

1 **Investigation of reward learning and feedback sensitivity in non-**  
2 **clinical participants with a history of early life stress.**

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20 **Abstract**

21

22 Early life stress (ELS) is an important risk factor for the development of depression.  
23 Impairments in reward learning and feedback sensitivity are suggested to be an intermediate  
24 phenotype in depression aetiology therefore we hypothesised that similar impairments are  
25 present in healthy adults with a history of ELS. We recruited 64 adults with high levels of ELS  
26 and no diagnosis of a current mental health disorder and 65 controls. Participants completed  
27 the probabilistic reversal learning task and probabilistic reward task followed by depression,  
28 anhedonia, social status, and stress scales. Participants with high levels of ELS showed  
29 decreased positive feedback sensitivity in the probabilistic reversal learning task compared to  
30 controls. High ELS participants also trended towards possessing a decreased model-free  
31 learning rate. This was coupled with a decreased learning ability in the acquisition phase of  
32 block 1 following the practice session. Neither group showed a reward induced response bias  
33 in the probabilistic reward task however high ELS participants exhibited decreased stimuli  
34 discrimination. Due to the PRT not meeting its primary endpoint a separate cohort of control  
35 participants were tested in a modified PRT where they showed a response bias. This indicates  
36 the PRT can be successfully carried out online. Overall, these data suggest that healthy  
37 participants without a mental health diagnosis and high levels of ELS show deficits in positive  
38 feedback sensitivity and reward learning in the probabilistic reversal learning task that are  
39 distinct from depressed patients. These deficits may be relevant to increased depression  
40 vulnerability.

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## 42 **1. Introduction**

43

44 Early life stress (ELS) is a major known risk factor for the development of depression [1–4].  
45 ELS has also been found to lower the threshold of stress required to precipitate depression  
46 [5], one of the major triggers in healthy populations [6]. Elevated levels of childhood stress  
47 lead to widespread functional and morphological alterations in the adult brain with the  
48 hippocampus, amygdala and prefrontal cortex being most impacted [7,8]. Amongst other  
49 functions, these regions are vital mediators of reward learning: the ability of reward to  
50 modulate future behaviour [9–16]. However, how ELS influences the developing brain to  
51 predispose individuals to psychiatric illness is not yet understood.

52

53 Reward learning deficits have been proposed to be an intermediate phenotype in the  
54 aetiology and maintenance of depression [17–20]. Depressed patients show decreased  
55 reward sensitivity in the probabilistic reward task (PRT), a test of reward learning [19]. These  
56 deficits have been observed to both predict the risk of disease development [21] and  
57 persistence [18,22]. Utilising a different reward learning assay, the probabilistic reversal  
58 learning task (PRLT), depressed patients show impaired accuracy following probabilistic rule  
59 reversal and increased sensitivity to probabilistic negative feedback [23,24]. Acute stress has  
60 also been observed to impair reward learning [25,26] suggesting a potential link between  
61 stress, reward processing deficits and depression aetiology. Therefore this suggests that a  
62 divergent developmental trajectory in regions involved with reward processing as seen in ELS  
63 could lead to depression vulnerability through impaired reward learning as an intermediate  
64 phenotype.

65 Previous studies have therefore investigated reward processing deficits in people who have  
66 experienced ELS. Hanson and colleagues [27] recruited adolescents with a history of physical  
67 abuse who then completed a probabilistic learning task where they showed lower associative  
68 learning compared to controls. Changes in reward learning have also been reported within  
69 another probabilistic reward task, the probabilistic stimulus selection task (PSST). Women  
70 with a history of childhood sexual abuse and a diagnosis of Major Depressive disorder (MDD)  
71 showed decreased performance on trials requiring learning of previously rewarded  
72 information compared to MDD only and control groups [28]. Although these studies provide  
73 valuable insights, they use different tasks to those previously used to study depressed  
74 populations making direct comparisons difficult. Additionally, studies are needed in adults  
75 without a current mental health diagnosis to understand if any reward processing changes  
76 are present in individuals at higher risk of mental health disorders.

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78 In this study it was hypothesised that ELS is associated with alterations in reward processing  
79 and feedback sensitivity in an otherwise healthy adult population. Two groups of adult  
80 participants that self-reported no current diagnosis of a mental health condition or  
81 Parkinson's disease were recruited online and completed a survey of adverse childhood  
82 experiences [29] before being split into high and no ELS groups based upon this. Participants  
83 completed the PRT (points based) and PRLT with PRLT data additionally being analysed using  
84 a Q-learning model to probe reward learning parameter changes. Participants were asked  
85 about stress exposure to enable exploratory analysis investigating if life stress interacts with  
86 ELS to cause reward processing deficits. Participants with a history of ELS showed evidence  
87 for decreased positive feedback sensitivity in the PRLT, however neither high ELS nor control

88 participants showed a response bias in the points based PRT. As this was the first reported  
89 attempt to utilise the PRT in an online environment and due to the failure of both groups to  
90 meet the primary endpoint we recruited an additional population of control participants using  
91 a modified task design using direct compensation to validate that the PRT can be successfully  
92 performed online.

93

94 By understanding the links between ELS and reward processing deficits as a hypothesised  
95 intermediate phenotype in depression this study aims to provide insights into how a person  
96 with a history of ELS is rendered at higher risk for depression.

97

## 98 **2. Methods**

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100 All procedures were approved by the Faculty of Life Sciences and Faculty of Science Research  
101 Ethics Committee at the University of Bristol and the study protocol was pre-registered  
102 ([www.osf.io/538yk](http://www.osf.io/538yk)). All methods were performed in accordance with the declaration of  
103 Helsinki in addition to all other institutional and national guidelines. All participants provided  
104 full written consent for the collection, analysis and publication of their data which is available  
105 open access ([www.ofs.io/63e8j](http://www.ofs.io/63e8j)) and were reimbursed at a rate of £6.00 per hour.

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## 109 **2.1 Participants**

110

111 A total of 586 participants were recruited using the Prolific ([www.prolific.co](http://www.prolific.co)) online platform  
112 to complete an online screening questionnaire (see supplementary Fig 1 for study overview  
113 and table 1 for participant demographics). These participants were 25 - 65 years of age, fluent  
114 in English, resident in the UK and had no mild cognitive impairments or dementia. Participants  
115 completed the early life stress questionnaire [29] (ELSQ) which asks if participants had prior  
116 exposure to specific adverse childhood experiences (ACEs). Participants were also asked  
117 “Have you got a current diagnosis of a mental health disorder or Parkinson’s disease?”.

118

119 Participants who met the inclusion criteria for high ELS or no ELS and did not report a diagnosis  
120 of a mental health disorder or Parkinson’s were then invited to take part in a second phase of  
121 the experiment online within a week of screening and were allocated into two groups. A no  
122 ELS group (n = 65) contained people reporting no ACEs on the ELSQ while a high ELS group (n  
123 = 64) consisted of those who reported  $\geq 3$  ACEs (estimated to be the top tercile of the  
124 population [29]). In this second phase of the experiment participants entered demographic  
125 information before completing the MacArthur Scale of Subjective Social Status [30], Beck’s  
126 depression inventory II [31] (BDI-II), the Snaith Hamilton pleasure scale [32] (SHAPS) and the  
127 Holmes and Rahe stress scale [33]. The SHAPS was additionally scored using the SHAPS-C  
128 criteria [34]. For the stress scale participants were asked if each event occurred in either their  
129 adult life or the last year to provide a measure of both total adult lifetime stress and recent  
130 stress. For all stages of the experiment participants were instructed to use a desktop or laptop  
131 only and that they should be in a quiet place with minimal distractions. Sample size was

132 estimated for a medium effect size (Cohen's  $d = 0.5$ ) and 80% power for a t-test at 64  
133 participants per group. While other studies have investigated different dimensions of ELS (i.e.  
134 emotional abuse vs psychosocial neglect) with regards to cognitive outcome [8] the present  
135 study was not powered to enable this.

136

137 Early life stress was highly prevalent in the study population with only 21.0% of participants  
138 having no adverse childhood experiences (ACEs) and 44.4% of the population suffering three  
139 or more ACEs in their childhood (see supplementary fig 2). 16.0% of respondents self-reported  
140 a diagnosis of a mental health disorder or Parkinson's with this being associated with a higher  
141 ELSQ score (Mann-Whitney,  $U = 15725$ ,  $p < 0.0001$ ).

142

143 The two study groups were well matched with respect to gender, age, education, ethnicity,  
144 relationship status, employment status and the presence of monetary worries (see table 1).  
145 However, high ELS participants had a self-reported lower social status coupled with higher  
146 depression scores in the BDI-II and elevated anhedonia scores in the SHAPS questionnaires.  
147 There was no evidence of a difference between groups when participants were asked about  
148 stress they encountered in both the last year and their adult lives. When the BDI-II scores  
149 were classified into either minimal, mild, moderate or severe depression (see supplementary  
150 fig 3 [31]) participants from the high ELS group were more likely to be in greater severity  
151 depression groupings ( $\chi^2$ ,  $\chi^2(3) = 12.9$ ,  $p = 0.005$ ). Similarly when SHAPS scores were  
152 classified into either normal ( $\leq 2$ ) or abnormal ( $\geq 3$ ) hedonic responses [32] members of the  
153 high ELS group were more likely to have abnormal scores (see supplementary fig 3,  $\chi^2$ ,  $\chi^2(1)$   
154  $= 6.3$ ,  $p = 0.012$ ).

Measure	No ELS (n = 65)	High ELS (n = 64)	Test statistic	p
Gender (% male)	44.6	37.5	$\chi^2(2) = 2.5$	0.28
Age (years)	37.3 ± 1.30	38.0 ± 1.24	U = 1936.0	0.50
Education (% graduates)	64.6	65.6	$\chi^2(5) = 4.9$	0.43
Ethnicity (% white)	95.4	82.8	$\chi^2(4) = 8.7$	0.070
Relationship status (% single)	18.5	28.1	$\chi^2(3) = 1.9$	0.60
Employment status (% full time)	64.6	60.9	$\chi^2(5) = 3.5$	0.61
Monetary concerns (% agree / strongly agree)	36.9	56.3	$\chi^2(3) = 4.4$	0.22
ELSQ	0 ± 0	4.36 ± 0.17	-	-
Social status	6.2 ± 0.17	5.2 ± 0.21	U = 1397.5	<b>0.001</b>
BDI-II	9.4 ± 1.0	15.2 ± 1.22	U = 1315.5	<b>0.0003</b>
SHAPS	1.4 ± 0.25	2.56 ± 0.32	U = 1496.5	<b>0.004</b>
SHAPS-C	24.3 ± 0.67	26.4 ± 0.86	$t_{119.4} = -1.92$	0.057
Lifetime stress	472.8 ± 22.4	529.2 ± 23.9	$t_{127} = -1.72$	0.088
Last year stress	111.4 ± 12.3	139.8 ± 17.0	U = 1939.5	0.51

155

156 **Table 1. Demographic and self-report measures in the study population.** Values are shown

157 for each group as mean ± standard error with significant p values ( $p \leq 0.05$ ) indicated in bold.

158

## 159 2.2 Behavioural testing

160

161 Following completion of self-report measures, participants completed the Probabilistic

162 reversal learning task [35,36] followed by the Probabilistic reward task [37]. To complete the

163 tasks participants were required to download and install the Millisecond Inquisit web player

164 (Millisecond, US) which ran both tasks using Millisecond Inquisit v6.2.1. Participants were



165 instructed they were able to earn an additional £2.00 for high performance on the  
166 behavioural tasks.

167

### 168 **2.2.1 Probabilistic Reversal Learning task**

169

170 The PRLT was conducted as previously described [35,36] using the task from the Millisecond  
171 test library [38]. Participants were instructed to choose between a “lucky” (rich) and  
172 “unlucky” (lean) pattern to maximise points. Selection of the rich stimulus enabled  
173 participants to gain a point 80% of the time and lose a point 20% of the time with the lean  
174 stimulus having opposite contingencies. If no stimulus was chosen within 2s then this was  
175 classified as incorrect and participants lost a point. After meeting the reversal criterion, the  
176 contingencies reverse such that the rich stimuli becomes lean and vice versa. This criterion  
177 was set randomly between 10 to 15 consecutive correct rich choices to stop participants  
178 counting to the criterion. Participants first completed a practice phase where they had to  
179 achieve the criterion for a single reversal before proceeding to the main task which was  
180 completed in three blocks each limited to 9 minutes where participants could reverse as many  
181 times as able within a block. Participants who did not pass the practice phase were excluded  
182 from analysis. Data were analysed as previously described [39]. Win-stay probability was  
183 defined as the probability that if a participant was rewarded for selecting a stimulus they  
184 would select the same stimulus for the next trial. Lose-shift probability was conversely the  
185 probability that if a participant lost a point at a stimulus they would switch to the opposite  
186 stimulus for the next trial. This enabled win-stay and lose-shift probabilities to be used as  
187 measures of positive and negative feedback sensitivity respectively. These were subdivided

188 into either true, feedback that matches with the underlying task rules (e.g. being rewarded  
189 for selecting the rich stimulus), or misleading feedback (e.g. being rewarded for selecting the  
190 lean stimulus), that which is opposite to the underlying task rule. The number of rule changes,  
191 how many times participants were able to meet criterion for a rule change, accuracy and  
192 response latency per block were additionally analysed. A Qlearn reinforcement learning  
193 model was applied to data as previously described [39,40] to give estimates of model free  
194 learning rate, accuracy compared to a model predicted perfect strategy (subjective accuracy)  
195 and beta, a measure of choice variability (low values indicate essentially random choices while  
196 high values show a deterministic choice strategy). Additionally, data per phase (practice,  
197 acquisition of the first rule in block 1 and the following two reversals) was analysed consisting  
198 of participant accuracy, errors to criterion and win-stay / lose-shift probability.

199

### 200 **2.2.2 Probabilistic Reward Task**

201

202 The PRT was conducted as previously described [37] using the task from the Millisecond test  
203 library [41]. Participants were instructed to identify whether the mouth of a presented  
204 cartoon face was long or short ( $\approx 11\%$  difference in mouth length) to win points over 3 blocks  
205 of 100 trials. Participants were shown a face before a mouth was rapidly presented for 100ms  
206 with participants given up to 1750ms to respond. Feedback was not provided on every trial  
207 but unknown to participants one mouth was rewarded with points three times more often  
208 than the other (rich = 60%, lean = 20%). Response key and rich/lean stimuli assignments were  
209 counterbalanced across participants and responses that were quicker than 150ms or slower  
210 than 1750ms were excluded from analysis. Additional responses that differed by more than 3

211 standard deviations from the mean following natural log transformation of latencies for each  
212 participant were excluded from analysis. Response bias ( $\log B$ ), a measure of reward learning,  
213 and discriminability ( $\log D$ ), a measure of task difficulty, were calculated as:

214

$$215 \quad \log B = \frac{Rich_{correct} \times Lean_{incorrect}}{Rich_{incorrect} \times Lean_{correct}}$$

$$216 \quad \log D = \frac{Rich_{correct} \times Lean^{correct}}{Rich_{incorrect} \times Lean_{incorrect}}$$

217

### 218 **2.2.3 Directly rewarded probabilistic reward task**

219

220 An additional cohort of 81 participants (no current or previously diagnosed mental health  
221 condition, aged 18-45) were recruited using the Prolific platform (see supplementary  
222 methods for more details). Participants completed a different reward learning task (not  
223 discussed here) over 5 days and on the final day completed the directly rewarded PRT  
224 alongside BDI and SHAPS questionnaires. The directly rewarded PRT was carried out  
225 identically to as previously described except participants were given direct monetary  
226 compensation for each rewarded trial (£0.04) as opposed to points which later converted to  
227 a bonus payment. Only participants with a minimal BDI score (<13) and normal SHAPS score  
228 ( $\leq 2$ ) were included in final analysis.

229

230

## 231 **2.3 Data Analysis**

232

233 Demographic and self-report measures were compared between groups using either  $\chi^2$ , t-  
234 tests or Mann-Whitney U tests where appropriate. The primary analysis for each measure  
235 was a direct comparison between no ELS and high ELS groups. Where data were not normally  
236 distributed then efforts were first made to transform data to normality and where this was  
237 not possible Mann-Whitney U tests were completed. Win-stay by block data were  
238 transformed using the bestNormalize package in R [42]. Where measures were split by a  
239 within subject factor such as block or feedback type these were analysed with repeated  
240 measures ANOVAs. Where Mauchly's test identified a violation of the Sphericity assumption  
241 then this was corrected using the Huynh-Feldt correction. T-tests were used for direct group  
242 comparisons.

243

244 Due to differences in social status, BDI-II score and SHAPS score between the no ELS and high  
245 ELS groups, principal component analysis (PCA) was conducted to reduce the dimensionality  
246 of these variables to account for depression symptomology as an analysis stage (see  
247 supplementary tables 1 and 2). Because only principal component 1 (PC1) differed between  
248 groups and explained 94.6% of variance this was used in ANCOVAs (analysis of covariance) to  
249 analyse whether parameter changes were due to ELS or due to changes in depression  
250 symptomology accounted for by the PC1 component. To understand if stress and gender  
251 interacted with ELS to modify reward learning, exploratory analysis was also undertaken using  
252 generalised linear mixed models (GLMMs) containing the factors: gender, ELS, lifetime stress,  
253 last year stress and age. GLMMs were fit using the glmmTMB package in R 4.0 [43,44] with

254 model refinement conducted utilising stepwise deletion based upon Akaike information  
255 criterion before being compared with a null model to protect against overfitting. PC1 was also  
256 added to each model following final model selection to assess the effects of depression  
257 symptomology.

258

259 Statistical analysis was conducted in SPSS v26 (IBM, US), MATLAB 2018a (Mathworks, USA)  
260 and R 4.0 [43] with output graphics constructed in GraphPad Prism 8 (GraphPad, US). For all  
261 analysis  $\alpha$  was set at 0.05. All data is shown as mean  $\pm$  SE with a bar and stars showing  
262 evidence of a main effect of ELS in the primary analysis. \*  $\leq$  0.05, \*\*  $<$  0.01, \*\*\*  $<$  0.001, \*\*\*\*  
263  $<$  0.0001.

264

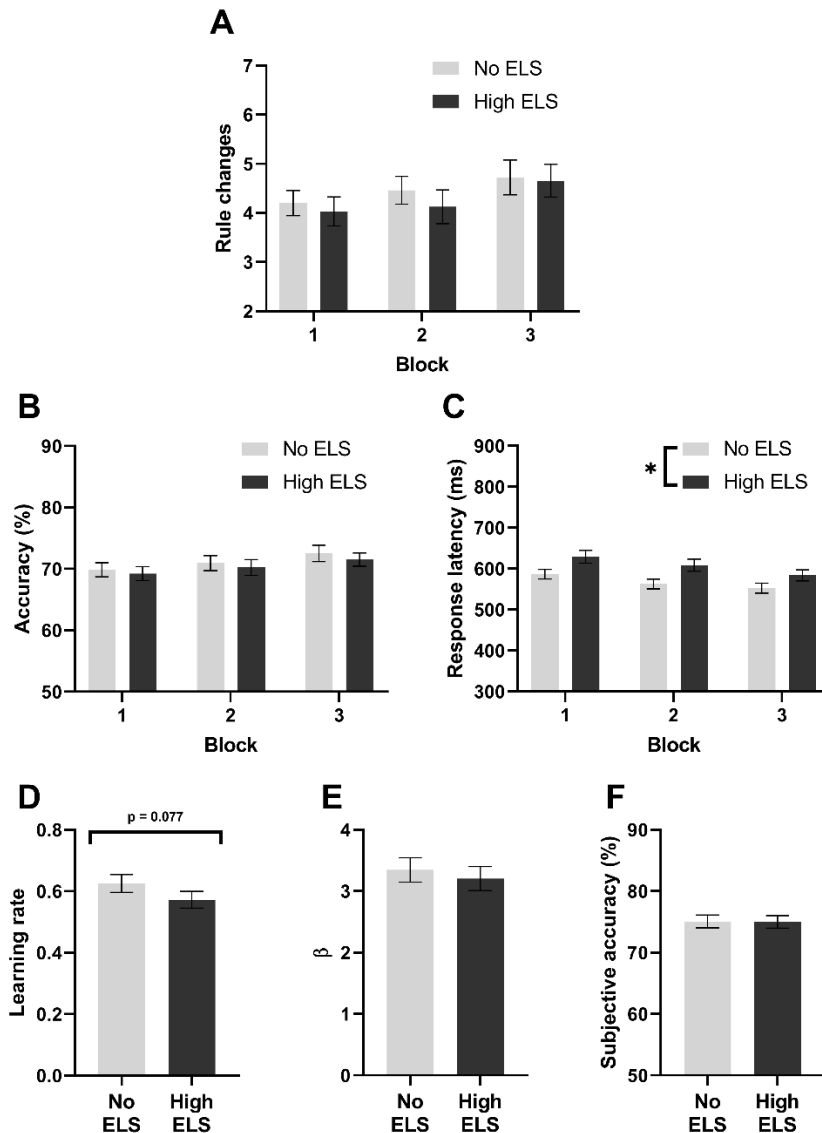
### 265 **3. Results**

#### 266 **3.1 Probabilistic reversal learning task**

267

268 There was no evidence of a difference between groups in either the number of rule changes  
269 participants were able to complete (Fig 1A) nor accuracy (Fig 1B). However, participants with  
270 a history of high ELS did have a slower average response latency (Fig 1C, RM-ANOVA,  $F_{1,126} =$   
271 5.03,  $p = 0.027$ ) with both groups getting equally faster over the course of the three blocks  
272 (RM-ANOVA,  $F_{1,88,236.7} = 16.1$ ,  $p < 0.0001$ ). Secondary analysis revealed no evidence of an  
273 effect of depression symptomology (RM-ANCOVA, PCA1:  $p > 0.05$ ) with the main effect of ELS  
274 persisting (RM-ANCOVA, ELS:  $F_{1,125} = 4.9$ ,  $p = 0.028$ ). Exploratory analysis on overall reaction  
275 times did not replicate a main effect of group but did observe older participants having slower

276 reaction times (GLMM,  $Z = 2.8$ ,  $p = 0.005$ ). This analysis also indicated weak evidence of an  
277 interaction between group and lifetime stress (GLMM,  $Z = 1.55$ ,  $p = 0.065$ ) but further  
278 investigation did not reveal an effect of lifetime stress in either group.



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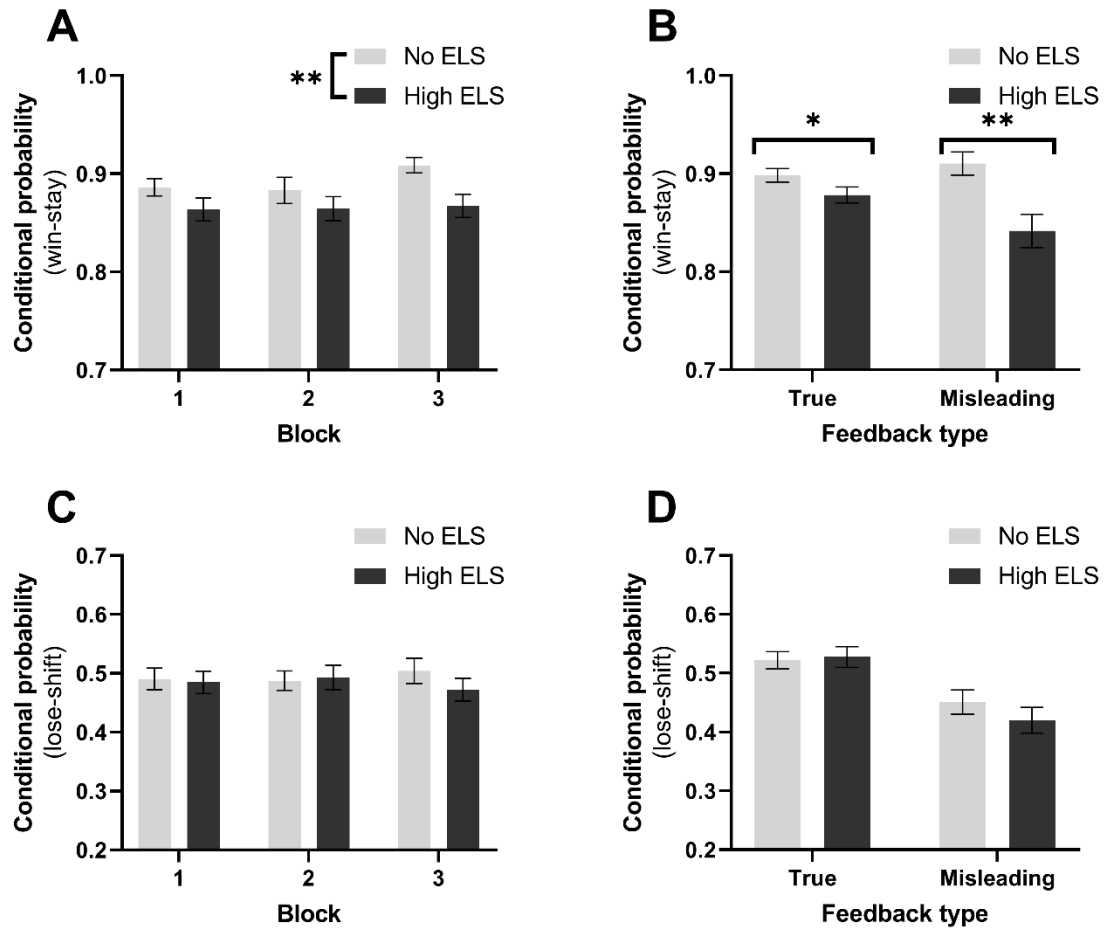
280 **Fig 1. Overall reward learning and reinforcement learning in the PRLT. (A)** Rule changes  
281 within each block, **(B)** accuracy by block and **(C)** average response latency per block. From the  
282 Q-learning reinforcement learning model: **(D)** learning rate, **(E)**  $\beta$ , the inverse of the softmax  
283 temperature and a measure of choice variability and **(F)** subjective accuracy, participant  
284 accuracy compared to a model predicted perfect strategy.

285 When data were analysed using the Q-learning reinforcement learning model a trend  
286 emerged towards high ELS participants having a lower learning rate compared to the no ELS  
287 study population (Fig 1D, t-test,  $t_{127} = 1.78$ ,  $p = 0.077$ ). Secondary analysis revealed no effect  
288 of PCA component 1 upon learning rate but removed any evidence for an effect of ELS. In  
289 exploratory analysis a main effect of ELS was observed (GLMM,  $Z = 2.1$ ,  $p = 0.037$ ) with the  
290 addition of PC1 impairing model fit ( $\Delta AIC = 1.69$ ,  $\chi^2(1) = 0.31$ ,  $p = 0.57$ ). Additionally, a  
291 relationship between stress in the last year and learning rate was observed whereby  
292 increased stress in the last year decreased learning rate (GLMM,  $Z = -2.3$ ,  $p = 0.024$ ). There  
293 was no difference in choice variability (Fig 1E) or accuracy compared to a model predicted  
294 perfect strategy (Fig 1F) between groups.

295

296 Participants with a history of high ELS exhibited reduced positive feedback sensitivity (PFS, Fig  
297 2A, RM-ANOVA,  $F_{1,122} = 10.4$ ,  $p = 0.002$ ) which persisted once depression symptomology was  
298 accounted for using PCA component 1 (RM-ANOVA,  $F_{1,121} = 6.6$ ,  $p = 0.01$ ). Exploratory analysis  
299 revealed an interaction between ELS and both lifetime stress (GLMM,  $Z = -2.15$ ,  $p = 0.031$ )  
300 and last year stress (GLMM,  $Z = -1.99$ ,  $p = 0.047$ ). Further investigation revealed effects of  
301 both stress types upon PFS in the low ELS group only (GLMM, lifetime stress:  $Z = -2.35$ ,  $p =$   
302  $0.019$ , last year stress:  $Z = -2.2$ ,  $p = 0.026$ ) whereby higher lifetime stress led to greater PFS  
303 but higher stress in the last year was associated with decreased PFS. However it should be  
304 noted that although all suggested terms were removed from the model the overall model was  
305 a poorer fit than the null when measured by AIC ( $\Delta AIC = 7.3$ ,  $\chi^2(13) = 18.7$ ,  $p = 0.13$ ).

306



307

308 **Fig 2. High ELS participants exhibited lower positive feedback sensitivity than those without**

309 **a history of ELS. Win-stay probability overall (A) and subdivided into true and misleading**

310 **feedback (B). Overall Lose-shift probability (C) and additionally subdivided into true and**

311 **misleading feedback (D).**

312

313

314 The effect of ELS upon PFS was consistent across feedback that matched (true feedback) or

315 clashed (misleading feedback) with the underlying task rules (Fig 2B, Mann-Whitney U, true:

316 U = 1443, p = 0.03; misleading: U = 1337, p = 0.005). This effect appeared to be constrained

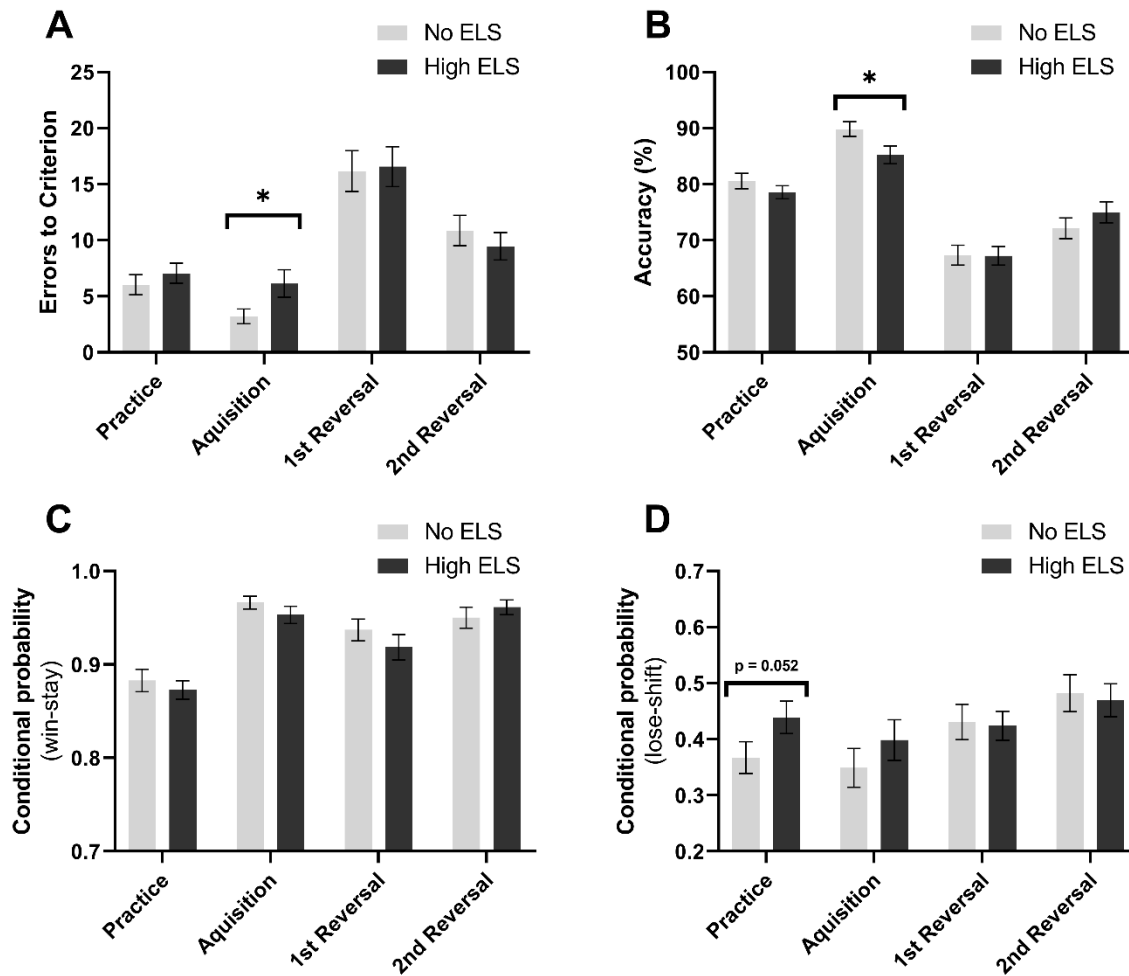


317 to PFS with no corresponding changes in lose-shift probability between no ELS and high ELS  
318 groups (Figs 2C and D).

319

320 When initial learning in the PRLT task was assessed, it was apparent that although ELS and  
321 control participants performed similarly during the practice phase there was a learning deficit  
322 during acquisition of the first reversal criterion in block 1 as evidenced by increased errors to  
323 criterion (Fig 3A, Mann-Whitney U,  $U = 1580$ ,  $p = 0.045$ ) and decreased accuracy (Fig 3B,  
324 Mann-Whitney U,  $U = 1584$ ,  $p = 0.036$ ). Both groups of participants however performed  
325 equally well at achieving criterion for a second and third reversal. Unlike the overall measures  
326 there was no difference in win-stay probability between groups (Fig 3C), however there was  
327 a trend for high ELS participants to show increased negative feedback sensitivity (NFS) in the  
328 practice phase (Fig 3D, Mann-Whitney U,  $U = 1532$ ,  $p = 0.052$ ).

329



330

331 **Fig 3. High ELS participants show impaired learning in the acquisition phase of block 1. (A)**

332 Errors made while reaching criterion for each phase, **(B)** accuracy within each phase, **(C** and

333 **D)** win-stay and lose-shift probabilities for each phase of block 1 and practice respectively.

334

### 335 **3.2 Probabilistic reward task**

336

337 There was no evidence that participants developed a response bias towards the more highly

338 rewarded stimulus in any block (Fig 4A) nor was there evidence for a response bias developing

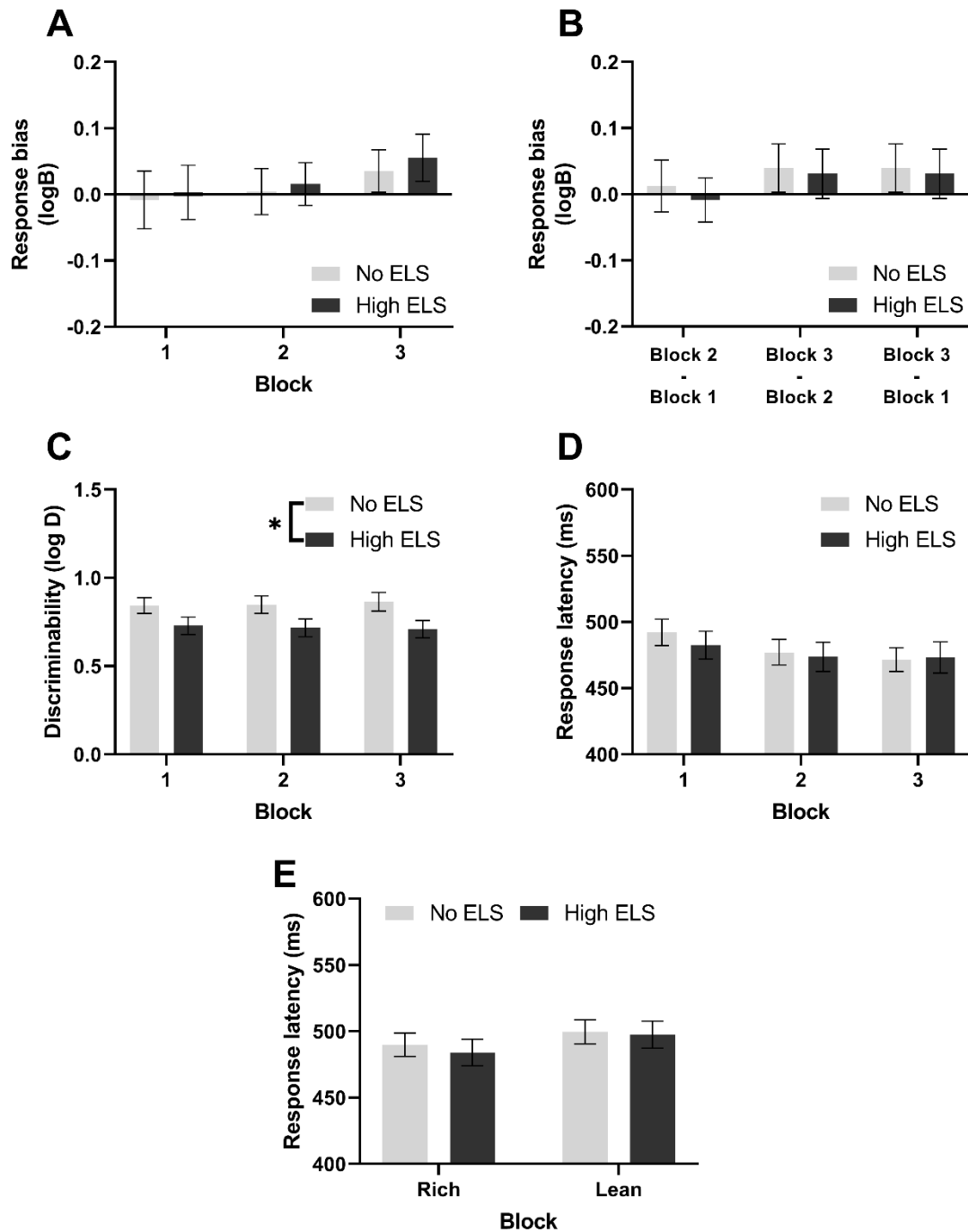
339 between blocks (Fig 4B). However, participants with a history of high ELS did show an

340 impaired ability to discriminate between stimuli (Fig 4C, ANOVA,  $F_{1,127} = 4.8$ ,  $p = 0.030$ ).  
341 Secondary analysis revealed that this difference between groups appeared to be driven by  
342 differences in depression symptomology with the effect of ELS disappearing when PCA  
343 component 1 was included in the analysis (ANCOVA, PCA1:  $F_{1,126} = 6.08$ ,  $p = 0.015$ ; ELS:  $F_{1,126}$   
344  $= 1.7$ ,  $p = 0.19$ ). Exploratory analysis further revealed a main effect of lifetime stress with  
345 higher lifetime stress corresponding to increased discrimination ability (GLMM,  $Z = 2.6$ ,  $p =$   
346  $0.007$ ). An effect of gender was also revealed (GLMM,  $Z = 2.04$ ,  $p = 0.04$ ) with males showing  
347 increased discrimination ability. Finally, there was no difference between groups in response  
348 latencies (Fig 4D) nor was there an effect of stimulus upon response latency (Fig 4E).

349

350 Consistent with Pizzagalli and colleagues [19] the probability of misclassifying a stimulus  
351 based upon the preceding trial outcome was also analysed (supplementary table 3).  
352 Participants with a history of high levels of ELS were more likely to misclassify rich stimuli if  
353 either the previous trial was a not rewarded rich trial or a lean not rewarded trial with these  
354 measures roughly corresponding with rich lose-shift and lean lose-stay probability in the PRLT  
355 respectively.

356



357

358 **Fig 4 Participants with a history of ELS show decreased discriminability in the PRT. (A)**

359 Response bias to the more highly rewarded stimulus, **(B)** response bias development between

360 blocks, **(C)** discriminability between long and short face lengths, **(D)** average response latency

361 split by block and **(E)** response latency split by stimulus type.

### 362 **3.3 Directly rewarded probabilistic reward task**

363

364 To further investigate the lack of overall response bias in the online version of this task, a  
365 second cohort of control participants completed the PRT using direct monetary compensation  
366 (£0.04 reward per correct trial) instead of points reward (see supplementary materials).  
367 Participants showed a response bias in blocks 1 and 3 (Fig S4A, Wilcoxon signed ranks test,  
368 block 1:  $W = 1087.5$ ,  $p = 0.001$ , block 3:  $W = 916.5$ ,  $p = 0.038$ ) but there was no overall effect  
369 of block. There was no evidence for response bias increasing over time (Fig S4B) nor was there  
370 evidence for any effect of block upon discriminability (S4C) and response latency (S4D).  
371 Participants did however respond more quickly to rich stimuli than lean (Fig S4E, Wilcoxon  
372 matched pairs signed ranks test,  $W = 814.0$ ,  $p = 0.0007$ ).

373

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375

376

## 377 **4. Discussion**

378

379 This study was designed to investigate whether healthy adults with a history of ELS show  
380 alterations in reward processing and feedback sensitivity. Nearly 600 participants were  
381 screened; ELS was highly prevalent in the population with 79.0% of participants experiencing  
382 one or more ACE and 44.4% experiencing three or more.

383

384 Participants with a history of high ELS had higher self-report depression and anhedonia  
385 symptoms. Although participants stated they did not have a diagnosis of depression, 54.7%  
386 of high ELS and 26.2% of no ELS participants showed at least mild symptoms based upon the  
387 BDI-II questionnaire. BDI-II scores in no ELS (mean:  $9.4 \pm 1.0$ ) and high ELS (mean:  $15.2 \pm 1.2$ )  
388 participants were higher than controls for similar studies [19,28,45] (range 1.3-3.62) but lower  
389 than depressed patients [19] (mean:  $32.1 \pm 8.6$ ) or participants described as exhibiting a high  
390 BDI [45] ( $>16$ ). These data are consistent with a large societal burden of un-diagnosed  
391 depression [46–48]. It should be noted that the present study was undertaken during the  
392 Covid-19 global pandemic with it being estimated that levels of depression had doubled  
393 during this period [49]. The high number of participants reporting mild to severe symptoms  
394 of depression is a major limitation of this study as depression and anhedonia are well known  
395 to reduce reward learning in both the PRLT [24] and PRT [18,19,37]. It is also worth  
396 considering that 75% of adults with mental health conditions experience the onset of  
397 symptoms before aged 24 [50]. This means that the study population, all 25 years of age or  
398 greater, is potentially biased towards those more protected from mental health disorders. In  
399 keeping with large bodies of previous literature this study used retrospective reporting  
400 however it is worth noting the difficulties in correlating retrospective and prospective  
401 measures of ELS [51] suggesting that these might encompass different populations with  
402 different mechanistic links between ELS and depression vulnerability. Studies have also  
403 interesting insights when ELS is split into different modalities [52,53], however the present  
404 study was not powered enough to merit investigating this.

405

#### 406 **4.1 Probabilistic reversal learning task**

407

408 In the PRLT participants with high ELS displayed decreased positive feedback sensitivity  
409 compared to controls as measured by win-stay probability. This finding was independent of  
410 depression symptomology and specific to PFS with no changes observed in lose-shift  
411 probability. Blunted striatal responses to reward in participants with a history of ELS have  
412 been previously reported [54,55] which speculatively may underlie the decreased PFS  
413 observed in the present study. Consistent with the present study, women with MDD and a  
414 history of childhood sexual abuse have also been found to have impaired performance in the  
415 PSST but only for trials requiring use of previously rewarded information and not those  
416 requiring use of previously punished information [28]. Within the PRLT depressed patients  
417 have been observed to show increased sensitivity to misleading negative feedback [23,24].  
418 This was not observed in the high ELS cohort in the present study. In other tasks depressed  
419 patients have also been reported to show increased NFS alongside attenuated PFS [56–60].  
420 These findings suggest that ELS is associated with changes in feedback sensitivity in the PRLT  
421 differently to depression with ELS decreasing PFS but not effecting NFS while depression has  
422 an opposite effect.

423 The PRLT also allows for assessment of reinforcement learning through the analysis of rule  
424 changes and accuracy in addition to parameters calculated through use of the reinforcement  
425 learning model. In contrast with our hypothesis, there was no evidence that ELS affected rule  
426 changes which is surprising considering evidence that both depression and ELS can impair  
427 cognitive flexibility [61,62]. Although rule changes were used as the main behavioural reward  
428 learning output, when data were analysed with the Q-learning model a trend towards

429 decreased learning rate was observed in high ELS participants. This became significant in  
430 exploratory analysis and decreased associative learning has been previously observed in  
431 juveniles previously exposed to physical abuse [27]. There is a lack of consistent evidence in  
432 depression studies as to whether model free learning rate differs between patients and  
433 controls [63,64]. These findings warrant future investigation due to this study being only  
434 powered to detect group differences between two groups meaning that ANCOVA and  
435 exploratory analysis is likely to be underpowered.

436

437 A slower response latency was also observed in high ELS participants which was specific to  
438 the PRLT with no congruent changes seen in the PRT. This discrepancy may be related to  
439 differing cognitive demands with the PRLT potentially requiring greater working memory.

440 No directly comparable studies have been carried out in humans. However, maternally  
441 separated marmosets, an animal model of ELS, showed no change in simple visual  
442 discrimination compared to controls but showed impairments when the contingencies  
443 reversed [65]. This is similar to that seen in both depressed and bipolar patients in the human  
444 PRLT [24,66] who acquire the initial rule successfully but then are impaired following reversal.  
445 This compares to ELS participants in the present study who performed equally well in the  
446 practice phase and reversal phases but showed a deficit in acquisition of the first rule in block  
447 1. This suggests a potential impairment in the ability to generalise the task rules between the  
448 practice and acquisition phase. However previous probabilistic learning studies did not  
449 include a practice phase meaning that this likely changed the way participants processed the  
450 start of block 1. This might explain the contrast with Pechtel and Pizzagalli, 2013 who reported



451 that women with remitted MDD and ELS learnt acquisition in the PSST at the same rate as  
452 controls [28].

453

454 One of the hypotheses of this study was that stress in adult life would modulate the  
455 relationship between reward processing deficits and ELS. There was little evidence that this  
456 was the case except for an observed interaction between PFS and ELS whereby stress only  
457 influenced PFS in participants without a history of ELS. Higher lifetime stress led to greater  
458 PFS but higher stress in the last year was associated with decreased win-stay probability.  
459 There are few previous studies investigating similar constructs but Berghorst and colleagues  
460 reported that after stress induction those who had higher cortisol reactivity and self-reported  
461 negative affect had lower reward but not punishment sensitivity [26]. Additionally, it is worth  
462 noting that due to the relatively poor model fit for this exploratory analysis that these findings  
463 should be taken as preliminary due to the risk of data overfitting.

464

465

466

467

#### 468 **4.2 Probabilistic reward task**

469

470 In contrast to previous studies employing the PRT neither ELS nor control groups showed a  
471 response bias toward the more highly rewarded stimulus [19,37] suggesting a general failure

472 of all participants to modulate their responses as a function of reward. This lack of response  
473 bias in the main study potentially indicates that the reward information was not salient  
474 enough therefore participants focussed upon correctly discriminating between mouth  
475 lengths. This makes comparison to previous literature challenging. There are no previously  
476 published studies carrying out the PRT online but in this study we failed to replicate the main  
477 outcome measure. The online testing could have been one reason for the lack of response  
478 bias likely leads to the high variability seen in the data as it is not possible to ensure that  
479 participants are completing the tasks in as controlled an environment as would be possible  
480 by laboratory testing.

481

482 However, another possibility for the lack of response bias seen was a key difference between  
483 laboratory and online versions of the task. While all other aspects of the task were similar,  
484 participants in the online task were informed that high performance would lead to a bonus  
485 payment with the actual reward in the task being points. Previous studies instead used direct  
486 monetary compensation in the task [37]. When the second population of control participants  
487 was tested in the PRT using direct monetary compensation a response bias was seen in blocks  
488 1 and 3, however there did not appear to be evidence for this bias strengthening over time  
489 like previously observed [37]. There was also robust evidence for participants responding  
490 more quickly to the rich than lean stimulus as also has been reported [22,37]. While this  
491 difference in compensatory mechanism may underly the difference in control population  
492 performance in the two implementations of the task it could also be because the direct  
493 reward population had lower BDI and SHAPS scores. However, when the direct reward  
494 experiment was re-analysed with no BDI and SHAPS cut-offs such that it more closely

495 approximated the control population in the main study the results were much the same as  
496 with the cut-offs (data not shown). These data therefore suggest that it is possible to  
497 successfully implement the PRT in an online setting using the directly rewarded task with the  
498 availability of reliable online psychological tasks being key under current circumstances.

499

500 While difficult to interpret for previously discussed reasons, participants with high levels of  
501 ELS did show impairments in discrimination, a measure of task difficulty. This however  
502 appeared to be driven by changes in depression symptomology as opposed to ELS specifically.

503

#### 504 **4.3 Conclusions**

505

506 These data suggest that participants who do not self-report a diagnosis of a mental health  
507 condition but do have a history of ELS show impairments in positive feedback sensitivity and  
508 reward learning in the PRLT compared to controls. These impairments may be important in  
509 understanding how ELS predisposes to depression with reduced reward learning being a key  
510 feature in MDD patients [20]. However, high levels of potentially undiagnosed depression are  
511 a potential confound and highlight a potential wider issue in terms of the number of people  
512 who meet criteria for MDD but are not formally diagnosed or receiving care. Future studies  
513 are needed to replicate these findings, investigate the neural circuit changes underlying these  
514 reward learning impairments and investigate whether these findings are directly related to  
515 psychiatric risk.

516

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518

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524 copyright licence to any Author Accepted Manuscript version arising from this submission.

525

## 526 **6. Data Availability Statement**

### 527 **7.**

528 This study was pre-registered and available at [www.osf.io/538yk](http://www.osf.io/538yk). Data and code will also be  
529 made available open access at [www.osf.io/63e8j](http://www.osf.io/63e8j).

530

531

532

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