p < .001, \eta p^2 =$
 356 $.366$) reached significance. Apart from GS1 with GS2, and GS4 with CS-, RTs showed
 357 an overall downward trend for those followed by Bonferroni corrected post-hoc
 358 analysis. The main effect of Emotion Type, $F_{(1,55)} = 3.042; p = .087, \eta p^2 = .052$, and
 359 the Conditioned Type by Emotion Type interaction, $F_{(2,326,127.911)} = 2.005; p = .078,$
 360 $\eta p^2 = .035$, were both non-significant (Figure 3 #4).

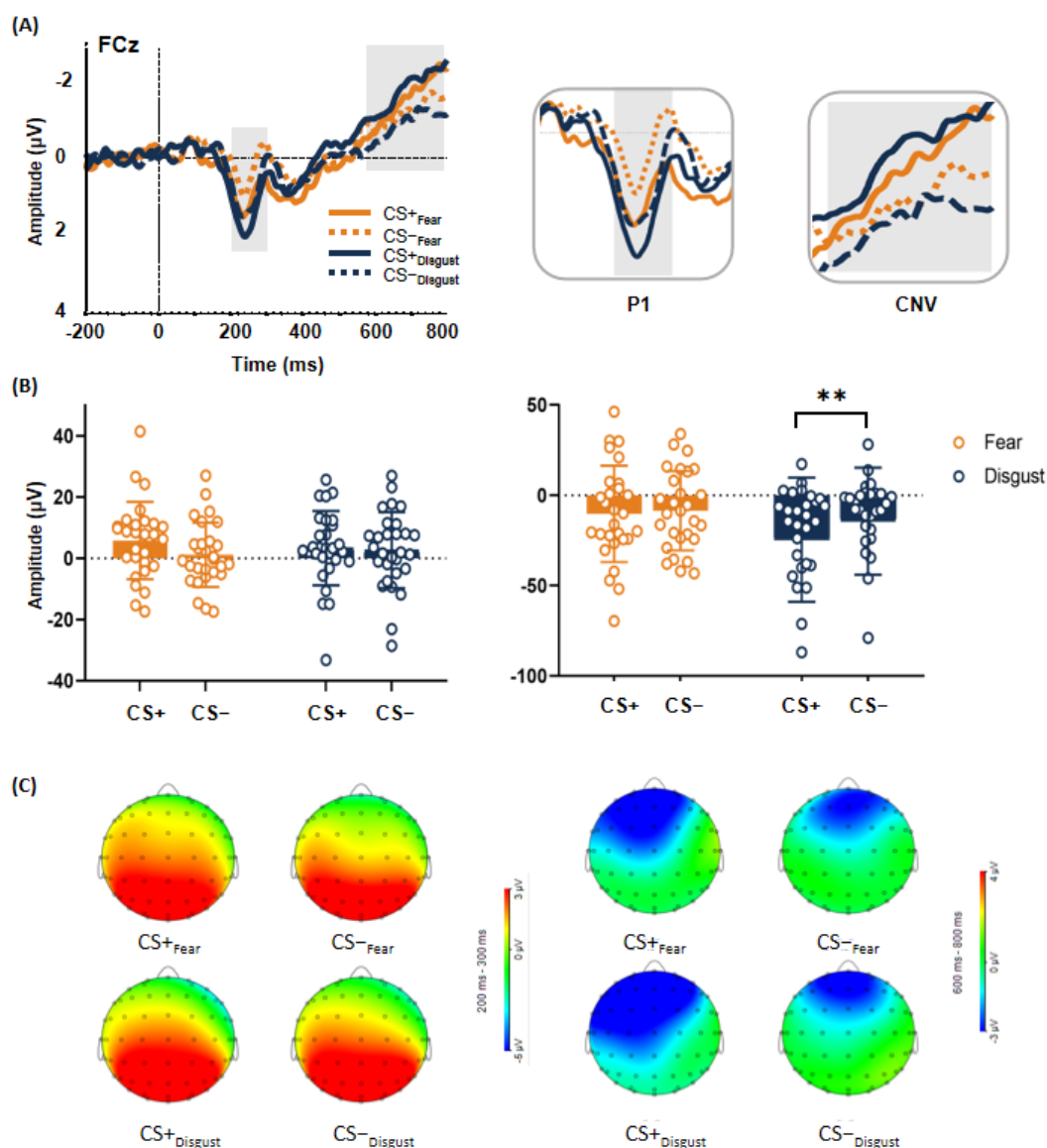
361 3.4 ERPs

362 3.4.1 Conditioning phase

363 3.4.1.1 P2

364 P2 was characterized by a marginal significant main effect of Conditioned Type
 365 ($F_{(1,55)} = 3.635; p = .062, \eta p^2 = .062$). Bonferroni corrected post-hoc analysis indicated

366 that CS+ evoked an enhanced P2 amplitude during the threat learning process compared
 367 with CS-. However, the Emotion Type ($F_{(1,55)} = .030$; $p = .864$, $\eta^2 = .001$) and
 368 Conditioned Type \times Emotion Type ($F_{(1,58)} = 2.090$; $p = .154$, $\eta^2 = .037$) were not
 369 significant (Figure 5).



370

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

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

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

379 **3.4.1.2 CNV**

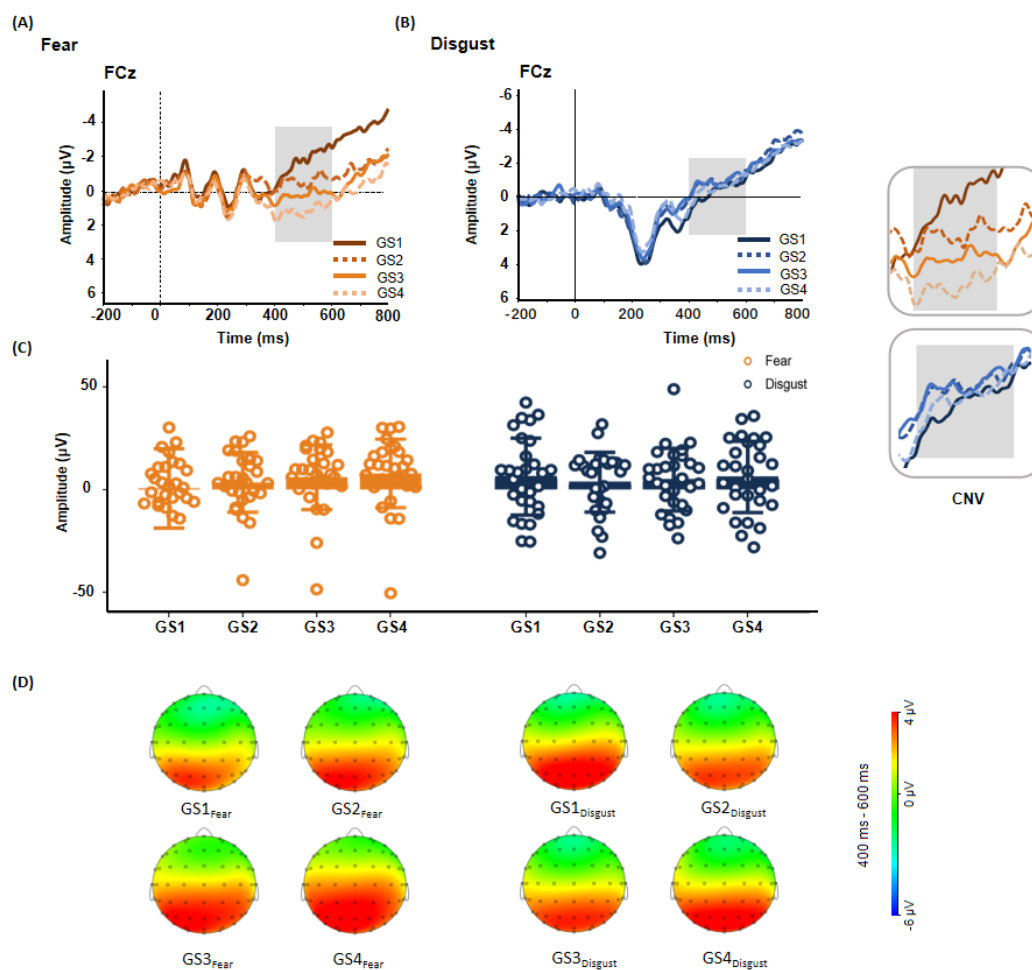
380 We found a significant main effect of Conditioned Type ($F_{(1,55)} = 7.630$; $p = .008$
381 , $\eta^2 = .122$) and a marginal significant interaction effect ($F_{(1,55)} = 3.788$; $p = .057$, η^2
382 = .064). Simple effect analysis showed that CNV amplitude was greater in response to
383 Disgust-CS+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

387 **3.4.2 Generalization phase**

388 **3.4.2.1 CNV**

389 CNV analysis yielded a significant main effect of Conditioned Type ($F_{(3,165)} =$
390 3.459 , $p = .018$, $\eta^2 = .059$) and a significant interaction effect ($F_{(3,165)} = 3.573$; p
391 = .015, $\eta^2 = .061$). However, we did not find a significant main effect of Emotion
392 Type ($F_{(1,55)} = .032$, $p = .859$, $\eta^2 = .001$). The simple effect analysis revealed that the
393 CNV amplitudes of GS1, GS2, GS3 and GS4 were not significantly different under the
394 disgust condition ($p > .05$), but the CNV amplitude of GS1 [DiffM -7.351, $p = .003$;
395 95%CI (-12.718; -1.985)] and GS2 [DiffM -4.418, $p = .032$; 95%CI (-8.592; -.245)]
396 were significantly higher than that of GS4. The difference between GS1 and GS3 was
397 marginally significant in the fear condition. Overall, the CNV amplitude showed a
398 generalization gradient (Figure 6).

399



400

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

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

408

409 4. Discussion

410 The present study aimed at determining common and differential behavioral and
 411 neural responses during disgust and fear generalization by means of capitalizing on a

412 multi-CS conditioning and generalization paradigm with concomitant ERP acquisition.
413 On the behavioral level we found greater US expectancy ratings for CS+ than for CS-
414 in both emotional domains, indicating successful acquisition of CS+-US contingencies
415 and an effective experimental manipulation (Koban et al., 2018; Wong & Lovibond,
416 2017). Individuals reported elevated US expectancy ratings for disgust-CS- as
417 compared to fear-CS-, possibly reflecting that fear induces a stronger discriminative
418 conditioning with respect to the safety signal (CS- , Takemoto & Song, 2019), or
419 alternatively that the fear-related CS- might show a stronger inhibition relative to
420 disgust-relevant CS-.

421 In the generalization phase, the US expectancy ratings showed a gradual decline
422 as a function of decreasing CS+ similarities across both emotion types. Ratings of US
423 expectancy provide an index of 'subjective CS discrimination' and drive the
424 conditioned response and associated generalization gradients (Lonsdorf et al., 2017;
425 Harvie et al., 2017). Expectancy ratings for disgust generalization stimuli were however
426 generally higher than for the fear generalization stimuli reflecting a stronger ratings of
427 'risk' for disgust than for fear. Fear may occur in response to immediate threats,
428 perceived as a risk of injury or death, whereas disgust is an emotional response to
429 stimuli considered distasteful or contaminative (Curtis, 2011). Although both represent
430 defensive avoidance reactions characterized by aversive negative arousal and
431 withdrawal, previous studies suggested that it was harder to remember contaminating
432 vs. threatening stimuli since disgust is associated with avoidance and suppressed
433 sensory exposure (Susskind et al., 2008). Thus, one possible explanation for this
434 stronger rating of 'risk' in disgust in turn lead to a relatively poor accuracy of the CS
435 memory representation. Similar stimuli were wrongly categorized to the original one,
436 leading to a border generalization gradient (Zenses et al., 2021). The stronger US

437 expectancy ratings in disgust could reflect an evolutionary adaptive mechanism given
438 the often less explicit indices of pathogen contamination as compared to a direct, e.g.
439 attack-related, threat. Together the findings underscore differential behavioral and
440 neural signatures of fear and disgust generalization which may contribute differentially
441 to psychiatric conditions with dysregulations in aversive avoidance mechanisms, e.g.
442 anxiety or obsessive-compulsive disorders (Armstrong & Olatunji, 2017).

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

455 Regarding the ERP results in the acquisition phase, we observed increased P2
456 amplitude for CS+ relative to CS- irrespective of emotion type. The early modulatory
457 effect on the P2 demonstrates an electrophysiological index of directed selective
458 attention (Ugland et al., 2013). A similar P2 modulation effect was found in the study
459 by Kluge et al. (2011) employing electric shock as US during a fear acquisition
460 paradigm. Previous studies suggested that increased early P2, in response to
461 emotionally aversive stimuli, may reflect automatic attention capture and threat-related

462 attention biases (Lei et al., 2019; Willner et al., 2020). The enhanced P2 amplitudes for
463 conditioned salient stimuli may index motivated attention (Zheng et al., 2019).
464 Together the findings indicate that conditioned fear and disgust engage comparable
465 early attentional resource engagement and salience processes. From a biological
466 perspective, both fear and disgust require rapid defensive avoidance responses in the
467 face of threatening stimuli, and thus early threat detection and deployment of attentional
468 resources towards both classes of stimuli represents a critical initial step of the
469 defensive avoidance response (Buck et al., 2018).

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

479 The current analyses showed that parietooccipital CNV amplitudes were
480 significantly larger in response to conditioned disgust-CS+ than to disgust-CS-, yet
481 interestingly the CNV amplitudes did not significantly differ for the fear-associated
482 CS+ than CS- stimuli. Previous aversive conditioning studies using ERPs found
483 increased CNV amplitude in response to CS+ in response to stimuli which may induce
484 subjective feelings of fear as well as disgust (e.g. small animal pictures Regan &
485 Howard, 1995), suggesting that biological salient threat stimuli can induce a
486 modulation of motivated attention or sustained attention bias. The findings resonate

487 with previous lesion and brain imaging studies suggesting common yet also separable
488 neural responses to fear and disgust-inducing stimuli (e.g. Stark et al., 2003, 2007).
489 Although some features of the defensive avoidance reaction in response to disgust and
490 fear are similar other features such as the specific facial expression or the subjective
491 experience differ. The behavioral responses may specifically differ in terms of the
492 evolutionary function in terms of danger avoidance. Moreover, disgust may manifest in
493 OCD with contamination fears thus suggesting differential underlying biological
494 processes (Knowles et al., 2018). Differentiating temporal dynamics of ERPs that
495 respond to the fear and disgust may thus represent an important neurobiological
496 differentiation between the defensive avoidance reactions and psychiatric conditions
497 characterized by fear versus disgust dysregulations.

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

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

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

537 **Conclusion**

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

549

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562 **Author Contributions:**

563 Conceived and designed the experiments: Xiaoying Sun, Jinxia Wang, Yi Lei

564 Performed the experiments: Xiaoying Sun

565 Analyzed the data: Xiaoying Sun, Jinxia Wang

566 Writing - original draft; Writing - review & editing: Jinxia Wang, Benjamin Becker

567 Funding acquisition: Yi Lei

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575 **References**

- 576 Abramowitz, J. S., Fabricant, L. E., Taylor, S., Deacon, B. J., McKay, D., & Storch, E.
 577 A. (2014). The relevance of analogue studies for understanding obsessions and
 578 compulsions. *Clinical psychology review*, *34*(3), 206–217.
 579 doi: 10.1016/j.cpr.2014.01.004.
- 580 Armstrong, T., & Olatunji, B. O. (2017). Pavlovian disgust conditioning as a model for
 581 contamination-based OCD: evidence from an analogue study. *Behaviour Research*
 582 *and Therapy*, *93*, 78–87. doi: 10.1016/j.brat.2017.03.009
- 583 Arnaudova, I., Kindt, M., Fanselow, M., & Beckers, T. (2017). Pathways towards the
 584 proliferation of avoidance in anxiety and implications for treatment. *Behaviour*
 585 *Research and Therapy*, *96*, 3–13. doi:10.1016/j.brat.2017.04.004
- 586 Askew, C., Cakır, K., Pöldsam, L., & Reynolds, G. (2014). The effect of disgust and
 587 fear modeling on children’s disgust and fear for animals. *Journal of Abnormal*
 588 *Psychology*, *123*, 566–577. doi:10.1037/a0037228
- 589 Badour, C. L., Feldner, M. T., Blumenthal, H., & Knapp, A. (2013). Preliminary
 590 evidence for a unique role of disgust-based conditioning in posttraumatic stress.
 591 *Journal of traumatic stress*, *26*, 280–287. doi:10.1002/jts.21796
- 592 Bhikram, T., Abi-Jaoude, E., & Sandor, P. (2017). OCD: obsessive–compulsive ...
 593 disgust? The role of disgust in obsessive–compulsive disorder. *Journal of*
 594 *Psychiatry and Neuroscience*, *42*, 300–306. doi:10.1503/jpn.160079
- 595 Buck, J. C., Weinstein, S. B., & Young, H. S. (2018). Ecological and evolutionary
 596 consequences of parasite avoidance. *Trends in Ecology & Evolution*, *33*, 619–632.
 597 doi:10.1016/j.tree.2018.05.001
- 598 Carretié, L., Ruiz-Padial, E., López-Martín, S., & Albert, J. (2011). Decomposing
 599 unpleasantness: differential exogenous attention to disgusting and fearful stimuli.
 600 *Biological psychology*, *86*(3), 247–253. https://doi.org/10.1016/
 601 j.biopsycho.2010.12.005
- 602 Charash, M., & McKay, D. (2002). Attention bias for disgust. *Journal of anxiety*
 603 *disorders*, *16*(5), 529–541. https://doi.org/10.1016/s0887-6185(02)00171-8
- 604 Cisler, J. M., Olatunji, B. O., & Lohr, J. M. (2009). Disgust, fear, and the anxiety
 605 disorders: a critical review. *Clinical Psychology Review*, *29*, 34–46.
 606 doi:10.1016/j.cpr.2008.09.007
- 607 Cisler, J. M., Olatunji, B. O., Lohr, J. M., & Williams, N. L. (2009). Attentional Bias

- 608 Differences between Fear and Disgust: Implications for the Role of Disgust in
609 Disgust-Related Anxiety Disorders. *Cognition & emotion*, 23(4), 675–687.
610 <https://doi.org/10.1080/02699930802051599>
- 611 Cogle, J. R., Summers, B. J., Harvey, A. M., Dillon, K. H., & Allan, N. P. (2016).
612 Contamination-focused exposure as a treatment for disgust-based fears: A
613 preliminary test in spider-fearful women. *Behavioural and Cognitive*
614 *Psychotherapy*, 44, 640–651. doi:10.1017/S1352465816000333
- 615 Craddock, P., Molet, M., & Miller, R. R. (2012). Reaction time as a measure of human
616 associative learning. *Behavioural Processes* 90, 189–197.
617 doi:10.1016/j.beproc.2012.01.006
- 618 Curtis, V. (2011). Why disgust matters. *Philosophical Transaction of The Royal Society*
619 *of London B: Biological Sciences*, 366, 3478–3490. doi:10.1098/rstb.2011.0165
- 620 Curtis, V., de Barra, M., & Auger, R. (2011). Disgust as an adaptive system for disease
621 avoidance behaviour. *Philosophical Transaction of The Royal Society of London*
622 *B: Biological Sciences*, 366, 389–401. doi:10.1098/rstb.2010.0117
- 623 Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of
624 single-trial eeg dynamics including independent component analysis. *Journal of*
625 *Neuroscience Methods*, 134, 9–21. doi:10.1016/j.jneumeth.2003.10.009
- 626 Dunsmoor, J. E., & Murphy, G. L. (2014). Stimulus typicality determines how broadly
627 fear is generalized. *Psychological Science*, 25, 1816–1821.
628 doi:10.1177/0956797614535401
- 629 Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., van den
630 Hout, M. A., & Baas, J. M. (2015). Updated meta-analysis of classical fear
631 conditioning in the anxiety disorders. *Depression and anxiety*, 32(4), 239 – 253.
632 doi: 10.1002/da.22353
- 633 Duits, P., Richter, J., Baas, J., Engelhard, I. M., Limberg-Thiesen, A., Heitland, I.,
634 Hamm, A. O., & Cath, D. C. (2017). Enhancing effects of contingency instructions
635 on fear acquisition and extinction in anxiety disorders. *Journal of Abnormal*
636 *Psychology*, 126, 378–391. doi:10.1037/abn0000266
- 637 Eyal, T., Dar, R., & Liberman, N. (2021). Is disgust in obsessive-compulsive disorder
638 mediated by fear of pathogens?. *Journal of anxiety disorders*, 77, 102340. doi:
639 10.1016/j.janxdis.2020.102340.
- 640 Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible

- 641 statistical power analysis program for the social, behavioral, and biomedical
642 sciences. *Behavior Research Methods*, 39, 175–191. doi:10.3758/BF03193146
- 643 Ghirlanda, S., Enquist, M., 2003. A century of generalization. *Animal Behaviour*. 66,
644 15 – 36. <https://doi.org/10.1006/anbe.2003.2174>
- 645 Glenn, C. R., Klein, D. N., Lissek, S., Britton, J. C., Pine, D. S., & Hajcak, G. (2012).
646 The development of fear learning and generalization in 8–13 year-olds.
647 *Developmental Psychobiology*, 54, 675–684. doi:10.1002/dev.20616
- 648 Harvie, D. S., Moseley, G. L., Hillier, S. L., & Meulders, A. (2017). Classical
649 Conditioning Differences Associated With Chronic Pain: A Systematic Review.
650 *The journal of pain*, 18(8), 889–898. <https://doi.org/10.1016/j.jpain.2017.02.430>
- 651 Hirai, M., Vernon, L. L., & Dolma, S. (2018). A gender invariant model of disgust
652 propensity in blood-injection-injury phobia in Latina/o individuals. *Psychology*
653 *Health and Medicine*, 23, 1275–1281. doi: 10.1080/13548506.2018.1487985
- 654 Jovanovic, T., Norrholm, S. D., Blanding, N. Q., Davis, M., Duncan, E., Bradley, B.,
655 & Ressler, K. J. (2010). Impaired fear inhibition is a biomarker of PTSD but not
656 depression. *Depression and anxiety*, 27(3), 244 – 251. doi: 10.1002/da.20663
- 657 Junghöfer, M., Bröckelmann, A. K., Küppers, K., Ohrmann, P., & Pedersen, A. (2015).
658 Abnormal, affect-specific modulatory effects on early auditory processing in
659 schizophrenia: magnetoencephalographic evidence. *Schizophrenia Research*, 161,
660 308–313. doi:10.1016/j.schres.2014.11.025
- 661 Junghöfer, M., Rehbein, M. A., Maitzen, J., Schindler, S., & Kissler, J. (2017). An evil
662 face? Verbal evaluative multi-CS conditioning enhances face-evoked mid-latency
663 magnetoencephalographic responses. *Social Cognitive and Affective*
664 *Neuroscience*, 12, 695–705. doi:10.1093/scan/nsw179
- 665 Klucken, T., Schweckendiek, J., Koppe, G., Merz, C. J., Kagerer, S., Walter, B.,
666 Sammer, G., Vaitl, D., & Stark, R. (2012). Neural correlates of disgust- and fear-
667 conditioned responses. *Neuroscience* 201, 209–218.
668 doi:10.1016/j.neuroscience.2011.11.007
- 669 Kluge, C., Bauer, M., Leff, A. P., Heinze, H. J., Dolan, R. J., & Driver, J. (2011).
670 Plasticity of human auditory-evoked fields induced by shock conditioning and
671 contingency reversal. *Proceedings of the National Academy of Sciences of the*
672 *United States of America*, 108, 12545–12550. doi:10.1073/pnas.1016124108
- 673 Knowles, K. A., Jessup, S. C., & Olatunji, B. O. (2018). Disgust in anxiety and

- 674 obsessive-compulsive disorders: recent findings and future directions. *Current*
675 *Psychiatry Reports*, 20, 68. doi:10.1007/s11920-018-0936-5
- 676 Koban, L., Kusko, D., & Wager, T.D. (2018). Generalization of learned pain
677 modulation depends on explicit learning. *Acta Psychologica*, 184, 75–84.
678 doi:10.1016/j.actpsy.2017.09.009
- 679 Krusemark, E. A., & Li, W. (2011). Do all threats work the same way? Divergent effects
680 of fear and disgust on sensory perception and attention. *The Journal of*
681 *Neuroscience*, 31, 3429–3434. doi:10.1523/JNEUROSCI.4394-10.2011
- 682 Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J.,
683 Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A.,
684 Nees, F., Pittig, A., Richter, J., Römer, S., Shibani, Y., Schmitz, A., Straube, B.,
685 Vervliet, B., ... Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological
686 considerations for the design and analysis of studies on human fear acquisition,
687 extinction, and return of fear. *Neuroscience and biobehavioral reviews*, 77, 247–
688 285. <https://doi.org/10.1016/j.neubiorev.2017.02.026>
- 689 Lei, Y., Wang, J., Dou, H., Qiu, Y., & Li, H. (2019). Influence of typicality in category-
690 based fear generalization: diverging evidence from the P2 and N400 effect.
691 *International Journal of Psychophysiology*, 135, 12–20.
692 doi:10.1016/j.ijpsycho.2018.11.002
- 693 Lissek, S., Biggs, A. L., Rabin, S. J., Cornwell, B. R., Alvarez, R. P., Pine, D. S., &
694 Grillon, C. (2008). Generalization of conditioned fear-potentiated startle in
695 humans: experimental validation and clinical relevance. *Behaviour Research and*
696 *Therapy*, 46, 678–687. doi:10.1016/j.brat.2008.02.005
- 697 Lissek, S., Kaczkurkin, A. N., Rabin, S., Geraci, M., Pine, D. S., & Grillon, C. (2014).
698 Generalized anxiety disorder is associated with overgeneralization of classically
699 conditioned fear. *Biological Psychiatry*, 75, 909–915.
700 doi:10.1016/j.biopsych.2013.07.025
- 701 Ludvik, D., Boschen, M. J., & Neumann, D. L. (2015). Effective behavioural strategies
702 for reducing disgust in contamination-related OCD: a review. *Clinical Psychology*
703 *Review*, 42, 116–129. doi:10.1016/j.cpr.2015.07.001
- 704 Marin, M. F., Zsido, R. G., Song, H., Lasko, N. B., Killgore, W. D. S., Rauch, S. L.,
705 Simon, N. M., & Milad, M. R. (2017). Skin conductance responses and neural
706 activations during fear conditioning and extinction recall across anxiety disorders.
707 *JAMA Psychiatry*, 74, 622–631. doi:10.1001/jamapsychiatry.2017.0329

- 708 Mason, E. C., & Richardson, R. (2010). Looking beyond fear: the extinction of other
709 emotions implicated in anxiety disorders. *Journal of anxiety disorders*, *24*(1), 63–
710 70. doi:10.1016/j.janxdis.2009.08.007
- 711 McGuire, J. F., Orr, S. P., Essoe, J. K., McCracken, J. T., Storch, E. A., & Piacentini,
712 J. (2016). Extinction learning in childhood anxiety disorders, obsessive
713 compulsive disorder and post-traumatic stress disorder: implications for
714 treatment. *Expert review of neurotherapeutics*, *16*(10), 1155–1174. doi:
715 10.1080/14737175.2016.1199276.
- 716 Moeck, E. K., Matson, L. A., & Takarangi, M. (2021). Mechanisms underlying memory
717 enhancement for disgust over fear. *Cognition & emotion*, 1–7. Advance online
718 publication. <https://doi.org/10.1080/02699931.2021.1936460>
- 719 Nelson, B. D., Weinberg, A., Pawluk, J., Gawlowska, M., & Proudfit, G. H. (2015). An
720 event-related potential investigation of fear generalization and intolerance of
721 uncertainty. *Behavior Therapy*, *46*, 661–670. doi:10.1016/j.beth.2014.09.010
- 722 Olatunji, B. O., Armstrong, T., & Elwood, L. (2017). Is disgust proneness associated
723 with anxiety and related disorders? A qualitative review and meta-analysis of
724 group comparison and correlational studies. *Perspectives on Psychological
725 Science*, *12*, 613–648. doi:10.1177/1745691616688879
- 726 Olatunji, B. O., Forsyth, J. P., & Cherian, A. (2007). Evaluative differential
727 conditioning of disgust: a sticky form of relational learning that is resistant to
728 extinction. *Journal of Anxiety Disorders*, *21*, 820–834.
729 doi:10.1016/j.janxdis.2006.11.004
- 730 Olatunji, B. O., Moretz, M. W., Wolitzky-Taylor, K. B., McKay, D., McGrath, P. B.,
731 & Ciesielski, B. G. (2010). Disgust vulnerability and symptoms of contamination-
732 based OCD: descriptive tests of incremental specificity. *Behavior therapy*, *41*(4),
733 475–490. <https://doi.org/10.1016/j.beth.2009.11.005>
- 734 Olatunji, B. O., Wolitzky-Taylor, K. B., Willems, J., Lohr, J. M., & Armstrong, T.
735 (2009). Differential habituation of fear and disgust during repeated exposure to
736 threat-relevant stimuli in contamination-based OCD: an analogue study. *Journal
737 of Anxiety Disorders*, *23*, 118–123. doi:10.1016/j.janxdis.2008.04.006
- 738 Pavlov, Y.G., & Kotchoubey, B. (2019). Classical conditioning in oddball paradigm: A
739 comparison between aversive and name conditioning. *Psychophysiology* *56*,
740 e13370. doi:10.1111/psyp.13370
- 741 Peyrot, C., Brouillard, A., Morand-Beaulieu, S., & Marin, M. F. (2020). A review on

- 742 how stress modulates fear conditioning: Let's not forget the role of sex and sex
743 hormones. *Behaviour research and therapy*, *129*, 103615.
744 <https://doi.org/10.1016/j.brat.2020.103615>
- 745 Pittig, A., Treanor, M., LeBeau, R. T., & Craske, M. G. (2018). The role of associative
746 fear and avoidance learning in anxiety disorders: gaps and directions for future
747 research. *Neuroscience & Biobehavioral Reviews*, *88*, 117–140.
748 doi:10.1016/j.neubiorev.2018.03.015
- 749 Proulx, G. B., & Picton, T. W. (1984). The effects of anxiety and expectancy on the
750 CNV. *Annals of the New York Academy of Sciences*, *425*, 617–622.
751 doi:10.1111/j.1749-6632.1984.tb23586.x
- 752 Regan, M., & Howard, R. (1991). Controllability, predictability, and event-related
753 potentials to fear-relevant and fear-irrelevant stimuli. *Journal of*
754 *Psychophysiology*, *5*, 43–57.
- 755 Regan, M., & Howard, R. (1995). Fear conditioning, preparedness, and the contingent
756 negative variation. *Psychophysiology*, *32*, 208–214. doi:10.1111/j.1469-
757 8986.1995.tb02950.x
- 758 Rehbein, M. A., Pastor, M. C., Moltó, J., Poy, R., López-Penadés, R., & Junghöfer, M.
759 (2018). Identity and expression processing during classical conditioning with
760 faces. *Psychophysiology*, *55*, e13203. doi:10.1111/psyp.13203
- 761 Sangha, S., Diehl, M. M., Bergstrom, H. C., & Drew, M. R. (2020). Know safety, no
762 fear. *Neuroscience & Biobehavioral Reviews*, *108*, 218–230.
763 doi:10.1016/j.neubiorev.2019.11.006
- 764 Sperl, M. F. J., Wroblewski, A., Mueller, M., Straube, B., & Mueller, E. M. (2021).
765 Learning dynamics of electrophysiological brain signals during human fear
766 conditioning. *NeuroImage*, *226*, 117569. doi:10.1016/j.neuroimage.2020.117569
- 767 Stark, R., Schienle, A., Walter, B., Kirsch, P., Sammer, G., Ott, U., . . . Vaitl, D. (2003).
768 Hemodynamic responses to fear and disgust-inducing pictures: an fMRI study.
769 *International Journal of Psychophysiology*, *50*(3), 225–234. doi:10.1016/S0167-
770 8760(03)00169-7
- 771 Stark, R., Zimmermann, M., Kagerer, S., Schienle, A., Walter, B., Weygandt, M., &
772 Vaitl, D. (2007). Hemodynamic brain correlates of disgust and fear ratings.
773 *NeuroImage*, *37*(2), 663–673. doi:10.1016/j.neuroimage.2007.05.005
- 774 Stein, D. J., Liu, Y., Shapira, N. A., & Goodman, W. K. (2001). The psychobiology of
775 obsessive–compulsive disorder: how important is the role of disgust? *Current*

- 776 *Psychiatry Reports*, 3, 281–287. doi:10.1007/s11920-001-0020-3
- 777 Steinberg, C., Bröckelmann, A.K., Rehbein, M., Dobel, C., & Junghöfer, M. (2013).
778 Rapid and highly resolving associative affective learning: convergent electro- and
779 magnetoencephalographic evidence from vision and audition. *Biological*
780 *Psychology*, 92, 526–540. doi:10.1016/j.biopsycho.2012.02.009
- 781 Steinberg, C., Dobel, C., Schupp, H.T., Kissler, J., Elling, L., Pantev, C., & Junghöfer,
782 M. (2012). Rapid and highly resolving: affective evaluation of olfactorily
783 conditioned faces. *Journal of Cognitive Neuroscience*, 24, 17–27.
784 doi:10.1162/jocn_a_00067
- 785 Susskind, J. M., Lee, D. H., Cusi, A., Feiman, R., Grabski, W., & Anderson, A. K.
786 (2008). Expressing fear enhances sensory acquisition. *Nature neuroscience*, 11(7),
787 843–850. <https://doi.org/10.1038/nn.2138>
- 788 Takemoto, M., & Song, W.J. (2019). Cue-dependent safety and fear learning in a
789 discriminative auditory fear conditioning paradigm in the mouse. *Learning &*
790 *Memory*, 26, 284–290. doi:10.1101/lm.049577.119
- 791 Tuominen, L., Boeke, E., DeCross, S., Wolthusen, R. P., Nasr, S., Milad, M., Vangel,
792 M., Tootell, R., & Holt, D. (2019). The relationship of perceptual discrimination
793 to neural mechanisms of fear generalization. *NeuroImage*, 188, 445 – 455.
794 doi:10.1016/j.neuroimage.2018.12.034
- 795 Ugland, C.C., Dyson, B.J., & Field, A.P. (2013). An ERP study of the interaction
796 between verbal information and conditioning pathways to fear. *Biological*
797 *Psychology*, 92, 69–81. doi:10.1016/j.biopsycho.2012.02.003
- 798 van Hooff, J. C., Devue, C., Vieweg, P. E., & Theeuwes, J. (2013). Disgust- and not
799 fear-evoking images hold our attention. *Acta psychologica*, 143(1), 1–6.
800 <https://doi.org/10.1016/j.actpsy.2013.02.001>
- 801 Ventura-Bort, C., Löw, A., Wendt, J., Dolcos, F., Hamm, A.O., & Weymar, M. (2016).
802 When neutral turns significant: brain dynamics of rapidly formed associations
803 between neutral stimuli and emotional contexts. *European Journal of*
804 *Neuroscience*, 44, 2176–2183.s. doi:10.1111/ejn.13319
- 805 Vriends, N., Michael, T., Blechert, J., Meyer, A.H., Margraf, J., & Wilhelm, F.H.
806 (2011). The influence of state anxiety on the acquisition and extinction of fear.
807 *Journal of Behavior Therapy and Experimental Psychiatry*, 42, 46–53.
808 doi:10.1016/j.jbtep.2010.09.001

- 809 Wang, J., Sun, X., Lu, J., Dou, H., & Lei, Y. (2021). Generalization gradients for fear
810 and disgust in human associative learning. *Scientific reports*, *11*(1), 14210.
811 <https://doi.org/10.1038/s41598-021-93544-7>
- 812 Waters, A.M., Peters, R.M., Forrest, K.E., & Zimmer-Gembeck, M. (2014). Fear
813 acquisition and extinction in offspring of mothers with anxiety and depressive
814 disorders. *Developmental Cognitive Neuroscience*, *7*, 30–42.
815 doi:10.1016/j.dcn.2013.10.007
- 816 Willner, C.J., Jetha, M.K., Segalowitz, S.J., & Gatzke-Kopp, L.M. (2020).
817 Neurophysiological evidence for distinct biases in emotional face processing
818 associated with internalizing and externalizing symptoms in children. *Biological*
819 *Psychology*, *150*, 107829. doi:10.1016/j.biopsycho.2019.107829
- 820 Wong, A.H.K., & Lovibond, P.F. (2017). Rule-based generalisation in single-cue and
821 differential fear conditioning in humans. *Biological Psychology*, *129*, 111–120.
822 doi:10.1016/j.biopsycho.2017.08.056
- 823 Woody, S.R., McLean, C., & Klassen, T. (2005). Disgust as a motivator of avoidance
824 of spiders. *Journal of Anxiety Disorders*, *19*, 461–475.
825 doi:10.1016/j.janxdis.2004.04.002
- 826 Woody, S.R., & Teachman, B.A. (2000). Intersection of disgust and fear: normative
827 and pathological views. *Clinical Psychology Science and Practice*, *7*, 291–311.
828 doi:10.1093/clipsy/7.3.291
- 829 Yau, J.O.Y., & McNally, G.P. (2018). Brain mechanisms controlling Pavlovian fear
830 conditioning. *Journal of Experimental Psychology: Animal Learning and*
831 *Cognition*, *44*, 341–357. doi:10.1037/xan0000181
- 832 Zenses, A. K., Lee, J. C., Plaisance, V., & Zaman, J. (2021). Differences in perceptual
833 memory determine generalization patterns. *Behaviour research and therapy*, *136*,
834 103777. <https://doi.org/10.1016/j.brat.2020.103777>
- 835 Zheng, P., Lyu, Z., & Jackson, T. (2019). Effects of trait fear of pain on event-related
836 potentials during word cue presentations that signal potential pain. *European*
837 *Journal of Neuroscience*, *50*, 3365–3379. doi:10.1111/ejn.14495
- 838