

# 1 **Psilocybin rescues sociability deficits in an animal model of autism**

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## 18 **Abstract**

19 Autism spectrum disorder (ASD) is characterized by core deficits in social interaction.  
20 The classic serotonergic psychedelic psilocybin has been suggested as a therapeutic  
21 agent that may ameliorate in the core symptomology of ASD. We found that the acute  
22 response to psilocybin was attenuated in the prenatal valproic acid exposure mouse  
23 model of ASD, and importantly, psilocybin rescued the social behavioural  
24 abnormalities present in these ASD model mice.

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## 28 **Main**

29 Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental disorder  
30 characterized by core deficits in social interaction and communication, repetitive or  
31 restricted behaviour and interests, and altered sensory sensitivity<sup>1</sup>. The aetiology and  
32 pathophysiology of ASD remains largely unknown, and is considered to be multi-  
33 factorial, encompassing both genetic and environmental factors<sup>2-4</sup>. The lack of a single  
34 molecular mechanism underlying the aetiology of ASD has contributed to the  
35 challenge of finding efficacious therapeutic interventions.

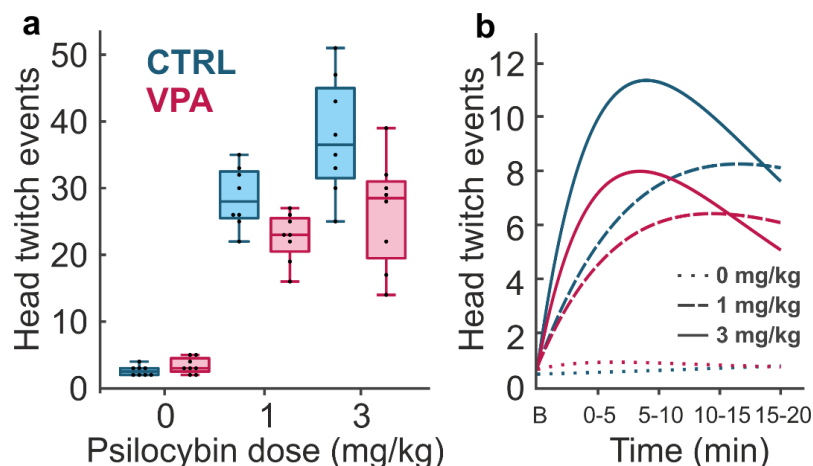
36 The regulation and functionality of the serotonergic (5-HT) system has been implicated  
37 to play an important role in the core pathophysiology of ASD<sup>5-9</sup>, hence its modulation  
38 is an evidence-based therapeutic target<sup>10-12</sup>. Psilocybin is produced by several species  
39 of mushrooms, and is one of the compounds responsible for the psychedelic effects  
40 that these mushrooms induce, likely via altering 5-HT signalling through 5-HT<sub>2A</sub>  
41 receptors<sup>13,14</sup>. Reduced cortical 5-HT<sub>2A</sub> receptor expression has been reported in ASD  
42 suggesting that this population may be less sensitive to the subjective effects of  
43 psilocybin<sup>8,9</sup>. Psychedelics have recently shown potential safety and efficacy for  
44 alleviating various neuropsychiatric disorders<sup>15</sup>. Recent human studies also showed  
45 that psilocybin can produce sustained prosocial behaviour<sup>16,17</sup>, and affects several  
46 facets of social cognition relevant to deficits in ASD<sup>18,19</sup>.

47 Preclinical evaluation of psilocybin's potential to ameliorate altered sociability requires  
48 a suitable animal model that recapitulates aspects of the social deficits observed in  
49 ASD. One such model, based on prenatal exposure to valproic acid (VPA), is  
50 particularly attractive as it does not bias towards a single genetic alteration as in  
51 genetic models of ASD and thus may better represent idiopathic ASD. VPA is clinically  
52 used for the treatment of epileptic seizures, bipolar mania, and as a migraine  
53 prophylactic. Through this long-standing clinical use, it has been observed that  
54 pregnant mothers treated with VPA are at an increased risk of giving birth to children  
55 that are diagnosed with ASD<sup>20</sup>. In mice, prenatal VPA exposure also results in  
56 offspring exhibiting many ASD-like behavioural phenotypes<sup>21-24</sup>, including altered  
57 social behaviour<sup>25-27</sup>. Here we explored the potential of psilocybin to ameliorate altered  
58 sociability in the prenatal VPA mouse model of autism. Offspring that have been  
59 exposed to VPA *in utero* are hereon referred to as VPA group, and those exposed to

60 saline *in utero* as Control group. VPA group displayed a modestly reduced body weight  
61 (**Extended Data Fig. 1**).

62 We first examined the acute effect of psilocybin on both VPA and Control groups by  
63 measuring the head twitch response (HTR), a 5-HT<sub>2A</sub> receptor-mediated measure that  
64 predicts hallucinogenic potency in humans<sup>28</sup>. All test mice (n = 8 / group) received a  
65 single intraperitoneal injection of psilocybin (low dose at 1 mg/kg or high dose at 3  
66 mg/kg) or saline, and we counted head twitch events immediately after injections.  
67 Psilocybin evoked HTRs both in VPA and Control groups with dose dependency (**Fig.**  
68 **1**). The efficacy of psilocybin to trigger HTR was significantly lower in VPA group than  
69 Control group ( $F_{\text{pre-treatment} \times \text{treatment}(2,42)} = 4.895$ ,  $P = 0.012$ , two-way ANOVA; **Fig. 1a**).  
70 The time course of the effects induced by psilocybin on both VPA and Control groups  
71 showed similar rise and decay times (**Fig. 1b**, **Extended Data Fig. 2**). There were no  
72 gender differences in VPA and Control groups treated with psilocybin or saline ( $F_{\text{pre-}}$   
73  $\text{treatment} \times \text{treatment} \times \text{gender}(2,36) = 0.03$ ,  $P = 0.969$ , three-way ANOVA).

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76 **Fig. 1: VPA group shows reduced head twitch response induced by psilocybin.**

77 **a**, Total count of head twitch events over 20 min, induced by an intraperitoneal injection  
78 of saline or psilocybin in Control and VPA groups. Psilocybin evoked dose-dependent  
79 HTR in both groups. HTR count was significantly lower with no significant dose-  
80 dependency in VPA mice ( $F_{\text{pre-treatment} \times \text{treatment}(2,42)} = 4.895$ ,  $P = 0.012$ ). *Boxplot: center*  
81 *line, median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range.*

82 **b**, Fitted time course of head twitch events above baseline (B) in 5-min time bins. VPA  
83 and Control groups showed similar HTR time course shapes. n = 8/group. For detail  
84 see **Extended Data Fig. 2, Supplementary Table. 1**.

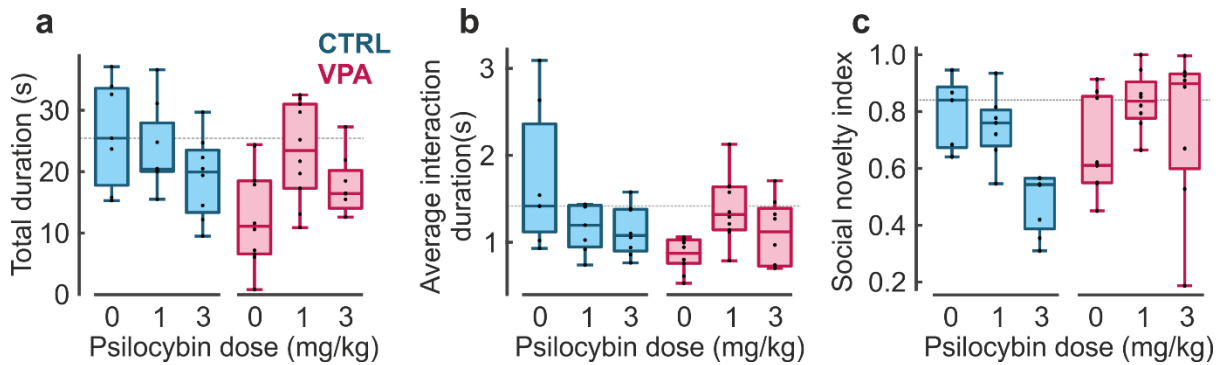
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86 24-hour after psilocybin/saline treatments, animals were tested for their social  
87 behaviour (sociability and social memory), to capture effects beyond the acute action  
88 of psilocybin as well as to avoid acute psychedelic-like effects confounding social  
89 behaviour. VPA group spent significantly less time engaging in social interaction  
90 compared to Control group, as quantified by the total duration of nose-to-nose  
91 interactions with the stranger mouse (VPA<sub>SAL</sub> vs CTRL<sub>SAL</sub>:  $t = 3.282$ ,  $P = 0.005$ ; **Fig.**  
92 **2a**). A low dose of psilocybin (1 mg/kg i.p.) restored the sociability behaviour of VPA  
93 group to a level similar to that of Control group (VPA<sub>SAL</sub> vs VPA<sub>PSI1</sub>:  $t = 2.928$ ,  $P =$   
94  $0.009$ ; **Fig. 2a**), but the rescue effect of psilocybin was not evident following the higher  
95 dose (3 mg/kg; VPA<sub>SAL</sub> vs VPA<sub>PSI3</sub>:  $t = 1.071$ ,  $P = 0.300$ ; **Fig. 2a**). Surprisingly,  
96 psilocybin treatment in the Control group showed a dose-dependent trend in reducing  
97 the total nose-to-nose interaction duration, although this effect was not statistically  
98 significant (CTRL<sub>SAL</sub> vs CTRL<sub>PSI1</sub>:  $t = 0.657$ ,  $P = 0.523$ ; CTRL<sub>SAL</sub> vs CTRL<sub>PSI3</sub>:  $t =$   
99  $1.799$ ,  $P = 0.953$ ; **Fig. 2a**). The reduced total nose-to-nose interaction duration in VPA  
100 group was due to reduced average duration of individual interactions (VPA<sub>SAL</sub> vs  
101 CTRL<sub>SAL</sub>:  $t = 2.952$ ,  $P = 0.010$ ). 1 mg/kg psilocybin substantially restored this  
102 component of social interaction behaviour and increased the duration of individual  
103 interactions when compared with the VPA saline group (VPA<sub>SAL</sub> vs VPA<sub>PSI1</sub>:  $t = 3.307$ ,  
104  $P = 0.004$ ; **Fig. 2b**). However, we did not observe any difference in the average time  
105 per interaction between VPA mice treated with 3 mg/kg psilocybin versus saline  
106 controls (VPA<sub>SAL</sub> vs VPA<sub>PSI3</sub>:  $t = 1.326$ ,  $P = 0.203$ ). The surprising trend (though  
107 statistically non-significant) of psilocybin-induced reduction in social interaction in  
108 Control group was also observed in a dose-dependent trend in the average duration  
109 of individual interactions in both high and low dose psilocybin treated control mice  
110 when compared to the control saline group (CTRL<sub>SAL</sub> vs CTRL<sub>PSI1</sub>:  $t = 1.698$ ,  $P = 0.115$ ;  
111 CTRL<sub>SAL</sub> vs CTRL<sub>PSI3</sub>:  $t = 1.911$ ,  $P = 0.078$ ).

112 Next, we assessed the effect of psilocybin on social novelty preference by introducing  
113 a new stranger mouse (S2) in addition to the presence of the existing stranger mouse  
114 (S1). The social novelty index derived from this measure quantifies the extent to which  
115 S2 is recognized as new. As this recognition required remembering S1, this index is  
116 also a measure of short-term social memory. The social novelty index was reduced  
117 for the VPA group, and a single treatment of psilocybin (at either low or high doses) in  
118 VPA group increased their social novelty preference to a level similar (higher) than

119 that of the Control group (**Fig. 2c, Supplementary Table. 1**). The opposite effect was  
120 observed in the Control group treated with either 1 mg/kg or 3 mg/kg psilocybin, where  
121 psilocybin tended to decrease the social novelty index (**Fig. 2c, Supplementary**  
122 **Table. 1**).

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124

125 **Fig. 2: Single administration of psilocybin improves sociability and social**

126 **memory in ASD model mice. a**, Total duration time of direct nose to nose interactions

127 during 10-min observation period ( $F_{\text{pre-treatment} \times \text{treatment}(2,45)} = 3.633, P = 0.034$ ), 24 hours

128 following a single administration of saline or psilocybin in Control and VPA groups. **b**,

129 Average time of direct nose to nose interactions ( $F_{\text{pre-treatment} \times \text{treatment}(2,44)} = 6.657, P =$

130  $0.003$ ), related to observations in **a**. **c**, Social novelty index is dose-dependently

131 reduced in the Control group 24 hours following a single administration of saline or

132 psilocybin ( $F_{\text{pre-treatment} \times \text{treatment}(2,37)} = 6.077, P = 0.0052$ ), but is increased in the VPA

133 group. Two-way ANOVA:  $n = 7$  control saline,  $n = 7$  control PSI 1,  $n = 8$  control PSI 3,

134  $n = 10$  VPA saline,  $n = 10$  VPA PSI 1,  $n = 8$  VPA PSI 3. Dotted line represents median

135 value from the Control group administered with saline. *Boxplot: center line, median;*

136 *box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; outliers not*

137 *shown*. For statistics see **Supplementary Table. 1**

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139 Psychedelic research is currently undergoing a renaissance, with the therapeutic

140 potential of these compounds being increasingly recognised. Psilocybin, for example,

141 has recently received “breakthrough designation” by the FDA in treatment-resistant

142 depression<sup>29</sup> and major depressive disorder<sup>30</sup>. Towards a reverse translational

143 approach, here we report the efficacy of psilocybin in an animal model of ASD as

144 evidence that psilocybin may be a promising pharmacotherapy for altered sociability

145 in ASD. More detailed mechanistic studies will be needed in future to understand the

146 molecular and circuit underpinnings of this therapeutic potential.

## 147 **Methods**

### 148 *Animals*

149 All experimental procedures were performed at Imperial College London UK in  
150 accordance with the United Kingdom Animal Scientific Procedures Act (1986), under  
151 Home Office Personal and Project Licences following appropriate ethical review. Time-  
152 mated C57BL/6J mice (Charles River, UK) were housed in groups, and separated two  
153 days prior to the expected littering date. Offspring were weaned at P28 and housed in  
154 groups of up to five animals per cage after weaning. All animals were maintained in  
155 ventilated cages, on a 12/12 h light/dark cycle at  $21 \pm 2^\circ\text{C}$  and  $55 \pm 10\%$  humidity.  
156 Water and food were provided *ad libitum*. Eight weeks old mice of both genders were  
157 used for behavioural experiments. All experiments were conducted during the daytime.

158

### 159 *Prenatal VPA treatment*

160 Valproic acid (2-propylpentanoic acid) sodium salt was obtained from Sigma Aldrich  
161 (P4543; Germany), and freshly dissolved in sterile saline (0.9% NaCl) to 50 mg/ml, pH  
162 7.4. On embryonic day 10.5 (E10.5), pregnant females were intraperitoneally  
163 administered with either a single dose of 500 mg/kg VPA or equal volume of saline.  
164 The dose and the embryonic day of VPA administration were based on previously  
165 published reports<sup>21-23</sup>. Prenatally exposed VPA animals showed significantly lower  
166 body weight than the prenatal saline control at weaning age (controls = 15.01 g, VPA  
167 = 12.09 g;  $P = 0.0002$ ;  $n = 24/\text{group}$ ; **Extended Data Fig. 1, Supplementary Table.**  
168 **1)** and remained lower at week 8 (controls = 20.95 g, VPA = 18.40 g;  $P = 0.009$ ;  $n =$   
169  $24/\text{group}$ ; **Extended Data Fig. 1, Supplementary Table. 1)**. Additionally, physical  
170 abnormalities were observed in the prenatal VPA animals: 60% showed kinked tail,  
171 10% had moderate facial abnormalities, 6% displayed fur problems, 3% had  
172 misaligned teeth. These abnormalities were not observed in the control group.

173

### 174 *Drug administration*

175 Psilocybin ([3-(2-dimethylaminoethyl)-1*H*-indol-4-yl] dihydrogen phosphate, Onyx  
176 Scientific Ltd, UK) was dissolved in sterile saline solution (0.9% NaCl) to appropriate  
177 concentrations.

178 For behavioural experiments, 8-week old offspring were intraperitoneally injected  
179 either with saline or psilocybin (1 mg/kg, PSI 1; or 3 mg/kg, PSI 3) 24 hours prior to

180 the sociability and social memory test. The treatments led to six different test groups:  
181 control saline, control psilocybin 1 mg/kg, control psilocybin 3 mg/kg, VPA saline, VPA  
182 psilocybin 1 mg/kg, VPA psilocybin 3 mg/kg.

183

#### 184 *Head twitch response*

185 Head twitch events were evaluated immediately after the i.p. administration of either  
186 saline or psilocybin for a period of 20 minutes. The mouse was placed into a  
187 customized behavioural box immediately after injection and was free to explore. The  
188 number of head-twitch events were counted by direct observation in 5-minute bins.  
189 The box (25.5 x 12.5 x 12.5 cm [L x W x H]) was made of red Plexiglass and the floor  
190 was covered with clean sawdust.

191

#### 192 *Sociability and social memory behavioural test*

193 Sociability and social novelty preference experiments were performed in a custom-  
194 built transparent red Plexiglass box with matt white acrylic floor. The total arena (60 x  
195 40 x 22 cm [L x W x H]) was divided in three smaller evenly sized chambers (20 x 40  
196 x 22 cm [L x W x H]) interconnected by 4 x 4 cm doors cut out of both central walls.  
197 Clear Plexiglass cylinders (10.5 cm internal diameter, 11 cm external diameter, 16 cm  
198 length) with 1-cm slits and 0.5-cm rods were used as cups. A red acrylic lid was placed  
199 on top of both cups to prevent animals from escaping or falling. The box was placed  
200 in a dark and quite room, illuminated from above with infrared LEDs located 1 meter  
201 over the arena.

202 Each behavioural testing experiment took place over 4 consecutive days (**Extended**  
203 **Data Fig. 1**). Animals were acclimatised to the testing room for at least one hour before  
204 the start of experiments on each day. Each test mouse was placed into the central  
205 chamber and allowed to freely explore the three-chamber setup for 10 minutes over 3  
206 consecutive days. During this pre-habituation time, doors to the side chambers were  
207 kept open and empty cups were placed into the two side chambers at similar positions  
208 as the final test day (day 4). Cup mice were individually pre-habituated to the cups  
209 also for 10 minutes over 3 consecutive days. On day 4, the three-chamber test was  
210 performed in three phases (Habituation, Sociability, Social Memory). Each test animal  
211 was allowed to freely explore all three chambers for 10 minutes with empty cups  
212 (Habituation Phase), then driven to the central chamber with the doors closed while

213 an age-, size-, and gender-matched unfamiliar mouse (stranger 1) was being placed  
214 into one of the cups. The test mouse was then allowed to freely explore chambers for  
215 10 minutes (Sociability Phase). The test mouse was then returned to the central  
216 chamber while a second unfamiliar mouse (stranger 2) was placed in the remaining  
217 empty cup. Finally, the test mouse was allowed to move freely across the three  
218 chambers for 10 minutes (Social Memory Phase).

219 All behavioural sessions were video-recorded using a CMOS camera (Basler  
220 acA2000-165umNIR) and Basler software (Basler AG, Germany). Video recordings  
221 were used to track the position of the body of the animal in each chamber, as well as  
222 to score the duration time of direct nose to nose interactions and interaction events by  
223 a blinded well-trained observer.

224

#### 225 *Data analysis and statistics*

226 No statistical methods were used to predetermine sample size, but our sample size  
227 was selected based on standards in the field. Experiments were blinded to VPA or  
228 control prenatal treatment, as well as treatment during automatically or manually  
229 analysis. If applicable, outliers were identified and excluded using a Grubb's test.  
230 Differences between two groups were compared using unpaired two-tailed Student's  
231 *t*-test when data were normally distributed, otherwise the Mann-Whitney U test was  
232 used. Multiple group differences were assessed using two- and three-way analysis of  
233 variance (ANOVA). Independent variables were defined as: pre-treatment (Control or  
234 VPA), treatment (PSI1: psilocybin 1 mg/kg, or PSI3: psilocybin 3 mg/kg, or SAL:  
235 saline), gender. Multiple comparisons were further assessed by Bonferroni's post hoc  
236 test. Definition of statistical significance was set at an alpha value of 0.05. Specific *P*  
237 values are reported for each analysis in the corresponding figure legend and  
238 Supplementary Table 1. All statistical analyses were performed using GraphPad Prism  
239 8 (San Diego, CA, USA) and InVivoStat (Cambridge, United Kingdom).

240

241 Social novelty index was calculated as the following:

$$242 \quad \text{Social novelty index} = \frac{\text{interaction duration with S2}}{\text{interaction duration with S1} + \text{interaction duration with S2}}$$

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244 HTR responses were fitted using MATLAB (R2019b) with a single dose  
245 pharmacokinetics curve with the following equation:

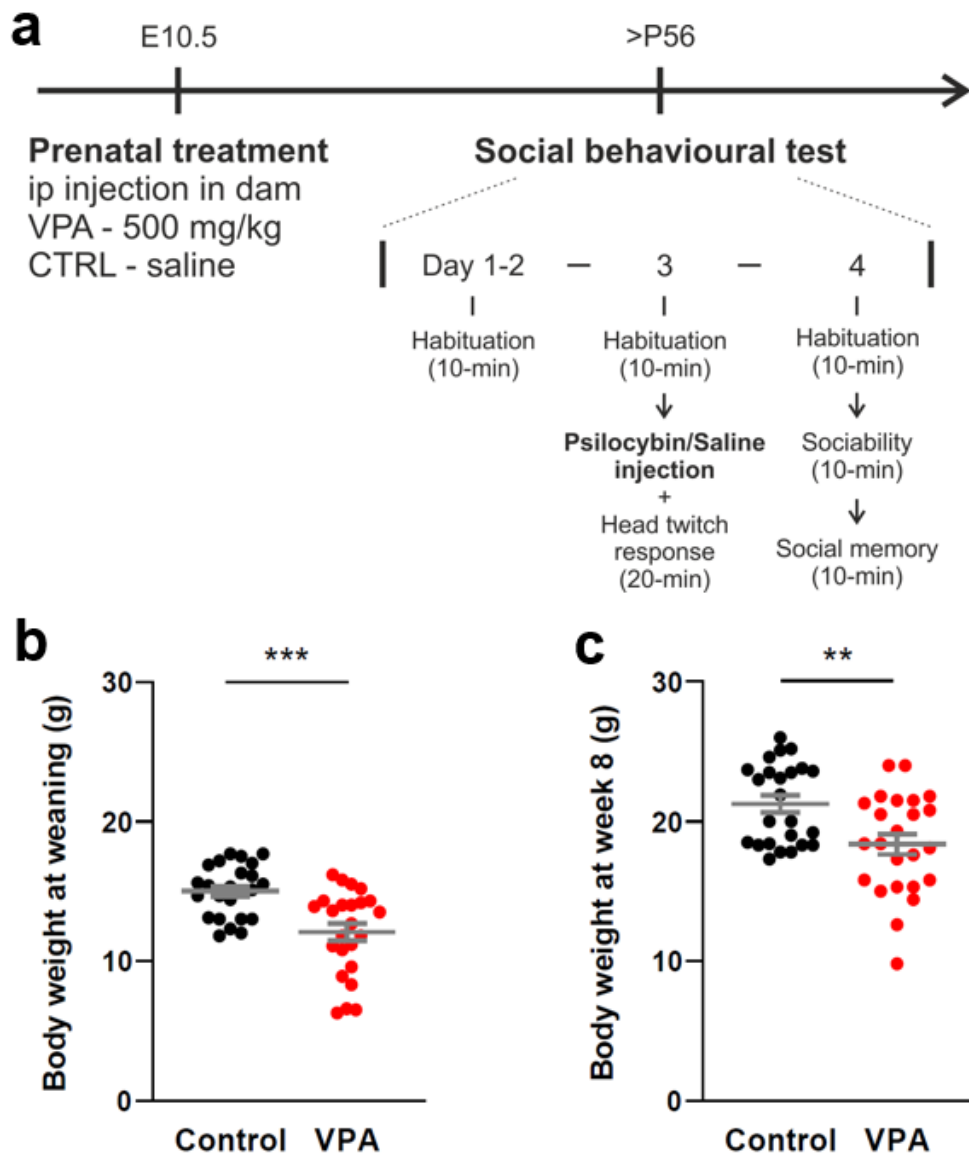


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$$\text{HTR} = \frac{F \cdot k_a}{(k_a - k_e)} \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) + B$$

247 Where: HTR = head twitch response; F = drug factor (dose and bioavailability);  $k_a$  =  
248 absorption rate constant,  $k_e$  = elimination rate constant; t = time; B = baseline count.

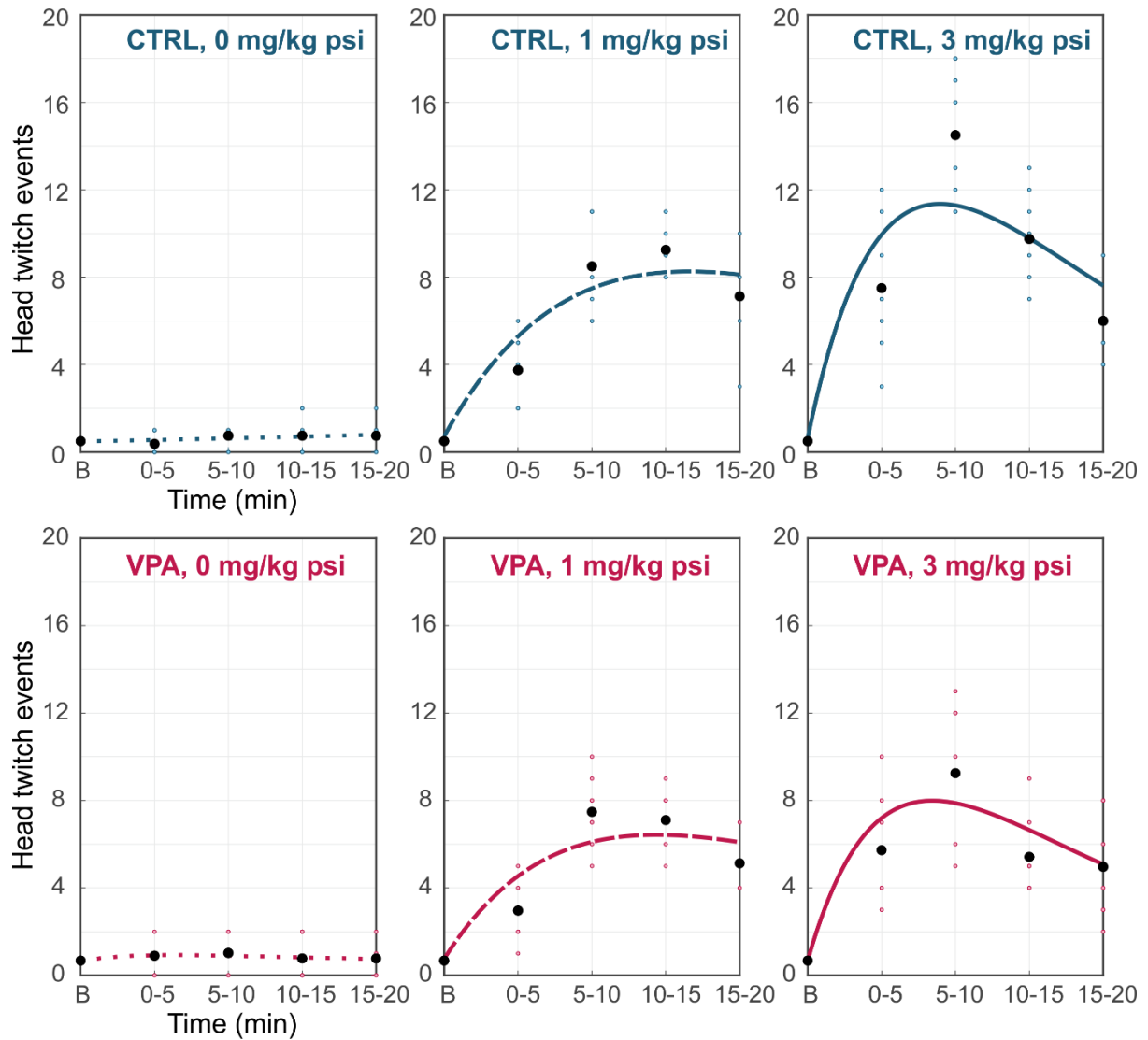
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279 **Extended data**



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281 **Extended Data Fig. 1: Experimental timeline and VPA model.** **a**, Experimental  
282 timeline. Pregnant mothers were intraperitoneally injected with saline or 500 mg/kg  
283 VPA at E10.5. 8-week old offspring were pre-habituated to the three-chamber arena  
284 for three consecutive days. After pre-habituation on day 3, saline or psilocybin was  
285 intraperitoneally injected, and the head twitch response (HTR) was counted. On day  
286 4, animals were tested for sociability and social memory using the three-chamber test.  
287 **b, c**, Mice from VPA group had lower body weight than the Control group at weaning  
288 age (**b**,  $t = 4.033$ ,  $P < 0.001$ ,  $n = 24/\text{group}$ ) and at 8-week old (**c**,  $U = 163.5$ ,  $P = 0.009$ ,  
289  $n = 24/\text{group}$ ). Mean  $\pm$  SEM. \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .



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308

309 **Author contributions**

310 I.M-G., M.S-R., and C.S. performed the experiments and analysed the data. I.M-G.,  
311 T.K., T.W., and C.S. conceived the project and wrote the paper. A.Soula, A.  
312 Selimbeyoglu and S.H. contributed to the study design.

313

314 **Competing interests**

315 T.W., A. Soula, A. Selimbeyoglu, and S.H. are employees of COMPASS Pathways  
316 Ltd. COMPASS Pathways Ltd. had no influence over the execution or publication of  
317 this study.

318

319 **Data and code availability**

320 The data and MATLAB scripts that support the findings of this study are available upon  
321 reasonable request from the corresponding author.

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