

Implicit but not explicit exposure to threat conditioned stimulus prevents spontaneous recovery of threat potentiated startle responses in humans

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32 ABSTRACT

33

34 It has long been posited that threat learning operates and forms under an affective and a
 35 cognitive learning system that are supported by different brain circuits. A primary drawback in
 36 exposure-based therapies is the high rate of relapse when higher order inhibitory structures
 37 failed to inhibit the emotional responses driven by the defensive circuit. It has been shown that
 38 implicit exposure of fearful stimuli leads to a long-lasting reduction of avoidance behavior in
 39 patients with phobia through the facilitation of fear processing areas in the absence of subjective
 40 fear. Despite the potential benefits of this approach in the treatment of phobias and PTSD,
 41 implicit exposure to fearful stimuli is still under-investigated. Here, we used unconscious
 42 presentation of threat-conditioned stimuli in healthy humans, using a continuous flash
 43 suppression technique. We found that implicit exposure of a conditioned stimulus reduced, on
 44 the following day, defensive responses to the conditioned stimulus measured by threat-
 45 potentiated startle responses but not by the electrodermal activity. Our results suggest that
 46 implicit exposure using CFS might facilitate the modulation of the affective component of
 47 fearful memories, representing an important therapeutic target to further advance exposure-
 48 based psychotherapies.

49

50 **Keywords: threat-potentiated startle responses, electrodermal activity, skin conductance**
 51 **response, fear conditioning, threat conditioning, extinction learning, implicit exposure.**

52

53

54 INTRODUCTION

55

56 The ability to learn that previously threatening stimuli are no longer a threat is critical for
 57 mental health since the disruption of this process can lead to anxiety disorders like phobias and
 58 post-traumatic stress disorder, PTSD. A long-standing critical issue in the treatment of threat-
 59 related memories is the high rate of relapse after initially successful therapy (Craske and
 60 Mystkowski, 2006).

61

62 It has been established that threat learning operates and forms supported by two distinct brain
 63 circuits (Hamm and Vaitl, 1996; LeDoux, 1993). The first is an affective learning system
 64 grounded in the defensive circuit based in the amygdala and operating implicitly (LeDoux,
 65 1993). The second is a cognitive learning system, associated with the acquisition of the
 66 declarative knowledge of stimuli contingencies, expectancy of threat and conscious experience

67 of fear that is sustained by hippocampal and prefrontal brain areas (Baeyens et al., 1995; Lang
68 et al., 2000; LeDoux and Brown, 2017; Purkis and Lipp, 2001).

69

70 Exposure-based therapy is the most used procedure to treat threat-related memories (Rothbaum
71 and Davis, 2003) and is founded on the principles of extinction learning (Craske, 1999; Milad
72 and Quirk, 2012) where the threat-predicting stimulus (i.e., conditioned stimulus, CS) is
73 repeatedly presented in the absence of the negative outcome (e.g., unconditioned stimulus, US).
74 Through this procedure, subjects learn an inhibitory memory that, relying on prefrontal
75 structures (e.g., dorsolateral and ventromedial prefrontal cortex) (Phelps et al., 2004; Schiller et
76 al., 2013), suppresses the expression of the defensive responses initiated by amygdala-
77 subcortical structures (Pare and Duvarci, 2012; Sotres-Bayon et al., 2006). However, this
78 inhibitory function often fails, and defensive responses are spontaneously recovered with the
79 passage of time (Rescorla, 2004).

80

81 It has been suggested that since extinction learning leaves the affective memory fairly intact
82 (Baeyens et al., 1995; Myers and Davis, 2002), such implicit trace could later motivate fear
83 recovery, especially when the inhibitory structures (i.e., the prefrontal cortex) are impaired, as is
84 the case with anxiety-related patients (Konarski et al., 2007; Sotres-Bayon et al., 2006), or under
85 stressful situations (J and Nadel, 1985). Some studies have shown that procedures that avoid
86 prefrontal cortex (PFC) engagement to inhibit threat-related memories are highly effective in
87 preventing the recovery of defensive responses to threat conditioned or phobic stimuli (Koizumi
88 et al., 2016; Schiller et al., 2013; Siegel and Weinberger, 2009). Of particular interest are the
89 works of Siegel and Weinberg (Siegel and Warren, 2013a, 2013b) showing that very brief
90 repeated masked exposure to phobic stimuli led to long-lasting reduction in avoidance
91 behaviour in spider-phobics. In a recent fMRI study, the authors (Siegel et al., 2017) suggested
92 that the beneficial effects of masked exposure might have been mediated through a facilitation
93 of threat memory processing and the activation of regulation areas as participants do not

94 experience subjective distress during exposure. To date, however, implicit exposure is still
95 under-investigated, harboring important theoretical as well as clinical implications.

96

97 Here, we investigated the effects of implicit exposure on a fearful memory after 24h, using a
98 continuous flash suppression technique (CFS). To model fear acquisition and exposure-based
99 therapy, healthy participants were threat conditioned on day 1 to fearful faces. On day 2 stimuli
100 were presented through a stereoscope, either invisibly (through CFS) for the implicit group or
101 explicitly for the explicit group. On day 3 participants were normally presented to threat
102 conditioned stimuli and recovery of defensive responses were tested by analyzing threat-
103 potentiated startle responses, electrodermal activity, and online expectancy reports.

104 As it has been suggested by other authors (“Anxious: The Modern Mind in the Age of Anxiety
105 by Joseph E LeDoux, book review,” n.d.; Brewin, 2001; Siegel et al., 2017), we predict that by
106 restraining cognitive-mediated fear processing, implicit exposure would promote threat memory
107 processing at the implicit level and hinder the recovery of defensive responses.

108

109

110 MATERIALS AND METHODS

111 Participants

112 **Implicit group.** Fifty-nine (46 female, $M = 22.95$ years, $SD = 3.78$) healthy students with normal
113 or corrected-to-normal vision were recruited for this group. On the first day, we excluded 16
114 participants that did not meet the threat acquisition criteria (see *exclusion criteria for*
115 *acquisition*). From these, 23 more participants were excluded on the second day because they
116 broke the suppression effect during implicit exposure (see *exclusion criteria for image*
117 *suppression*). A final sample of 20 participants fulfilled the criteria for inclusion and followed
118 the three consecutive-days experimental protocol of the implicit group.

119 **Explicit group.** Thirty-two healthy students with normal or corrected-to-normal vision were
120 recruited for this group (25 female, $M = 20.5$ years, $SD = 2.39$). On day 1, we excluded 13

121 participants that were not threat conditioned and three that were non-responders (see *exclusion*
122 *criteria for acquisition*). One participant did not return for day 3. A final sample of 15
123 participants fulfilled the criteria for inclusion and followed the three consecutive-days
124 experimental protocol of the explicit group.

125 The study was approved by the Institute of Biomedical Research of Bellvitge ethics committee
126 and all subjects from both groups signed an informed consent before their participation.

127

128 **Psychological Inventories**

129 In order to control for psychological individual differences that could influence threat learning,
130 all participants completed the Spanish version of the Spielberger State-Trait (STAI-T), the
131 State-State (STAI-S) Anxiety Inventory (Spielberger, 1983) and the Spanish version of the 25-
132 item English Resilience Scale (Wagnild and Young, 1993) containing the ‘Acceptance of Self
133 and Life’ (ASL) and “Personal Competence” (PC) subscales.

134

135 **Stimuli**

136 **Visual Stimuli.** We employed Ekman’s fearful faces (Ekman, 1976) as the conditioning stimuli
137 (CS) as they can be processed in the absence of awareness through a rapid subcortical amygdala
138 route (McFadyen et al., 2017). Faces were presented for 5 seconds with inter-trial intervals (ITI)
139 of 10-12 seconds (after electrodermal activity was stabilized). Stimuli order presentation was
140 randomized with the constraint that no more than 3 repetitions of the same stimuli occurred.
141 Stimuli were displayed on a 22-inch computer monitor (resolution = 1,024 × 768 pixels; refresh
142 rate = 60 Hz) and were controlled using Psychophysics Toolbox software (Brainard, 1997; Pelli,
143 1997). Stimulus contrast was equally set for all participants, at a level that was clearly visible
144 when viewed on its own but was also easily suppressed with continuous flash suppression
145 (CFS) (see CFS in experimental task below).

146

147 **Electrical Stimulation.** We used a mild electric shock to the wrist as the unconditioned stimulus
 148 (US) during threat conditioning on day 1. Shocks were delivered through an electrode attached
 149 with a Velcro strap to participants' dominant inner wrist, with a maximum intensity of 15mA
 150 and 50 ms duration and co-terminated with faces presentation (Oyarzún et al., 2012). A Grass
 151 Medical Instruments stimulator (Grass S48 Square Pulse Stimulator) charged by a stabilized
 152 current was used with a Photoelectric Stimulus Isolation Unit (Model PSIU6). At the beginning
 153 of the session, participants regulated shock intensity to a level which they described as very
 154 uncomfortable yet not painful.

155 **Air-puffs.** In order to measure threat-potentiated startle responses (see below), we mechanically
 156 provoked blink responses by delivering 40 ms air-puffs, through a hosepipe directed to the
 157 anterior part of the temporal region between the outer canthus of the eye and the anterior margin
 158 of the auditory meatus (Haerich, 1994; Hawk and Cook, 1997) of the dominant-hand side. Air-
 159 puffs were delivered 4.5 s after every face presentation onset (did not overlap with electrical
 160 stimulations) and during every other intertrial interval (ITI). In order to habituate subjects to air-
 161 puff stimulation, each day started with 10 startle probes (Sevenster et al., 2012a).

162

163 **Experimental Task**

164 **Day 1. Fear acquisition**

165 On day 1, participants were randomly presented with 3 fearful faces, 8 times each. Two of them
 166 (CS1 and CS2) co-terminated with a mild electric shock to the wrist on 75% of the trials
 167 (reinforcement was omitted in the 1st and 5th trial) and a third one was never followed by the
 168 aversive stimulus (neutral stimulus, NS). Face gender was counterbalanced and randomized
 169 across participants. To acquire asymptotic levels of learning, participants were instructed that
 170 two faces were going to be followed, most of the time, by an electric shock, while the third one
 171 was safe (Figure 1).

172 **Exclusion criteria for acquisition.** The first exclusion criterion aimed to ensure that participants
 173 were fear-conditioned. We selected participants that showed differential electrodermal activity
 174 and startle potentiation to both threat-conditioned stimuli compared to neutral, this is; the

175 average of the final 4 trials, in the acquisition session, for both CSs was greater than for the NS
176 stimulus in the EDA or SR index. In addition, we excluded non-responder participants who
177 showed below 0.02 μ S peak to peak amplitude in the EDA index in more than 75% of
178 unreinforced trials during acquisition (Raio et al., 2012).

179

180 **Day 2. Exposure session**

181 ***Implicit exposure group***

182 Twenty-four hours after threat conditioning, using a stereoscope and the CFS technique (see
183 CFS below) participants were unconsciously exposed with only two of the images presented on
184 day 1: CS1 and NS, 16 times each in the absence of electric shocks. In order to control for
185 participants' awareness of the face presentation, we asked for a subjective report using the
186 keyboard arrows. After each trial, they were asked: 'Do you think you might have seen a face?'
187 'Yes' or 'No', and then 'Was it a male or a female?' Subjects then indicated 'male' or 'female'
188 and how sure they were of their answer with 'sure' or 'not sure'.

189 *Detection task.* In order to dissuade participants to voluntarily explore the non-dominant eye (by
190 closing one eye) and thus break the CFS effect, we included a simple detection task on the
191 dominant eye during Mondrian display (see CFS below). Three seconds after Mondrian onset, a
192 central grey dot would randomly change to a different color for 1 second. At the end of the three
193 awareness questions participants had to answer whether the dot had turned to green or not;
194 although no feedback was received after each response participants were encouraged to be
195 accurate in this task. Participants were pre-trained for this task in the training session (see
196 training session below).

197 ***Exclusion criterion for image suppression.*** To ensure full image suppression we excluded
198 participants that answered, in at least one trial: 'yes' to the first question ('*Do you think you*
199 *might have seen a face?*') and were correct and confident (answered 'sure') in indicating the
200 gender of the perceived face. Following this selection criteria, all the participants included in the

201 final sample reported not seeing anything besides the Mondrian at all trials; this is, for every
202 trial the participants included in the sample answered ‘No’ to the first question (except for one
203 subject that answered seeing something on one trial), they all guessed faces at chance in the
204 second question (main percentage of hits 46.71%; SD= 7.5; [34.38% – 58.06%]) and responded
205 to be ‘*not sure*’ about the guess in the third question. Participants learned to answer these 3
206 awareness questions during the training session on day 2.

207

208 **Continuous Flash Suppression (CFS).** We employed the continuous flash suppression (CFS)
209 technique, a binocular rivalry-based method capable of reliably suppressing visual awareness
210 despite stimulus presentation for long periods of time (Fang and He, 2005; Lin and He, 2009;
211 Tsuchiya and Koch, 2005). Using a mirror stereoscope (Stereoaids, Australia) placed 45 cm
212 from the screen, we presented a continuously flashing colorful pattern (Mondrian) (at 10Hz) to
213 the dominant eye and low-contrast (albeit visible) faces to the other, non-dominant eye.
214 Mondrians were created with Matlab (MathWorks, Natick, MA) and the Psychtoolbox
215 (Brainard, 1997; Pelli, 1997) and were presented for 5.5 seconds, starting 500 ms before face
216 onset. In this manner, target faces were rendered invisible to the participants and thus processed
217 without awareness. To determine eye dominance we used a sighting dominance test (Porac and
218 Coren, 1976) where we asked participants to hold, with extended arms, a plastic board and look
219 through a central small aperture to a picture placed on the wall at a 2-meter distance. The
220 investigator would then cover one participants’ eye at a time and ask for a subjective report of
221 the image. If the image was no longer seen when covering a certain eye then that eye was
222 considered dominant.

223 **Training session.** After the eye dominance test and before starting the experiment on day 2,
224 participants had a training session for 5 minutes to calibrate the stereoscope, ensure image
225 suppression and familiarize participants with the task and questions. First, a black and white
226 image of a zebra was presented to one eye and the zebra outline was presented to the other. The
227 subjects adjusted the mirrors of the stereoscope using two knobs so that each eye in isolation
228 saw either the full zebra or the full zebra outline, and with two eyes the zebra was aligned

229 within the zebra outline. Then, subjects in both groups initiated a training sequence using 6
230 presentations of random objects (instead of the faces) where they were familiarized with the 3
231 awareness questions and, in the case of the implicit group, with the detection task.

232 **Explicit exposure group.**

233 Participants followed the same procedure as the implicit group (same number, ITI, and length of
234 stimuli presented through the stereoscope). However, for this group, face-pictures were
235 explicitly presented. Mondrians were presented (in the dominant eye) for only 500 ms before
236 face-picture presentation, so faces were fully visible to the participants, for the following 5
237 seconds (the same duration as in the implicit group), in the non-dominant eye. In the same way,
238 as with the implicit group, the same three questions regarding picture awareness followed each
239 image presentation. In order to encourage participants to pay attention to faces presentation, this
240 group did not perform the color detection task. All participants reported seeing the faces at all
241 trials; this is, they answered ‘Yes’ to the first question (except for one subject that reported not
242 seeing a face on one trial), presented 100% accuracy in gender detection and were always sure
243 about their response.

244

245 **Day 3**

246 **Spontaneous recovery test.** After 24 hours we tested for recovery of defensive responses to all
247 stimuli. Participants were presented with the three faces they saw on the first day, 6 times each
248 in the absence of the shock. To remove attentional orienting effects on the first trials, an extra
249 presentation of the neutral stimulus, which was not included in the analysis, was presented at the
250 beginning of this session.

251

252 **Online threat expectancy ratings.** During the spontaneous recovery test participants had to
253 indicate whether they expected to receive, or not, an electric shock after seeing each face on the
254 screen. One second after face presentation the question ‘Are you expecting to receive a shock?’

255 appeared on the screen for 3 seconds. Participants answered, using the arrows of the keyboard,
256 ‘Yes’, ‘No’ or ‘I don’t know’.

257

258 **Measures**

259 **Threat-potentiated startle responses (SR)**

260 Startle responses were analyzed after delivery of air-puffs. We performed a monocular
261 electromyography (EMG) on the orbicularis ocular muscle of the dominant eye. A 6 mm
262 Ag/AgCl electrode filled with a conductive gel was placed 1.5 cm below the lower eyelid in line
263 with the pupil at forward gaze, a second electrode was placed 2 cm lateral to the first one
264 (center-to-center), and a signal ground electrode was placed on the forehead 2 cm below the
265 hairline (Blumenthal et al., 2005).

266 **EMG data analysis for SR.** Raw EMG data were notched and band-pass filtered (28-500 Hz,
267 Butterworth, 4th order), and afterward rectified (converting data points into absolute values) and
268 smoothed (low-pass filter 40 Hz) (Blumenthal et al., 2005). Peak blink amplitude was
269 determined in a 30-150 ms interval following air-puff delivery. EMG values were standardized
270 using within-participant Z scores for each day, and outliers ($Z > 3$) were replaced by a linear
271 trend at point (Sevenster et al., 2012a). For comparisons between exposure on day 2 and
272 spontaneous recovery test on day 3, Z scores were calculated using both exposure and recovery
273 test data. For comparisons within stimuli (CS1, CS2 and NS) on day 3, Z scores were calculated
274 using only recovery test data.

275

276 **Electrodermal activity (EDA)**

277 Electrodermal activity and EMG was sampled at 1000Hz and was recorded during the whole
278 session using Brain Amps amplifiers. EDA was assessed using two Ag-AgCl electrodes
279 connected to a BrainVision amplifier. The electrodes were attached to the middle and index
280 fingers of the non-dominant hand.

281 **EDA data analysis.** EDA waveforms were low-pass filtered (1Hz) and analyzed offline with
282 Matlab 7.7. F. Single-trial changes in EDA were determined by taking the base-to-peak

283 difference for a 4.5 s window after stimulus onset and before air-puff (or electric shock)
 284 delivery. The resulting amplitude of the skin conductance response (SCR) value was
 285 standardized using within-participant Z scores for each day, and outliers ($Z > 3$) were replaced
 286 by a linear trend at point (Sevenster et al., 2012a). As for EMG analyses, comparisons between
 287 exposure on day 2 and spontaneous recovery test on day 3 used Z scores calculated using both
 288 exposure and recovery test data. For comparisons within stimuli (CS1, CS2 and NS) on day 3, Z
 289 scores were calculated using only recovery test data.

290

291 **Online US-expectancy ratings (OER)**

292 Since explicit evaluation of contingencies could affect learning during fear acquisition and
 293 extinction learning during exposure, expectancy ratings were made only during day 3. After
 294 each image presentation, the question “Are you expecting to receive an electrical shock?”
 295 appeared on the top of the screen for 3.5 seconds to which participants answered “Yes” (scored
 296 3), “No” (scored 1) or “*I don’t know*” (scored 2) using the keyboard. Participants were
 297 encouraged to maintain their hands over the keyboard at all times and to restrict hand and head
 298 movement as much as possible.

299

300

301 **RESULTS**

302

303 **Acquisition**

304 **Equivalent levels of threat acquisition for conditioned stimuli in both groups and in both**
 305 **measures.**

306 *Threat Potentiated Startle responses (SR).* A two-way mixed analyses of variance (ANOVA)
 307 with group (implicit versus explicit) as a between-subject factor and stimuli (CS1 CS2 and NS)
 308 as a within-subject factor showed equivalent levels of SR for both groups in the last 4 trials (all
 309 p values $> .1$ for group and group x stimuli interaction) but a main effect of stimuli ($F_{(2,66)} =$

12.23; $p < .001$; $\eta^2 = .27$) (Figure 2A). A Repeated Measures ANOVA (RM-ANOVA) combining both groups showed successful threat conditioning results: a main effect of stimuli ($F_{(2,68)} = 12.12$; $p < .001$; $\eta^2 = .26$) with equal responses for CS1 and CS2 (Paired t-test, $t_{34} = -.59$; $p = .55$; $d = .10$) that were greater in comparison with NS (Paired t-test CS1-NS, $t_{34} = 4.51$; $p < .001$; $d = .76$, CS2-NS $t_{34} = 3.75$; $p = .001$; $d = .63$).

Electrodermal activity (EDA). EDA analyses showed similar results. Responses were equivalent between groups (all p values $> .1$ for group and group x stimulus interaction) but a main effect of stimuli was observed ($F_{(2,66)} = 26.61$; $p < .001$; $\eta^2 = .44$) (Figure 3A). A RM-ANOVA combining both groups showed successful threat conditioning results with a main effect of stimulus ($F_{(2,68)} = 28.48$; $p < .001$; $\eta^2 = .45$) where CS1 and CS2 showed equivalent responses (paired t-test $t_{34} = .29$; $p = .76$; $d = .05$) but greater than the NS (CS1-NS $t_{34} = 6.04$; $p < .001$; $d = 1.02$, CS2-NS $t_{34} = 5.88$; $p < .001$; $d = .99$).

Exposure session

Gradual overall decrease of responses during exposure session with no differences between groups nor between stimuli, in both measures.

We then analyzed the course of extinction learning during exposure using a two-way mixed ANOVA with group (implicit versus explicit) as an inter-subject factor and stimulus (CS1 and NS) and time (first trials 1-2 and last trials 15-16) as intra-subject factors.

Threat Potentiated Startle reflex (SR). We found no differences in responses between groups nor differential responding between stimuli (all p values $> .5$ for group, stimulus, and group x stimulus interaction). When looking at differences across time we found a decrease in responses from beginning to end of the session (main effect of time; $F_{(1,33)} = 55.57$; $p < .001$; $\eta^2 = .62$) that was equivalent between groups and stimuli (all p values $> .1$) (Figure 2B).

Electrodermal activity (EDA). EDA analyses showed similar results; no differences between groups nor between stimuli (all p values $> .1$ for group, stimulus, and group x stimulus interaction) (Figure 3B). Again, we found a decrease in responses from beginning to end of the

session (main effect of time; $F_{(1,33)} = 57.50$; $p < .001$; $\eta^2 = .63$) that was equivalent between groups and stimuli (all p values $> .1$).

Spontaneous Recovery Test

To test the recovery of defensive responses on day 3, we compared the last trial of the exposure session with the first trial of the spontaneous recovery test for CS1 and NS (Oyarzún et al., 2012; Schiller et al., 2010, 2013; Soeter and Kindt, 2011; Warren et al., 2014) (Figure 4).

We first compared recovery of defensive responses between groups, for the startle responses and for the electrodermal activity. And secondly, we compared the differential responses between the EDA and the SR measures within each group.

CS1, in the implicit group, showed no recovery of responses from the end of exposure session to the beginning of the recovery test. Only CS1 in the implicit group showed lower responses in comparison with CS2.

Threat potentiated Startle Reflex (SR). A two-way mixed ANOVA with group (implicit versus explicit) as a between-subjects factor, and phase (exposure and recovery test) and stimulus (CS1 and NS) as within-subject factors, revealed no main effect of group ($F_{(1,33)} = .30$, $p = .58$; $\eta^2 = .00$). A main effect of phase ($F_{(1,33)} = 38.92$; $p < .001$; $\eta^2 = .54$) that was equivalent between groups (phase $\times$ group $F_{(1,33)} = 1.06$; $p = .31$; $\eta^2 = .03$) indicated that SR responses increased at recovery in both groups. However, we found a significant stimuli $\times$ group interaction ($F_{(1,33)} = 10.0098$, $p < .005$; $\eta^2 = .23$) (Figure 4A-B). We thus compared stimuli responses between groups. Unpaired t-test showed similar responses for the NS in both groups ($t_{(33)} = 1.52$; $p = 1.13$; $d = .49$) but lower responses for the CS1 in the implicit than the explicit group ($t_{(33)} = -2.19$; $p = .03$; $d = .74$). Intra-group comparison of stimuli showed, in the implicit group, lower responses for the CS1 in comparison with the NS ($t_{(19)} = -2.97$; $p = .008$; $d = .66$). In contrast,

362 similar responses for NS and CS1 were found in the explicit group ($t_{(14)} = 1.68$; $p = .11$; $d =$
363 $.43$), indicating that implicit but not explicit exposure reduced SR responses to CS1.

364 We then compared CS1 responses with CS2 on day 3; another homologous stimulus that was
365 equally threat conditioned in the first session, but that was not exposed to participants on day 2
366 (Figure 2C). A two-way mixed ANOVA with group (implicit versus explicit) and stimulus
367 (CS1, CS2 and NS, standardized within day 3) as a between and within-subject factors
368 respectively, revealed a significant group x stimulus interaction ($F_{(2,66)} = 3.93$; $p = .02$; $\eta^2 = .11$).
369 Whereas in the explicit group all stimuli (i.e. CS1 NS CS2) showed comparable high responses
370 (all p values $> .1$), differences across stimuli were found in the implicit group (implicit $F_{(2,38)} =$
371 3.44 ; $p = .04$; $\eta^2 = .15$, explicit $F_{(2,28)} = 1.37$; $p = .26$; $\eta^2 = .09$), where only CS1 showed reduced
372 response compared to the CS2 ($t_{(19)} = -2.09$; $p = .04$, $d = .46$) and NS ($t_{(19)} = -2.77$; $p = .01$, $d =$
373 $.62$).

374

375 **EDA remained equivalent in both groups, with an overall increased activity from exposure**
376 **session to recovery test but greater recovery for CS1s that was comparable to CS2s**
377 **responses.**

378 *Electrodermal activity (EDA)*. A two-way mixed ANOVA with group (explicit versus implicit)
379 as an inter-subject factor, and phase (exposure and test) and stimuli (CS1 and NS) as within
380 factors revealed a main effect of phase ($F_{(1,33)} = 70.04$; $p < .001$; $\eta^2 = .69$), stimuli ($F_{(1,33)} =$
381 15.98 ; $p < .001$; $\eta^2 = .32$) and phase x stimuli interaction ($F_{(1,33)} = 18.02$; $p < .001$; $\eta^2 = .35$), but
382 no differences were found between groups (all p values $> .1$ for group, group x stimulus and,
383 group x stimulus x phase interaction) (Figure 4 C-D). We thus combined groups and compared
384 stimuli responses between phases. As expected, responses significantly increased from the end
385 of the exposure session to the recovery test in both stimuli (paired t-test NS $t_{(34)} = -5.37$; $p <$
386 $.001$; $d = -0.90$, CS1 $t_{(34)} = -7.10$; $p < .001$, $d = -1.2$). And, although responses between stimuli
387 were comparable at the end of the exposure session ($t_{(34)} = -.40$; $p = .68$; $d = -.06$), responses in

the recovery test were greater for CS1 than for NS ($t_{(34)} = 3.93$; $p < .001$; $d = 0.66$). Thus, showing that in both groups, CS1 and NS, incremented EDA responses from the end of day 2 to test, but with greater recovery for CS1.

We then explored whether such recovery in the CS1 was similar to the response of its conditioned homologous CS2 on day 3 (Figure 3C). A mixed ANOVA with group and stimuli (CS1, CS2 and NS) showed no differences across groups (all p values $> .5$ for group and group x stimulus interaction) but a main effect of stimulus ($F_{(2,66)} = 15.21$; $p < .001$; $\eta^2 = .32$) that was driven by equal responses for CS1 and CS2 on day 3 (paired t-test $t_{(34)} = .70$, $p = .48$, $d = .11$) but greater than NS (CS1-NS $t_{(34)} = 5.48$, $p < .001$, $d = .92$, CS2-NS $t_{(34)} = 5.15$, $p < .001$, $d = .87$). Thus, in the EDA measure, regardless of type of exposure, conditioned stimuli CS1 showed equivalent increased recovery than CS2 on day 3.

Comparisons between measures within groups. The implicit group showed a down-modulation of CS1 in the recovery test in the SR but not in the EDA. In contrast, the explicit group showed greater responses for CS1 and CS2 than NS in both the EDA and SR.

In order to directly compare the differential responses in the EDA and the SR measures we tested whether the recovery of defensive responses was different between measures within each group. We performed RM-ANOVA with measure (SR and EDA), phase (exposure and test) and stimulus (CS1 NS) as within-subject factor, separately for each group. The implicit group showed a main effect of stimuli ($F_{(1,19)} = 44.83$, $p < .001$; $\eta^2 = .70$), and interestingly a significant interaction of stimulus x measure ($F_{(1,19)} = 8.81$, $p < .01$; $\eta^2 = .31$) and stimulus x measure x phase ($F_{(1,19)} = 6.32$, $p = .02$; $\eta^2 = .25$) (Figure 4 A-C). Follow-up paired t-test showed greater CS1 responses from exposure to test in the EDA measure ($t_{(19)} = -4.15$, $p < .005$; $d = -.92$) but not in the SR measure ($t_{(19)} = -1.87$, $p = .07$; $d = -.42$). In contrast, the NS showed increment of responses in both measures (EDA $t_{(19)} = -4.13$, $p = .001$; $d = -.92$; SR $t_{(19)}$

414 = -4.2, $p < .001$; $d = -.95$). Thus, indicating that CS1 responses were divergently down-
415 modulated in the SR index but not in the EDA.

416 The explicit group showed a main effect of phase ($F_{(1,14)} = 66.65$, $p < .001$; $\eta^2 = .82$), stimuli ($F_{(1,14)} = 10.72$, $p = .006$; $\eta^2 = .43$) and again significant interactions of: stimulus x phase ($F_{(1,14)} = 8.32$, $p = .01$; $\eta^2 = .37$), stimulus x measure ($F_{(1,14)} = 7.66$, $p = .01$; $\eta^2 = .35$) and stimulus x phase x measure ($F_{(1,14)} = 5.25$, $p = .03$; $\eta^2 = .27$) (Figure 4 B-D). First, we looked for stimuli responses increments from the exposure session to test. In this case, significant increments were found in both measures for both stimuli [CS1 (EDA $t_{(19)} = -6.77$, $p < .001$; $d = -1.51$; SR $t_{(19)} = -4.01$, $p = .001$; $d = -.89$), and NS (EDA $t_{(14)} = -3.59$, $p = .003$; $d = -.92$, SR $t_{(19)} = -3.74$, $p = .002$; $d = -.96$). We then looked for stimuli responses between phases. In the recovery phase, we found that whereas CS1 and NS responses were equivalent in SR (paired-t-test $t_{(14)} = -1.34$, $p = .20$, $d = -.34$) responses in the EDA were greater for the CS1 (paired-t-test $t_{(14)} = 4.25$, $p = .001$, $d = 1.09$). Thus showing that the explicit group increased responses for both stimuli in both measures but in the EDA the recovery was greater for the CS1.

428

429 **Online Threat Expectancy Ratings (OER) on day 3**

430 **Participants' explicit contingency learning was not modulated by either implicit or explicit**
431 **exposure.**

432 We then explored on day 3 whether participants expected to be shocked after the presentation of
433 the faces (Figure 5). A two-way mixed ANOVA with group (implicit versus explicit) as
434 between-subject factor and stimuli (CS1, CS2 and NS) and time (mean of the first 2 trials versus
435 mean of the last 2 trials) as within-subject factor showed no differences between groups (all p
436 values $> .1$ for group, group x stimuli and group x time interaction). Thus, these results
437 indicated that our experimental manipulation did not affect OER. However we found a main
438 effect of stimuli ($F_{(2,66)} = 50.34$; $p < .001$, $\eta^2 = .33$), time ($F_{(2,66)} = 16.25$; $p < .001$, $\eta^2 = .33$) and
439 stimuli x time interaction ($F_{(2,66)} = 5.16$; $p < .005$, $\eta^2 = .13$). We thus explored stimuli responses

across time. We found that participants expectancy scored for CS1 and CS2 stimuli decreased from beginning to the end during the recovery session (CS1 $t_{(34)} = 3.39, p < .005; d = .57$, CS2 $t_{(34)} = 3.72, p < .005; d = .63$). Interestingly and congruent with the threat generalization responses to the NS in the first trials of the recovery test, NS also showed a decrease of responses from beginning to the end of session (NS $t_{(34)} = 2.71, p = .01; d = .45$), as some subjects reported not to be sure of expecting to be shocked when presented with the NS (scored = 2) in the first trials. As expected, although shock expectancy was similar between CS1 and CS2 at both the beginning and end of the session (all p values $> .5$), NS scores were significantly lower at both the beginning (CS1-NS $t_{(34)} = 8.90, p < .001; d = 1.52$, CS2-NS $t_{(34)} = 8.44, p < .001; d = 1.42$) and end of the session (CS1-NS $t_{(34)} = 5.60, p < .001; d = .94$, CS2-NS $t_{(34)} = 5.23, p < .001; d = .88$). Thus, participants maintained the cognitive threatful representation for conditioned stimuli from the beginning to the end of the session.

452

453 **PSYCHOLOGICAL INVENTORIES**

454 **Equivalent scores between groups**

Since anxiety traits have been previously related to aspects of implicit emotional learning (Raio et al. 2013) we checked whether our participants presented equivalent scores between groups in the psychological inventories. No significant differences were found between groups in any of the psychological inventories (see Table 1 for descriptive statistics); participants showed similar scores in the Spanish version of the STAI-state Inventory (unpaired t -test; $t_{(33)} = -.55, p = .58, d = .19$), the STAI-trait inventory ($t_{(33)} = -1.55, p = .12, d = .52$) and the Spanish version of the 25-item English Resilience with ASL and PC subscales (Group, $F_{(1,33)} = .69; p = .41; \eta^2 = .02$, group x scale interaction, $F_{(1,33)} = 1.00; p = .32; \eta^2 = .03$).

These results indicate that the differences observed for the implicit and explicit groups are unlikely to be due to differences in anxiety and resilience traits between the groups.

465

466

467 **DISCUSSION**

468

469 Two groups of participants underwent a partial reinforced threat-conditioning paradigm using
470 three fearful faces. Two of the faces co-terminated with a mild electric shock to the wrist on
471 75% of trials (conditioned stimuli; CS1 and CS2) while a third face served as the neutral
472 stimulus (NS).

473 On the second day, one group of participants underwent implicit while the other underwent
474 explicit exposure to one of the threat conditioned stimulus. For the implicit condition, CS1 and
475 NS were presented unconsciously using the continuous flash suppression (CFS) technique and
476 no shocks were administered, while CS2 was not presented. The explicit group followed the
477 same procedure except that pictures were explicitly presented (see Materials and Methods
478 section). On the following day, we tested spontaneous recovery, by presenting all participants
479 explicitly with the three faces in the absence of electric shocks (see design in Figure 1). We used
480 a combination of measures to examine defensive responses: threat-potentiated startle reflex
481 (SR), electrodermal activity (EDA) and online expectancy ratings (OER).

482

483 We found that exposing participants implicitly with previously threat conditioned stimulus
484 reduced the recovery of defensive responses after 24h, measured by SR, but not by EDA or
485 OER.

486 Our results highlight the divergent expression between two physiological measures (EDA and
487 SR) where implicit exposure only modulated threat potentiated SR. Dissociation between both
488 measures has long been recognized and although there is still much debate about the nature of
489 each measure it has been suggested that they are differently modulated by different neural
490 systems during threat memory encoding, extinction, and retrieval (Sevenster et al., 2014; Soeter
491 and Kindt, 2010).

492 In our experiment on day 3, EDA followed a similar pattern of responses as those presented by
 493 the OER, but only at the beginning of the test session; higher responses for CS1 and CS2 than
 494 for NS that gradually decreased throughout the session. Such correspondence across both
 495 measures fits well with the idea that EDA is sensitive to modulations of threat explicit
 496 expectancies (Lovibond, 2003; Sevenster et al., 2014; Soeter and Kindt, 2010). However, the
 497 fact that OER and EDA, increasingly dissociated as the session progressed; with a stronger drop
 498 in EDA to all stimuli (Figure 3) but sustained high OER (Figure 5) suggest that EDA reflects
 499 subjective feelings of fear and it might behave independently from contingency knowledge, as
 500 reported in other studies (Raio et al., 2012). Indeed, previous studies suggest that EDA is driven
 501 by amygdala activity (Koizumi et al., 2016; Schiller et al., 2013).

502 Critically, the fact that implicit exposure only modulated SR in the first trial during the recovery
 503 test might suggest that SR is more sensible than EDA, to subtle modulations in the affective
 504 system, potentially induced during implicit exposure of CS1. In fact, SR as an automatic reflex,
 505 has been considered to be tightly regulated by the defensive circuit reflecting amygdala activity
 506 for negative affective valence (Hamm and Vaitl, 1996; Lang et al., 1990), whereas EDA appears
 507 be more sensible to cognitive modulations by the explicit expectations of upcoming relevant
 508 events (Sevenster et al., 2012b, 2014). Critically, if this is the case, our results would suggest
 509 that implicit exposure might separately modulate the implicit trace of fearful memories.

510

511 Of note, NS showed an increment of defensive responses in the recovery test in both groups and
 512 for both measures (when comparing the last trial of the exposure session with the first trial of
 513 the spontaneous recovery test session), suggesting a global threat generalization effect.
 514 Generalization in the physiological responses was further supported by the results in the OER
 515 where participants reported to be ‘not sure’ of being shocked with NS presentation in the first
 516 trials on day 3. Generalization of defensive responses in this type of paradigm has been
 517 reported previously by other studies (Kindt and Soeter, 2013; Oyarzún et al., 2012; Soeter and
 518 Kindt, 2011). In the context of our current design, it is possible that threat generalization was

519 transferred via shared element among all stimuli (Dunsmoor and Murphy, 2015); this is, air-
520 puffs which were always presented at the end of each picture (to induce the blinking response)
521 (see Materials and Methods section), and were frequently followed by the electric shock (75%
522 of times for the CSs).

523

524 An important point to consider is the fact that no differential responses between conditioned and
525 neutral stimuli, nor between groups (implicit vs explicit) were observed throughout the course
526 of the exposure session. One possible explanation is that the use of the stereoscope during
527 exposure (and not during day 1 or 3) added new contextual cues that impaired the retrieval of
528 threatful associations and precluded discrimination among stimuli. The use of the stereoscope
529 only on day 2 was aimed to increase ecological validity of the exposure task, as the acquisition
530 of fear associations and re-exposure to fearful stimuli would be unlikely to occur throughout a
531 stereoscope in a real context.

532

533 Our results are consistent with and build on previous studies using a very brief exposure (VBE)
534 approach, in which pictures of spiders were presented very rapidly (i.e., 25 ms) in phobic
535 patients, leading to long-lasting reduction of avoidance behavior (Siegel and Warren, 2013a,
536 2013b). In an attempt to look for the mechanism underlying this effect, the authors (Siegel et al.,
537 2017) scanned patients while exposed to either masked or clear visible phobic stimuli (in two
538 separated groups). Counterintuitively, they showed that presentations of either masked or visible
539 phobic stimuli activated or deactivated, respectively, brain regions that support emotional
540 regulation like ventromedial PFC. They posited that limited awareness during exposure and lack
541 of subjective fear as well as amygdala activity reduction might facilitate fear processing and
542 emotional regulation. In addition, in other studies, it has been shown that when the prefrontal
543 cortex is not engaged during extinction learning (due to a lesion or due to early development
544 stage) subjects do not present recovery of defensive responses and amygdala is more involved
545 during extinction, leading to a permanent extinction (Kim and Richardson, 2010; Koenigs et al.,
546 2008). These results, point out the possibility that implicit exposure in our experiment might

547 have engaged similar mechanism that leads to attenuation of defensives responses, albeit only
548 detected by SR measure.

549 Although the neural mechanism underlying CFS suppression effects are still largely unknown, a
550 functional neuroimaging study using CFS and invisible presentations of fearful faces (Lapate et
551 al., 2016) showed that while awareness of cues promoted PFC-amygdala functional
552 connectivity, invisible presentation of faces did not engage such regulatory circuit. In the case of
553 our implicit exposure paradigm, it is possible that faces are repetitively processed by the
554 amygdala, via a fast subcortical pathway (Méndez-Bértolo et al., 2016) and by sensory areas
555 representing CS while unaware and thus in the absence of activation of the defensive circuit.
556 This, in turn, would promote emotional memory processing perhaps by the desensitization of
557 low-level threat related regions, as posited by Siegel et al. 2017 (Siegel et al., 2017). In fact, it
558 has been reported that ex-spider phobic patients that showed permanent extinction after 6
559 months presented low activity in ventro-visual regions that were hyperresponsive to spiders
560 before the therapy. Further, the authors revealed that reduced activity in a restricted portion of
561 the same visual cortical region (right lateralized lingual gyrus) immediately after therapy
562 predicted long-term permanence of extinction learning (Hauner et al., 2012). These results
563 suggest that tapping into sensorial and low-level defensive networks might change the
564 association between stimulus and defensive response, leading to permanent extinction without
565 the need of prefrontal inhibitory control. As our experiment cannot account for any neural
566 mechanism underlying CFS exposure further research is still imperative to examine such
567 argument.

568 An important disadvantage and methodological limitation from CFS technique is that image
569 suppression is often broken when presenting threatful images (Yang et al., 2007) which might
570 limit its use as a sole tool in clinical settings. In our experiment, to reduce subject attrition by
571 image suppression failure, we implemented a task where participants had to report the color of a
572 central dot within the Mondrian. However, the fact that participants needed to hold their answer
573 for a couple of seconds, might have comprised higher cognitive demand load during image

574 presentation. Whether this could have affected our results is unknown and more research would
575 be needed to clear out this possibility. Despite implementation of this task, around half of our
576 participants needed to be ruled out in this study for having broken the suppression effect. The
577 fact that the selection criteria eliminated so many participants might constitute a potential
578 confound as selected participants might share psychological features that make them more likely
579 to show reduced defensive responses in the SR during spontaneous recovery. Although our
580 selected participants rated equivalent scores in all psychological inventories, these results urge
581 the need for further investigation and replications that could circumvent bias selection of
582 participants by improving suppression effect during CFS exposure.

583 Our results deviate from those of Golkar & Ohman (2012) (Golkar and Öhman, 2012). In their
584 experiment, the authors extinguished two conditioned stimuli; one under masked and the other
585 under visible conditions. In contrast to our results, in their study the stimulus that was
586 unconsciously extinguished presented more fear recovery than the one explicitly extinguished.
587 However, it might well be the case that the parallel engagement of explicit and implicit learning
588 could jeopardize the latter, as both explicit and implicit systems share encoding resources (Turk-
589 Browne et al., 2006, p.) and might interact in a competitive manner (Kim and Baxter, 2001).
590 Indeed, it has been suggested that the strong cognitive component of exposure-based therapies
591 may actually preclude extinction learning at the implicit level (“Anxious: The Modern Mind in
592 the Age of Anxiety by Joseph E LeDoux, book review,” 2015).

593 We believe that implicit exposure using CFS might promote processing of fearful memories in
594 the subcortical threat related networks and facilitate emotional regulatory areas. The fact that
595 fearful stimuli are experienced in the absence emotional distress in patients might help to
596 change the threatful trace and improve the course of the therapy. Although our results provide
597 encouraging evidence supporting these ideas, our findings call out the need for further
598 investigation to circumvent methodological limitations, precise the mechanism involved, and
599 uncover the potential of CFS implicit exposure as a valuable complementary procedure to
600 further advance exposure-based psychotherapies.

601

602

603 **Acknowledgements**

604 The authors would like to thank Bert Molenkamp and David Cucurell for their technical
605 assistance and Dieuwke Sevenster and Joaquín Morís for their advice on the experimental
606 methodology. They are also thankful to Miguel Fullana and Rafael Torrubia for supplying
607 critical equipment for this study and Ivonne Heideman for helping during data collection.

608 **Author Contributions**

609 J.O. conducted the experiments and analyzed the data, J.O., R.D.B and L.F. designed
610 the experiments and wrote the paper, and J.O., E.C., and S.K. programmed the task.

611

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773 LEGENDS

774 **Figure 1. Three-day experimental design: acquisition exposure and spontaneous**
775 **recovery test.** Two faces were fear-conditioned on day 1 (CS1 and CS2) whereas a
776 third face served as the neutral stimulus NS. CS1 and the NS were presented with no
777 reinforcement on the second day using a continuous flash suppression (CFS) setting
778 (with a stereoscope and colorful patches). These Mondrians were continuously flashing
779 during picture presentation in the implicit group but were fixed and briefly presented in
780 the explicit group. Acquisition on day 1 and Recovery Test on day 3 were conducted
781 explicitly with faces at the center of the screen and without CFS setting.

782

783 **Figure 2. Threat potentiated startle responses trial by trial throughout the 3-day**
 784 **experiment for both experimental groups. The top panel depicts implicit exposure**
 785 **group. The lower panel depicts explicit exposure group.** Mean standardized startle
 786 responses were calculated using all trials within each session for each group. Plots
 787 represent the mean response of (A) CS1 CS2 and NS during acquisition on day 1 (B)
 788 CS1 and NS during exposure on day 2 (C) CS1 CS2 and NS during spontaneous
 789 recovery on day 3. EMG: electromyography. Error bars represent standard error of the
 790 mean (SEM).

791

792 **Figure 3. Trial-by-trial electrodermal activity throughout the 3-day experiment**
 793 **for both experimental groups. The top panel depicts implicit exposure group. The**
 794 **lower panel depicts explicit exposure group.** Mean standardized electrodermal
 795 activity was quantified using all trials within each session for each group. Plots
 796 represent the mean electrodermal activity of (A) CS1 CS2 and NS during acquisition on
 797 day 1 (B) CS1 and NS during exposure on day 2 (C) CS1 CS2 and NS during
 798 spontaneous recovery on day 3. EDA: electrodermal activity. Error bars represent
 799 standard error of the mean (SEM).

800

801 **Figure 4. Recovery of defensive responses for both experimental groups.** Mean
 802 standardized startle responses were calculated using all trials for CS1 and NS during
 803 exposure and spontaneous recovery sessions for each group in each measure. Plots
 804 represent the last trial of exposure on day 2 and the first trial of spontaneous recovery on
 805 day 3. (A) Mean of startle response for the implicit group. (B) Mean of startle response
 806 for the explicit group (C) Mean of electrodermal activity for the implicit group. (D)

807 Mean of electrodermal activity for the explicit group. EMG: electromyography; EDA:
 808 electrodermal activity, small*: $p < .05$ comparison for each stimuli between phases,
 809 big*: main effect of phase. Error bars represent standard error of the mean (SEM).

810

811 **Figure 5. Online threat expectancy ratings during recovery test.** During each picture
 812 presentation, subjects indicated whether they either expected (pressed 3), did not expect
 813 (pressed 1) or were not sure about (pressed 2) imminent shock occurrence. Error bars
 814 represent standard error of the mean (SEM); (a.u) arbitrary unit.

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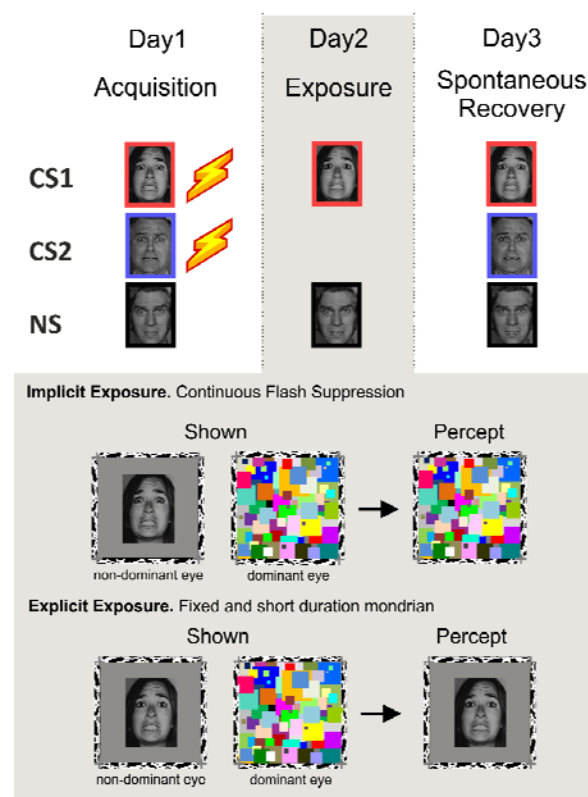
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820 **FIGURES**

821 **Figure 1.**



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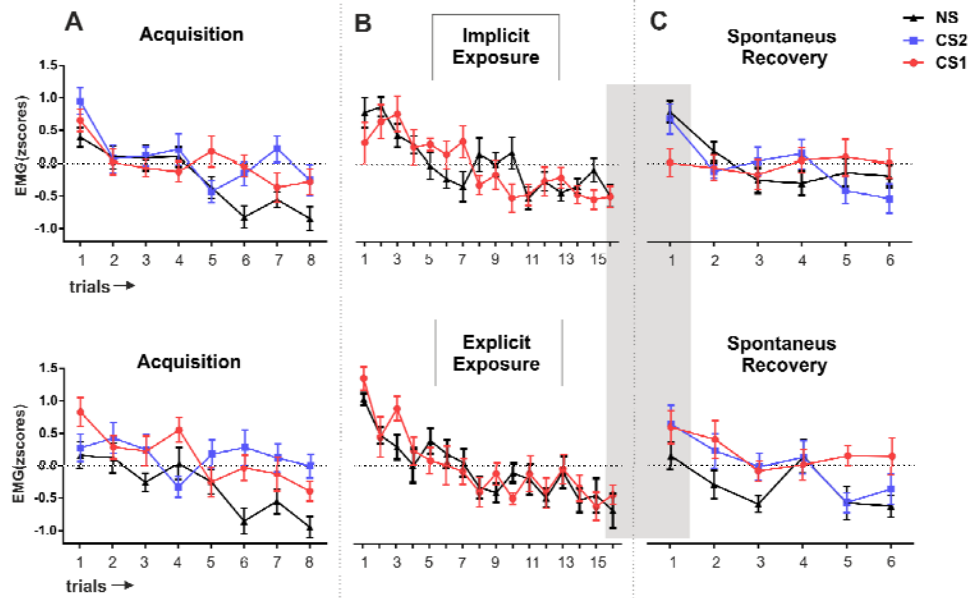
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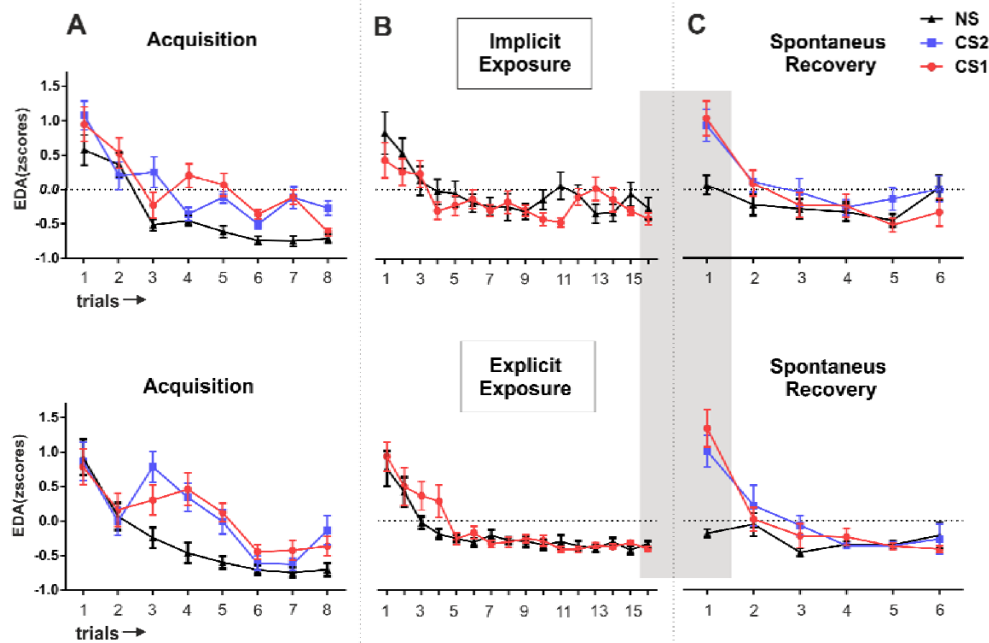
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830 **Figure 2.**



831

832 **Figure 3.**

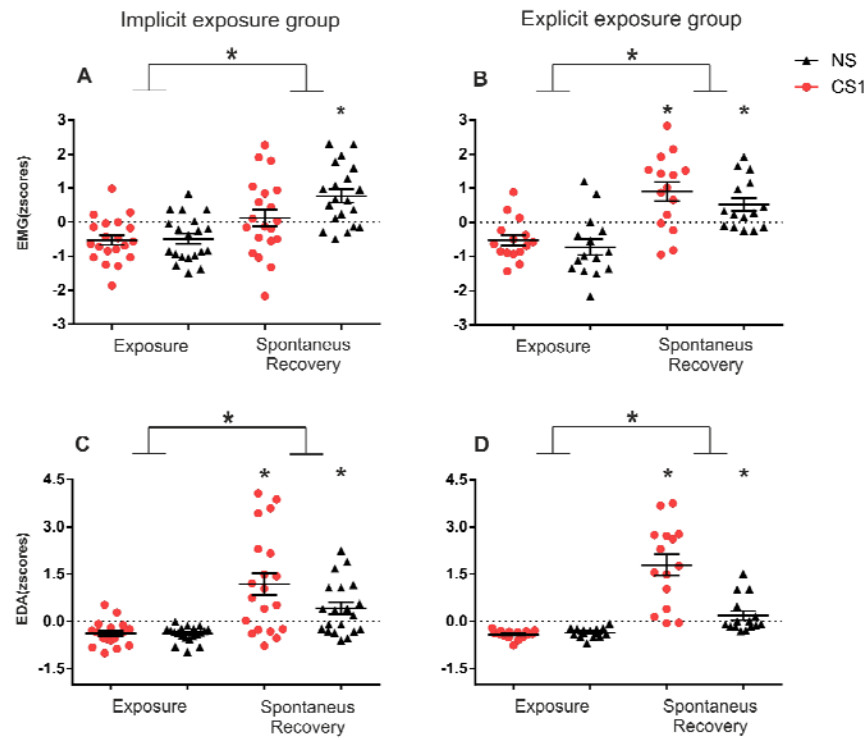


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835 **Figure 4.**

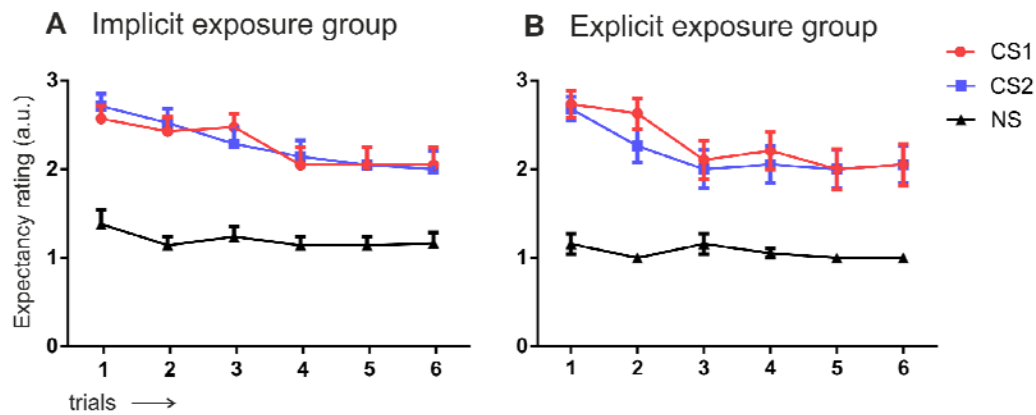
Spontaneous Recovery test



836

837

838 **Figure 5.**



839

840

841

842 **Table 1**

843 Descriptive statistics of inventory scores

Inventory	Implicit		Explicit	
	Mean	SD	Mean	SD
STAI-state	10.15	5.33	11.06	4.13
STAI-trait	9.7	7.6	13.0	3.4
PC	91.22	12.56	91.46	9.04
ASL	37.11	5.77	40.26	4.11

844 *Note:* PC = Personal Competence; ASL = Acceptance of Self and Life

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848