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## Subthalamic high-frequency deep brain stimulation reduces addiction-like alcohol use and the possible negative influence of a peer presence

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1 **Title: SUBTHALAMIC HIGH-FREQUENCY DEEP BRAIN STIMULATION REDUCES**  
2 **ADDICTION-LIKE ALCOHOL USE AND THE POSSIBLE NEGATIVE INFLUENCE OF A**  
3 **PEER PRESENCE**

4  
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14  
15 **Abstract:**

16 *Rationale:* The immediate social context significantly influences alcohol consumption in humans.  
17 Recent studies have revealed that peer presence could modulate drugs use in rats. The most efficient  
18 condition to reduce cocaine intake is the presence of a stranger peer, naive to drugs. Deep brain  
19 stimulation (DBS) of the Subthalamic Nucleus (STN), which was shown to have beneficial effects on  
20 addiction to cocaine or alcohol, also modulate the protective influence of peer's presence on cocaine  
21 use.

22 *Objectives:* This study aimed to: 1) explore how the presence of an alcohol-naive stranger peer affects  
23 recreational and escalated alcohol intake, and 2) assess the involvement of STN on alcohol use and in  
24 the modulation induced by the presence of an alcohol-naive stranger peer.

25 *Methods:* Rats with STN DBS and control animals self-administered 10% (v/v) ethanol in presence, or  
26 absence, of an alcohol-naive stranger peer, before and after escalation of ethanol intake (observed after  
27 intermittent alcohol (20% (v/v) ethanol) access).

28 *Results:* Neither STN DBS nor the presence of an alcohol-naive stranger peer modulated significantly  
29 recreational alcohol intake. After the escalation procedure, STN DBS reduced ethanol consumption. The  
30 presence of an alcohol-naive stranger peer increased consumption only in low drinkers, which effect  
31 was suppressed by STN DBS.

32 *Conclusions:* These results highlight the influence of a peer's presence on escalated alcohol intake, and  
33 confirm the role of STN in addiction-like alcohol intake and in the social influence on drug consumption.

34  
35 **Keyword:** alcohol, social context, subthalamic nucleus, deep brain stimulation, peer's presence

36  
37 **Main text:**

38 **Introduction**

39 Drug consumption is a complex behavior influenced by a multitude of factors, including  
40 environmental context and social interactions. Social context has been demonstrated to play a crucial  
41 role in modulating drug intake in both human and animal models. Indeed, social factors are known to  
42 affect multiples aspects of drug use such as initiation, maintenance, attempts to quit, and relapse,  
43 potentially boosting, mediating, or reducing addictive behaviors (Bardo et al. 2013; Pelloux et al. 2019;  
44 Venniro et al. 2018). Proximal social factors, such as the presence of peers during drug consumption,  
45 have a significant influence by decreasing or increasing drug intake (Pelloux et al. 2019; Strickland and  
46 Smith 2014; 2015). The identity of the peer is also a critical element that can modulate drug  
47 consumption. For cocaine, the presence of a non-familiar (stranger) peer leads to a stronger reduction in  
48 cocaine intake than the presence of a familiar one in both rats and humans (Giorla et al. 2022). The  
49 largest reduction was observed in presence of a stranger cocaine-naive peer. A similar beneficial effect

50 of presence of such a peer has been also shown on addictive-like (i.e. escalated) cocaine consumption  
51 in rats (Vielle et al. preprint).

52 However, while the presence of peers is protective against cocaine use, its effect might be opposite for  
53 alcohol. Indeed, rats chose alcohol over social interaction in a choice procedure (Augier et al. 2022;  
54 Marchant et al. 2022), and consumed more alcohol in presence of a non-naive alcohol peer, regardless  
55 of their familiarity (Sicre et al., unpublished data). These results suggest that the influence of social  
56 presence on drug intake depends on the substance used. Nevertheless, the effect of the presence of an  
57 alcohol-naive stranger has not been assessed. Furthermore, the influence of social presence has only  
58 been examined in the context of recreational alcohol use. Consequently, the modulation of recreational  
59 and escalated ethanol intake by the presence of a stranger peer, naive to alcohol remains to be explored.  
60 Over the past few years, the Subthalamic Nucleus (STN), the only glutamatergic structure of the basal  
61 ganglia, has gained increasing significance in the reward circuit, in motivational processes and in drug  
62 addiction (Baunez and Lardeux 2011). STN inactivation induced by lesions, deep brain stimulation  
63 (DBS) or optogenetic manipulations, has shown beneficial effects across various addiction criteria:  
64 motivation (Baunez et al. 2005; Lardeux and Baunez 2008; Rouaud et al. 2010; Pelloux and Baunez  
65 2017), escalation of drug intake (Pelloux and Baunez 2017; Pelloux et al. 2018), maintenance of  
66 escalated drug intake (Vielle et al. preprint) and compulsive drug-seeking behavior (Degoulet et al.  
67 2021). Additionally, it has been demonstrated that the STN is involved in mediating the influence of the  
68 social context on cocaine and alcohol use. Indeed, inactivation of the STN modulates the modifications  
69 caused by the social context (presence of a peer or playback of ultrasonic vocalizations) on cocaine and  
70 alcohol intake (Giorla et al. 2022; Montanari et al. 2018; Sicre et al., unpublished data , Vielle et al.  
71 preprint; 2021).

72 In this study, we thus examined the influence of the presence of an alcohol-naive male stranger peer on  
73 both recreational and escalated alcohol intake in male rats. Furthermore, we investigated the contribution  
74 of the STN in these processes by using high-frequency (130 Hz) DBS.

## 75 **Materials and Methods**

### 76 **Animals**

77 32 Adult Lister-Hooded rats (~400 g, Charles River Laboratories, Saint-Germain-sur-l'Arbresle,  
78 France) were used in these behavioral experiments. Only male rats were used to avoid inter-variability  
79 of the hormonal cycle. Animals were paired housed, in Plexiglas cages with unlimited access to food  
80 and water. Temperature- and humidity-controlled environments were maintained with an inverted 12 h  
81 light/dark cycle (light -onset at 7 pm). All experiments were conducted during the dark cycle (8am-  
82 8pm). Animals were handled daily. All animal care and use were conformed to the French regulation  
83 (Decree 2013-118) and were approved by local ethic committee and the National French Agriculture  
84 Ministry (authorization #3129.01). Experimental group sizes were determined by taking into accounts  
85 the 3Rs rules to reduce the number of animals used.

### 86 **Electrode design for STN DBS**

87 Electrodes were made of Platinum-Iridium wires coated with Teflon (75  $\mu\text{m}$ ). Coating was removed  
88 over 0.5 mm at the tips and two wires were inserted into a 16 mm stainless steel tubing to form an  
89 electrode. Two electrodes, separated by 4.8 mm (twice the STN laterally), were soldered to an electric  
90 connector, allowing connection with the stimulator. Electrodes (impedance= $20 \pm 2.25 \text{ k}\Omega$ ) and  
91 connector were subsequently deeply bound, using a custom mold and dental cement. Finally, electrodes  
92 were checked with an isolated battery to avoid electrical short circuits.

### 93 **Surgery**

94 All the animals underwent bilateral electrode implantation into the STN. They were anesthetized with  
95 ketamine (Imalgen, Merial, 100 mg/kg, *i.p.*) and medetomidine (Domitor, Janssen, 0.5 mg/kg, *i.p.*). They  
96 also received an antibiotic treatment by injection of amoxicillin (Citramox, LA, Pfizer, 100 mg/kg, *s.c.*)  
97 and an injection of meloxicam (Metacam, Boehringer Ingelheim, 0.5 mg/kg, *s.c.*) for analgesia. Animals  
98 were then placed in the stereotaxic frame (David Kopf apparatus) for the bilateral electrodes'  
99 implantation into the STN (coordinates in mm: -3.7 AP,  $\pm 2.4$  L from bregma, -8.35 DV from skull

100 surface (Paxinos and Watson 2014), with the incisor bar at -3.3 mm). The electrodes were maintained  
101 with a head-cap made of dental cement and screws anchored on the skull. Rats were awakened with an  
102 injection of atipamezole (Antisedan, Janssen, 0.15 mg/kg, i.m.), an antagonist of medetomidine. Rats  
103 were allowed to recover from the surgery for at least 7 days.

#### 104 **Behavioral apparatus**

105 Behavioral experiment took place in homemade self-administration chambers (60x30x35 cm) divided  
106 into two compartments by a metallic grid. The wall of one compartment per cage was equipped with  
107 two non-retractable levers and a light above each. A recessed magazine (3.8-cm high and 3.8-cm wide  
108 located 5.5 cm above the grid floor) containing a cup liquid receptacle with an 18-gauge pipe was  
109 positioned between the two levers and connected to a pump outside the chamber. A syringe filled with  
110 ethanol was positioned on the pump and connected with the 18-gauge pipe of the receptacle via a  
111 catheter. All the chambers were controlled by a custom-built interface and associated software (built  
112 and written by Y. Pelloux).

#### 113 **Behavioral procedure**

114 An overview of the behavioral procedure is illustrated in **Fig. 1**.

#### 115 **1-Experiment 1: recreational ethanol self-administration**

116 At least one week after surgery, rats began ethanol self-administration training. The ethanol delivery  
117 was assigned to one of the two levers ('active lever') and counterbalanced between rats. An FR1  
118 schedule of reinforcement was used, so each lever press delivered 100  $\mu$ L of 10 % ethanol in the cup  
119 receptacle and switched on the cue-light above the lever. Each delivery was followed by a 20-s time-  
120 out period, during which any press on the active lever was recorded as a perseveration but had no  
121 consequence. Presses on the other lever ('inactive lever') had no consequence either. Each daily session  
122 lasted 1h.

123 Rats were first trained to self-administer ethanol with sucrose, using a fading sucrose technique in which  
124 the sucrose concentration in the 10% ethanol solution gradually decrease over sessions until zero. They  
125 were also habituated to be connected to an electric cable (but without stimulation). Once consumption  
126 became stable (<25% of variability in the number of ethanol rewards for 5 consecutive days), animals  
127 were exposed to the testing period, during which rats were either STN-stimulated with DBS (ON group,  
128 n=16) or remained unstimulated (OFF control group, n=16). This testing period consists of 5x1h  
129 consecutive daily sessions of ethanol self-administration alone, followed by 5x1h-sessions in presence  
130 of an alcohol-naive stranger peer ('With peer' condition), placed on the other side of the grid. To prevent  
131 the emergence of a familiarity effect resulting from constantly using the same social stimulus, the peer  
132 was changed every day.

#### 133 **2-Escalation of ethanol intake through intermittent access to alcohol (IAA)**

134 After this initial testing period, animals (n=30, two animals were excluded at this point, see results  
135 section) underwent an escalation of their ethanol intake, using the intermittent access to alcohol (IAA)  
136 protocol for 15 sessions, as previously used in Pelloux and Baunez (2017). During each 12h-session  
137 (from 8:00 am to 8:00 pm), animals were isolated in a homecage with access to food and two bottles.  
138 One bottle contained water, and the other held a 20% ethanol solution. Both bottles were weighted before  
139 and after each session to calculate consumption levels. The weight of each rat was also measured prior  
140 to every IAA session. Following the 12h-period of IAA, rats were returned to their homecage with their  
141 cagemate, and observed a 36h-period without ethanol access before the next session. The placement of  
142 the bottles in the cage was alternated from session to session to avoid side preferences. There was no  
143 DBS stimulation applied during this period.

#### 144 **3- Experiment 2: Addiction-like ethanol consumption**

145 36 hours after the last session of IAA, rats were subjected to the same 10% ethanol self-administration  
146 procedure than for Experiment 1, for 10x1h other sessions: 5 consecutive sessions alone ('Alone') and  
147 5 consecutive sessions in presence of an alcohol-naive stranger peer ('With peer'). Operant chambers  
148 were the same as those used in the first procedure. The order of the conditions 'Alone' vs. 'With peer'

149 were counterbalanced between rats. To avoid a possible long-term effect of former STN DBS (i.e.,  
150 during recreational alcohol use) on addiction-like alcohol intake, we counterbalanced animals subjected  
151 to STN DBS between experiment 1 and 2. Thus, half of the animals subjected to STN DBS OFF during  
152 experiment 1 remained OFF for experiment 2, while the other half were subjected to DBS ON for  
153 experiment 2, and vice versa for the other group. The DBS was turned ON during the 10 sessions for  
154 the STN DBS group (n=15) and remained OFF for the control group (n=15).

### 155 **Deep Brain Stimulation**

156 Electrodes were connected to homemade electric stimulation cables, themselves connected to a digital  
157 stimulator (DS8000, WPI) via a stimulus isolator (DLS100, WPI) and a rotating commutator (Plastic-  
158 One). Stimulation parameters were adapted from previous studies (Degoulet et al. 2021; Pelloux et al.  
159 2018). Individual stimulation intensity was determined using 130 Hz frequency and 80  $\mu$ s pulse width  
160 stimulation. Intensity was progressively increased until the appearance of hyperkinetic movements or  
161 abnormal behavior. Stimulation intensity (50 to 150  $\mu$ A) was set just below the abnormal behavior  
162 threshold. In any case, the maximal intensity was set at 150  $\mu$ A in order to prevent heating and tissue  
163 damage.

164 Before each behavioral session, animals were connected to the stimulation device, DBS was turned ON,  
165 and stimulation intensity was progressively increased to reach the predetermined stimulation intensity.  
166 Stimulation at 130 Hz was applied continuously during the 1-hour session.

### 167 **Histology**

168 At the end of the experiments, rats were deeply anesthetized with an injection of pentobarbital (Euthasol  
169 Vet, Dechra, 300 mg/kg *i.p.*). Then, brains were extracted and rapidly frozen into liquid isopentane (-  
170 40°C) and cut in 40  $\mu$ m thick frontal slices using a cryostat. A staining with cresyl violet allowed to  
171 perform histological control. Animals with incorrect electrode placement were excluded from the ON  
172 group. Representative correct electrodes implantation is illustrated in **Fig. 1**.

### 173 **Statistical Analyses**

174 Only the number of rewards obtained (i.e., rewarded active lever presses) are shown and expressed as  
175 mean number  $\pm$  SEM. Using R software, and p-value threshold set at  $\alpha=0.05$ , data were analyzed by  
176 performing two-tailed, one, two or three-way mixed ANOVA, followed by Bonferroni post-hoc tests  
177 when applicable. Graphs were performed using GraphPad Prism 8 (version 8.0.2).

178 The consumption of ethanol or water in the IAA protocol was calculated as difference in bottle weight  
179 before and after each session. This difference was then divided by the weight of the rat.

180 In Experiment 1 and 2, the outlier's test was conducted using the mean baseline of ethanol intake of all  
181 rats in the "alone" condition.

182 Correlation between the amount of ethanol intake during the last 3 sessions of IAA and the number of  
183 lever presses/rewards obtained during the first session of operant self-administration after the IAA were assessed  
184 by a Pearson's correlation analysis. A Cohen's d was used to confirm that our sample size of low drinkers control  
185 animals (n=5) was sufficient to detect reliable changes in social context (power >95% at a level of confidence of  
186  $p<0.05$ )

### 187 **Results**

188 In total, 28 rats were included in the analyses of Experiment 1. Four animals were excluded: electrodes'  
189 mislocation (n=2, ON group), one rat (OFF group) was identified as an outlier (estimation based on the  
190 mean baseline of ethanol intake of all rats), one rat (ON group) did not drink ethanol.

191 To avoid a possible long-term effect of former STN DBS during Experiment 1, we counterbalanced  
192 animals subjected to STN DBS between experiment 1 and 2. In Experiment 2 (escalated alcohol  
193 consumption), out of 30 rats, 24 were included in the analyses. 5 rats (n=2 ON and 3 OFF) did not  
194 escalate their ethanol intake in the IAA protocol, and one rat (ON group) was identified as an outlier  
195 (estimation based on the mean baseline of ethanol intake of all rats).

### 196 **Experiment 1:**

## 197 **Influence of a Peer's Presence and Contribution of STN on Recreational Alcohol Intake**

198 To study the influence of social context and the role of STN, a three-way ANOVA was used (social  
199 context x STN DBS + session) to assess the number of rewards obtained (i.e. active lever presses outside  
200 of the timeout period). No main effects were observed for social context ( $F(1, 270)=0.015$ ;  $p=0.901$ ),  
201 STN DBS ( $F(1, 270)=0.040$ ;  $p=0.842$ ) and session ( $F(4, 270)=0.649$ ;  $p=0.628$ ). The interactions of STN  
202 DBS and social context were also non-significant (STN DBS x social context ( $F(1, 270)=0.001$ ;  
203  $p=0.972$ ).

204 Indeed, in the alone condition, **control rats** ( $n=15$ ) had a stable intake of ethanol (*mean*  $7.88 \pm 0.29$   
205 *rewards*), that remained similar in presence of a peer (*mean*  $8.36 \pm 0.48$  *rewards*). Thus, the presence of  
206 an alcohol-naive stranger peer, had no effect on recreational ethanol consumption.

207 In **STN stimulated rats** ( $n=13$ ), the alcohol intake in the alone condition (*mean*  $7.60 \pm 0.25$  *rewards*)  
208 was comparable to the control group. STN DBS seems not to influence recreational alcohol use in this  
209 experiment. In presence of an alcohol-naive unfamiliar peer, STN DBS did not change significantly the  
210 ethanol consumption compared to when STN-stimulated rats were in the alone condition (*mean*  $8.09 \pm$   
211  $0.15$  *rewards*), and was similar to the control group's intake (**Fig. 2a**).

## 212 **Influence of the Alcohol Preference**

213 Because substantial variations in alcohol consumption and preference were observed between rats, they  
214 were split into two groups: high drinkers (HD) and low drinkers (LD) depending on their mean ethanol  
215 consumption in the alone condition (Spoelder et al. 2015). The effects of the social context and STN  
216 DBS were assessed with a three-way ANOVA (social context x STN DBS + sessions) independently  
217 for each group according to their preference for ethanol.

218 In **HD rats** ( $n=14$ , **Fig. 2b**), there were no effect of the STN DBS ( $F(1, 130)=0.061$ ;  $p=0.805$ ), nor of  
219 the sessions ( $F(4, 130)=0.759$ ;  $p=0.554$ ) nor of the interaction STN DBS x social context ( $F(1,$   
220  $130)=0.159$ ;  $p=0.691$ ), although a trend for the social context effect ( $F(1, 130)=3.518$ ;  $p=0.063$ ).  
221 Indeed, HD control rats ( $n=8$ ) had similar ethanol consumption in the alone condition (*mean*  $10.95 \pm$   
222  $0.36$  *rewards*) and in a presence of an alcohol-naive stranger peer (*mean*  $11.05 \pm 0.72$  *rewards*). STN  
223 DBS did not affect alcohol consumption in HD animals ( $n=6$ ) (*alone: mean*  $10.37 \pm 0.40$ , *with a peer:*  
224 *mean*  $9.73 \pm 0.53$  *rewards*), that was equivalent to the control group in the same circumstances.

225 In **LD rats** ( $n=14$ , **Fig. 2c**), the ANOVA analysis indicated a trend for an STN DBS effect ( $F(1,$   
226  $130)=3.669$ ;  $p=0.058$ ) and for the social context ( $F(1, 130)=3.415$ ;  $p=0.067$ ), but no significant effect of  
227 the repeated sessions ( $F(4, 130)=0.459$ ;  $p=0.766$ ), nor interaction STN DBS x social context ( $F(1,$   
228  $130)=0.356$ ;  $p=0.552$ ).

229 LD control rats ( $n=7$ ) consumed ethanol at the same level in the alone condition (*mean*  $4.37 \pm 0.23$   
230 *rewards*) and in presence of a peer (*mean*  $5.29 \pm 0.39$  *rewards*). STN DBS in LD rats ( $n=7$ ) did not  
231 change ethanol consumption when compared to that of control animals, regardless of whether they were  
232 in the alone condition (*mean*  $5.23 \pm 0.27$  *rewards*) or in a social context (*mean*  $6.69 \pm 0.19$  *rewards*).

233 Overall, our results showed that despite tendencies for slight modulations, neither the presence of an  
234 alcohol-naive stranger peer, nor the STN DBS alters significantly recreational alcohol consumption,  
235 regardless of alcohol preference (i.e., low vs. high drinkers).

## 236 **Experiment 2: Influence of peer's presence and STN contribution following escalation of ethanol** 237 **use**

### 238 *Rats subjected to IAA procedure escalated their ethanol consumption over sessions*

239 Alcohol consumption during IAA was analyzed with a two-way ANOVA with STN DBS group as  
240 between factors (control group vs. "to be stimulated group" although there is no stimulation during IAA)

241 and sessions as within factors. During the intermittent access to alcohol, rats showed a progressive  
242 increase of their alcohol consumption (**Fig. 3a**) over the sessions ( $F(4.34, 95.43)=18.083$ ;  $p<0.0001$ ),  
243 with no difference between the control group and the “to be stimulated” group ( $F(1, 22)=1.197$ ;  $p=0.286$ )  
244 and no interaction between these two factors ( $F(4.34, 95.43)=1.749$ ;  $p=0.140$ ). Post-hoc analyses  
245 confirmed the progressive increase of alcohol intake over the sessions, reaching a level of consumption  
246 during the last session ( $mean\ 3.01 \pm 0.35\ g/kg\ ethanol$ ) that was significantly higher than that of the first  
247 session ( $mean\ 1.66 \pm 0.13\ g/kg\ ethanol$ , Bonferroni’s test:  $p=0.00015$ ).

248 Two-way ANOVA (STN DBS group x sessions) of water consumption during IAA (**Fig. 3b**) revealed  
249 a main effect of session ( $F(5.40, 118.80)=7.893$ ;  $p<0.0001$ ) and no difference between the two future  
250 groups ( $F(1, 22)=0.170$ ;  $p=0.5$ ) nor the interaction between session x STN DBS ( $F(5.40, 118.80)=1.011$ ;  
251  $p=0.418$ ). The session effect is due to inter-session variability but no difference between the first ( $mean$   
252  $16.22 \pm 0.92\ g/kg\ water$ ) and the last sessions ( $mean\ 22.39 \pm 2.27\ g/kg\ water$ , Bonferroni’s test,  $p=1$ )  
253 was found.

254 As a result, both control and ‘to be stimulated’ groups exhibited comparable escalation and loss of  
255 control only over alcohol intake.

### 256 *Influence of Peer’s Presence and STN Contribution on Escalated Alcohol Intake*

257 To assess the effect of the peer’s presence and STN DBS after a loss of control over alcohol use, a three-  
258 way ANOVA was conducted (STN DBS x social context x sessions). This investigation disclosed  
259 significant main effects of STN DBS ( $F(1, 215)=39.752$ ;  $p < 0.0001$ ) but no effect of the social context  
260 ( $F(1, 215)=0.232$ ;  $p=0.631$ ), and sessions ( $F(4, 215)=0.337$ ;  $p=0.852$ ). No significant interaction was  
261 found (STN DBS x social context ( $F(1, 215)=1.230$ ;  $p=0.269$ ; STN DBS x sessions ( $F(4, 215)=1.090$ ;  
262  $p=0.363$ ; social context x session ( $F(4, 215)=0.073$ ;  $p=0.990$ ) and STN DBS x social context x session  
263 ( $F(4, 215)=0.250$ ;  $p=0.909$ )).

264 In the **control group** ( $n=12$ , **Fig. 3c black**), after escalation of alcohol intake, the introduction of an  
265 alcohol-naive stranger peer, did not modulate ethanol consumption; control rats displayed equivalent  
266 ethanol intake whether in the alone condition ( $mean\ 9.30 \pm 1.10\ rewards$ ) or in presence of the peer  
267 ( $mean\ 10.58 \pm 1.08\ rewards$ , Bonferroni’s test,  $p=0.341$ ).

268 When **STN DBS** ( $n=12$ , **Fig. 3c**) was applied, post-hoc analysis revealed that in the alone condition, rats  
269 consumed a significantly less ethanol ( $mean\ 6.13 \pm 0.55\ rewards$ , Bonferroni’s test,  $p=0.004$ ) than the  
270 control group in the same alone condition. This decreased consumption persisted in the presence of a  
271 peer, where STN-stimulated rats consumed significantly less ( $mean\ 5.63 \pm 0.62\ rewards$ , Bonferroni’s  
272 test,  $p=0.0004$ ) than the control groups in the same condition. However, within the stimulated group, no  
273 significant difference was observed between the level of consumption in the two conditions ‘alone’ and  
274 ‘with peer’ (Bonferroni’s test,  $p=0.567$ ). Together, these results suggest that STN DBS reduces escalated  
275 ethanol intake, irrespective of the social context.

276 To confirm that STN DBS reduced ethanol intake independently of the social context, we reordered the  
277 sessions in the proper sequence independently of the social conditions (i.e., the order of passage in the  
278 two social conditions were counterbalanced between animals, **Fig. 3d**). We then performed a two-way  
279 ANOVA including the controls and STN DBS rats (STN DBS x reordered session) to assess the effects  
280 of the STN DBS over time on alcohol intake. Our results revealed a significant effect of the STN DBS  
281 ( $F(1, 219)=43.299$ ;  $p<0.0001$ ) and an effect of the reordered session ( $F(9, 219)=5.924$ ;  $p<0.0001$  but no  
282 effect of the interaction STN DBS x reordered session ( $F(9, 219)=0.559$ ;  $p=0.83$ )), confirming that the  
283 STN DBS decreased alcohol intake whatever the social context.

### 284 285 *Correlation between the amount of ethanol intake during the last 3 sessions of IAA and the number* 286 *of lever presses/rewards obtained during the first session of operant self-administration*

287  
288 In order to make sure that the slight non-significant difference between the “off control” and the “to be  
289 stimulated/ ON” groups in alcohol intake during the last 3 sessions of the intermittent access protocol  
290 would not affect the number of lever presses/rewards obtained during the first session, we tested a

291 possible correlation between these measures by performing a Pearson's correlation. For both groups,  
292 there was no correlation between the number of lever presses and the 13th session of the intermittent  
293 access (OFF:  $r(10)=-0.0210$ ;  $p=0.95$ ; ON:  $r(10)=0.24$ ;  $p=0.45$ ), nor the 14th sessions of IAA (OFF:  
294  $r(10)=0.27$ ;  $p=0.40$ ; ON :  $r(10)=0.25$ ;  $p=0.43$ ), nor the 15th sessions of IAA (OFF:  $r(10)=0.4$ ;  $p=0.20$ ;  
295 ON:  $r(10)=0.14$ ;  $p=0.66$ ) nor the average of the last 3 IAA sessions (OFF:  $r(10)=0.25$ ;  $p=0.44$ ; ON:  
296  $r(10)=0.22$ ;  $p=0.49$ ). It thus suggests that the difference between the two groups during the operant  
297 protocol is due to the STN DBS and not to a baseline difference

## 298 **Impact of Alcohol preference Following a Loss of Control over Alcohol Intake**

299 An additional possible contributor to inter-individual variation is the individual alcohol preference. This  
300 alcohol preference is calculated on the level of alcohol consumption in the alone condition after the  
301 escalation procedure. This alcohol preference allows splitting rats into two categories: High Drinkers  
302 (HD) and Low Drinkers (LD).

303 **For HD rats** ( $n=12$ , **Fig. 3e**), a three-way ANOVA was run to explore the influence of social context,  
304 STN DBS, and repeated sessions. While no impact of the social context ( $F(1, 95)=0.724$ ,  $p=0.397$ ) and  
305 sessions ( $F(4, 95)=0.698$ ;  $p=0.595$ ) emerged, effect of STN DBS ( $F(1, 95)=10.003$ ;  $p=0.002$ ) was  
306 significant. No interaction effects were found (STN DBS x social context:  $F(1, 95)=0.792$ ;  $p=0.376$ ),  
307 STN DBS x session:  $F(4, 95)=0.434$ ;  $p=0.784$ , social context x session:  $F(4, 95)$ ;  $p=0.248$ ;  $p=0.910$  and  
308 STN DBS x social context x session:  $F(4, 95)=0.192$ ;  $p=0.942$ ).

309 HD control animals ( $n=7$ ) had a similar ethanol consumption in the alone condition and in the presence  
310 of a peer (*mean*  $12.83 \pm 1.59$  and  $12.69 \pm 1.78$  rewards respectively, Bonferroni's test,  $p=0.948$ ),  
311 revealing that the peer presence did not influence escalated alcohol use in HD rats. The STN DBS  
312 reduced the consumption in HD STN-stimulated animals ( $n=5$ ) compared to the HD control group in  
313 both social conditions: alone (Bonferroni's test,  $p=0.037$ , *mean*  $9.48 \pm 0.92$  rewards for stimulated  
314 animals) and in presence of a peer (Bonferroni's test,  $p=0.021$ , *mean*  $6.72 \pm 1.15$  rewards for STN-  
315 stimulated rats). However, no significant difference was found in alcohol intake between the two social  
316 conditions within the HD STN-stimulated group (Bonferroni's test,  $p=0.117$ ), revealing the beneficial  
317 effect of the STN DBS on escalated alcohol use in HD rats, independently of the social context.

318 **For LD rats** ( $n=12$ , **Fig. 3f**), the three-way ANOVA revealed a significant effect of the social context  
319 ( $F(1, 95)=10.631$ ;  $p=0.002$ ) and STN DBS ( $F(1, 95)=10.108$ ;  $p=0.002$ ), but no influence of the session  
320 ( $F(4, 95)=0.443$ ;  $p=0.778$ ). No significant interaction was found (STN DBS x social context:  $F(1,$   
321  $95)=2.919$ ;  $p=0.091$ , STN DBS x session:  $F(4, 95)=0.395$ ;  $p=0.812$ , social context x session:  $F(4,$   
322  $95)=0.317$ ;  $p=0.867$  and STN DBS x social context x session:  $F(4, 95)=0.315$ ;  $p=0.868$ ).

323 LD control animals ( $n=5$ ) consumed more alcohol in presence of a peer (*mean*  $7.64 \pm 0.34$  rewards)  
324 than when they were in the alone condition (*mean*  $4.40 \pm 0.42$  rewards, Bonferroni's test,  $p=0.0006$ ,  
325 with a power effect above 80% (Cohen's effect size value  $d=0.99$ )). Although STN DBS ( $n=7$ ) did not  
326 affect ethanol intake when rats were in the alone condition (Bonferroni's test compared to LD controls,  
327  $p=0.366$ , *mean*  $3.74 \pm 0.45$  rewards), it prevented the overconsumption induced by the presence of a  
328 peer (*mean*  $4.86 \pm 0.47$  rewards) (lower consumption in LD STN DBS compared with LD controls,  
329 Bonferroni's test,  $p=0.005$ ). Consequently, STN DBS effectively suppressed the excessive consumption  
330 triggered by the presence of a peer in LD rats.

## 331 **Discussion**

332 The present study showed that neither the presence of an alcohol-naive stranger peer, nor STN  
333 DBS, significantly modulate the recreational use of alcohol. In contrast, after a loss of control over  
334 ethanol intake, STN DBS induced a decrease of the alcohol use over time. After escalation of ethanol  
335 intake, the presence of an alcohol-naive stranger peer modulated the consumption depending on the  
336 initial alcohol preference. HD rats were insensitive to the presence of the peer, and maintained a stable  
337 high level of ethanol intake, while LD rats exhibited an overconsumption in presence of the peer. STN  
338 DBS decreased ethanol intake in HD rats in both conditions (alone and with peer), while it only reduced  
339 the overconsumption induced by the peer's presence in LD rats.



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### ***Presence of a peer during alcohol consumption: Importance of the peer's identity***

342 Studies investigating the effect of a peer's presence on alcohol self-administration have yielded  
343 mixed results. Several showed that the presence of a social partner drinking alcohol promotes alcohol  
344 drinking in humans (Dallas et al. 2014; Larsen et al. 2009). Our recent study in rats further revealed that  
345 the presence of a peer, whether familiar or stranger, but who had a regular consumption of alcohol,  
346 induced an increase of recreational alcohol consumption (Sicre et al., unpublished data). In the present  
347 study, the presence of an alcohol-naive stranger peer during recreational use of alcohol had no significant  
348 influence. These results highlight that the peer's history with alcohol plays an important role. If peers  
349 consumed alcohol orally recently before being used as the "peer", it is possible that olfactory cues of  
350 alcohol consumption could be transmitted to the subject rat through mouth-to-mouth contacts. These  
351 ethanol cues might induce a social transmission of ethanol preference, as observed for food (Strupp and  
352 Levitsky 1984), and this would result in an overconsumption of alcohol. Such olfactory cues could not  
353 be transmitted by a completely alcohol-naive peer, preventing alcohol preference facilitation and  
354 therefore no changes in consumption for the subject rat. On the other hand, the absence of increase of  
355 alcohol intake during the recreational experiment could be due to a ceiling effect that does not leave  
356 room for an increase. However, we have observed an increased effect by the presence of a peer in LD  
357 rats after escalation of alcohol consumption and the level reached then by these LD was equivalent to  
358 that recorded in the recreational experiment. So, although there was room for an increase in consumption  
359 in the recreational experiment, the peer presence had no significant effect. The ceiling effect is thus  
360 probably to be ruled out.

361 Once the control over ethanol intake was lost, the influence of an alcohol-naive peer varied  
362 depending on alcohol preference. For LD rats, the presence of a peer induced an overconsumption of  
363 ethanol while for HD rats, there was no modulation. An appealing hypothesis would be that after an  
364 escalation of alcohol intake, LD rats had an enhanced sensitivity to the presence of a peer. Indeed, social  
365 interactions are rewarding (Krach 2010), and after undergoing intermittent ethanol exposure during late  
366 adolescence, male rats having low doses of ethanol in adulthood displayed an increased social behavior  
367 (Varlinskaya et al. 2014). The potentiation between the rewarding effect of low doses of alcohol and  
368 social interaction could be magnified, resulting in the overconsumption even if the peer is an alcohol-  
369 naive stranger peer. In the case of HD rats after a loss of control, their lack of sensitivity to the peer's  
370 presence could be attributed to a preference for alcohol consumption over social interaction. It has been  
371 shown that when rats had a high dose of ethanol, they show less social investigation, contact behavior  
372 and social avoidance (Varlinskaya and Spear 2002). Moreover, after a protocol of intermittent access to  
373 alcohol rats exhibit preference for alcohol over social rewards (Augier et al. 2022; Marchant et al. 2022).  
374 In our experiment, however, rats were not offered the choice, the social presence was imposed, and the  
375 rats could consume alcohol while interacting with a peer as much as they liked.

376 Nonetheless, from our results, the presence of a stranger peer that never consumed ethanol had  
377 not much detrimental effect, which is in contrast to the consequences of presence of a peer that has  
378 previously consumed alcohol. These results confirm the significant influence of the immediate social  
379 context on drug consumption. This effect is influenced by factors such as the peer's identity (e.g.,  
380 familiarity, drug history) and the specific type of drug being used (e.g., psychostimulant vs. depressive  
381 drug).

### ***STN as a neurobiological substrate ...***

#### ***...Of escalated but not recreational alcohol use...***

382 During recreational alcohol use (Experiment 1), the present study showed no significant effect  
383 of STN DBS on ethanol intake. These results are consistent with a previous work showing that lesion of  
384 STN did not affect rats' alcohol intake in a forced consumption test, and in a two-bottle choice protocol  
385 (Lardeux and Baunez 2008). Moreover, similar to alcohol, STN manipulation was ineffective at  
386 decreasing recreational cocaine use (Baunez et al. 2005; Rouaud et al. 2010; Giorla et al. 2022; Vielle  
387 et al. preprint). However, while no effort was required in the present study that used continuous  
388 reinforcement, when the demand was increased, as in a progressive ratio task, STN manipulation was  
389 efficient at reducing cocaine motivation (Baunez et al. 2005; Rouaud et al. 2010). For alcohol, this effect  
390  
391

392 has been shown to depend on the loss of control over ethanol intake. If rats did not undergo an IAA  
393 protocol, the effect of STN lesion depended on the rat's alcohol preference (Lardeux and Baunez 2008).  
394 After an IAA protocol, STN lesion decreased the level of ethanol motivation (Pelloux and Baunez 2017).  
395 Thus, like for cocaine, STN manipulation could blunt alcohol addiction-like criteria, without altering  
396 recreational drug use.

397 Indeed, applying DBS at high frequency to the STN after escalation of ethanol intake reduced  
398 alcohol consumption. There is a possibility that the disparities observed between the control group and  
399 the STN stimulated group could be explained by the slight difference, although non-significant, during  
400 the last three days of IAA protocol. However, as indicated in the result section, further analyses have  
401 shown a lack of correlation between the level of intake during the last 3 sessions of the intermittent  
402 access and the number of rewards obtained during the first session, suggesting that the decreased lever  
403 pressing for alcohol is due to STN DBS and not to a lower baseline consumption. These effects of STN  
404 DBS are in line with previous works showing that lesion of STN prevented escalation of ethanol intake  
405 and diminished the rebound intake after abstinence (Pelloux and Baunez 2017). This has been shown  
406 for cocaine, heroin and alcohol (Pelloux and Baunez 2017; Pelloux et al. 2018; Vielle et al. preprint;  
407 Wade et al. 2016). Interestingly, in contrast to our former results with cocaine that failed to show an  
408 effect of STN DBS on the maintained escalated intake (Pelloux et al. 2018), it was here reduced for  
409 alcohol. This disparity in the impact of STN DBS on escalated alcohol and cocaine consumption could  
410 potentially be attributed to the type of drug available. Cocaine is a psychostimulant, while alcohol has  
411 depressant effects. The road of administration could also explain the differences observed between  
412 alcohol and cocaine. Alcohol is consumed orally, leading to different pharmacokinetics and longer  
413 absorption time compared to intravenously administration that enters directly in the bloodstream  
414 (Robinson et al. 2002). This delay deferred the activation of the reward system and pleasurable effects  
415 (Robinson et al. 2002). Introducing a delay before obtaining a reward has been shown to decrease  
416 motivation (Jarmolowicz and Hudnall 2014). Consequently, it might thus be comparatively easier to  
417 reduce motivation for alcohol compared to cocaine with STN DBS. However, one might also consider  
418 that having a direct sensory input with alcohol in the mouth, but also its smell, could lead to anticipation  
419 of ethanol effects, while intravenous injection might be less efficient at anticipating the physiological  
420 and psychoactive effects of cocaine. The differences are therefore difficult to simply explain with the  
421 mean of administration. It is interesting to note however that, although the DBS or lesion procedure did  
422 not lead to changes in sustained escalated intake of cocaine, a precise targeting of the STN using  
423 optogenetics has been shown to be efficient (Vielle et al. preprint).

424 Finally, differences in the experimental protocol would account for such differences. Indeed,  
425 cocaine escalation, and maintenance in Pelloux et al. (2018), were performed in the same context  
426 (operant cages). In the present experiment, escalation of alcohol intake occurred in different cages than  
427 the maintenance, and the access (intermittent *vs.* daily), and concentrations of ethanol were also different  
428 between escalation procedure and the operant measure of consumption (20 *vs.* 10%). Thus, in this  
429 experiment, such differences between escalation and maintenance could have facilitated STN DBS  
430 effect on the maintenance of ethanol use in comparison with the cocaine experiment (Pelloux et al.  
431 2018).

432 The level of consumption seems to be an important factor to ensure STN DBS efficiency since  
433 STN DBS decreased the consumption of alcohol only in HD rats. The lack of impact of STN DBS in  
434 LD rats might be attributed to a floor effect, implying that the LD rats did not consume enough ethanol  
435 to exhibit further a reduction triggered by STN DBS. Another hypothesis would be that the  
436 neurobiological effect of alcohol consumption does not induce the same changes in LD and HD rats.  
437 Indeed, when consuming alcohol, HD rats exhibit an increased power in gamma range and coherence in  
438 the medial prefrontal cortex (mPFC) compared to LD rats (Henricks et al. 2019). The mPFC is directly  
439 connected to the STN via the hyperdirect pathway (Maurice et al. 1998; Nambu et al. 2002).  
440 Additionally, abnormal increase in low frequency oscillations has been observed within the STN during  
441 cocaine escalation, and STN DBS was shown to reduce STN oscillatory activity (Pelloux et al. 2018).  
442 If such abnormal activity raised in the STN during alcohol escalation of HD rats, as that seen with  
443 cocaine, STN high frequency DBS could suppress it and also disturb the pathological oscillatory  
444 coherence between STN-mPFC as observed in PD (de Hemptinne et al. 2015; Delaville et al. 2015;  
445 Moran et al. 2012). This would lead to a decrease of alcohol intake only for HD rats after the loss of  
446 control.

447           Nonetheless, STN DBS appears to offer a potential therapeutic benefit for alcohol-related  
448 disorders, as suggested previously for other drugs.

#### 449           ...*And of social influence during alcohol drinking*

450           The influence of the social context was observed here in LD rats having escalated their alcohol  
451 consumption. Interestingly, in these animals, STN DBS effectively abolished the overconsumption  
452 induced by the presence of the peer. These results align with precedent findings, in which STN DBS has  
453 suppressed recreational alcohol overconsumption triggered by different types of peer (Sicre et al.,  
454 unpublished data). STN optogenetic inhibition was also found to suppress the protective effect of a peer  
455 on cocaine recreational use (Vielle et al. preprint). The STN could thus be part of the neurobiological  
456 substrate of the influence of the social context on behavior. Indeed, studies focusing on the effects of  
457 ultrasonic vocalizations (USV) playback on cocaine intake showed that STN lesion abolished the  
458 beneficial influence of positive USV emitted by a stranger rat (Montanari et al. 2018; Vielle et al. 2021).  
459 Additionally, STN lesion suppressed the rewarding effect of positive USVs when rats were pressing a  
460 lever to listen to USVs (Vielle et al. 2021). It is important to note however that the combination of social  
461 context and STN manipulation does not systematically lead to neutralization or additivity of opposite  
462 effects, nor potentiation of similar effects. For example, STN lesions could decrease further the cocaine  
463 intake in presence of a peer (Giorla et al 2022), while STN neuronal optogenetic inhibition did not  
464 potentiate the decreased cocaine intake after escalation (Vielle et al preprint). All these findings suggest  
465 that presence of a peer effects on drug use probably involves STN as a neurobiological substrate. In  
466 human studies, STN DBS has been shown to induce deficits in facial and voice emotional decoding  
467 (Biseul et al. 2005; Brück, Kreifelts, and Wildgruber 2011; Kalampokini et al. 2020; Péron et al. 2010;  
468 2013). A recent study has also shown that STN activity assessed with fMRI, was modulated by the  
469 presence of an observer during the performance of a stop-signal reaction time task by cocaine-addicted  
470 individuals (Terenzi et al. preprint). All these results converge to suggest the involvement of STN in  
471 mediating the impact of social interactions on drug-related behavior. Social interaction has been shown  
472 to trigger the release of oxytocin within the brain's reward circuit (Dölen et al. 2013; Hung et al. 2017).  
473 Additionally, there are evidences suggesting that the STN possesses oxytocin receptors that can regulate  
474 locally dopamine transmission (Baracz and Cornish 2013, 2016). Furthermore the injection of oxytocin  
475 into the STN has been demonstrated to reduce methamphetamine-induced reinstatement (Baracz et al.  
476 2015). Through oxytocin release induced by social interaction, the STN activity could thus be modulated  
477 and potentially affect drug consumption behavior.

478           Additional researches are required to elucidate further the role of the STN in social behaviors  
479 and its impact on drug-related effects.

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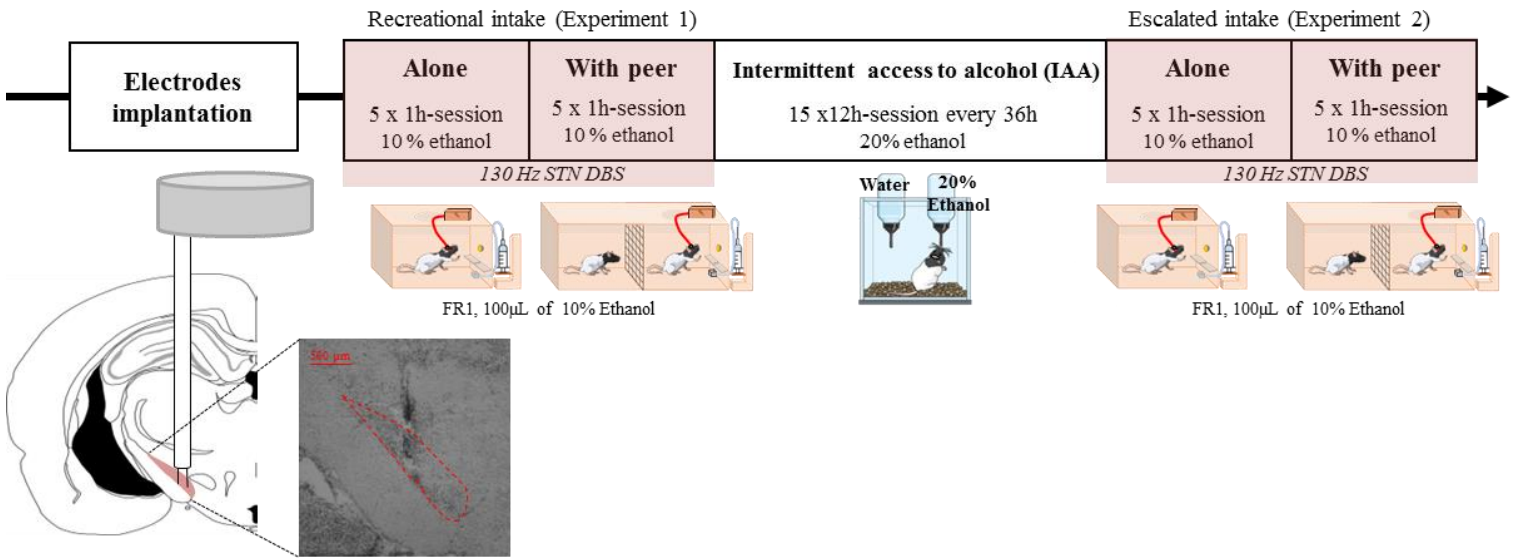
650 **Author contributions:**

651 Conceptualization: CB, CV, LV  
652 Research performance: CV, LV, MW, NM  
653 Data analyses: CV, LV  
654 Funding acquisition: CB, LV  
655 Writing – original draft: CB, CV, LV  
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660 **Fig. 1 Timeline of the behavioral experiment**

661 Top: Behavioral experiment timeline

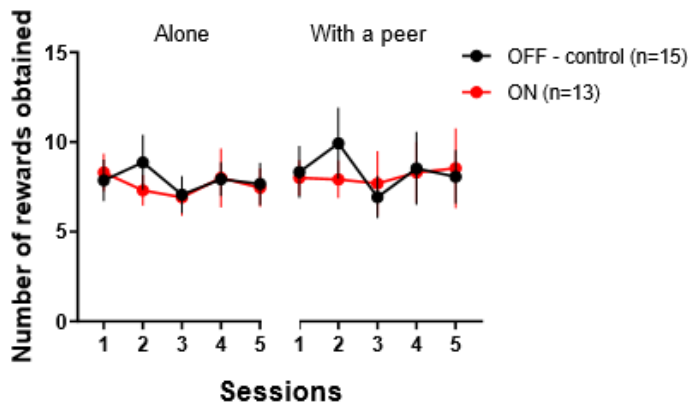
662 Down: (left) schematic representations of the electrode implanted in the STN,

663 (right) Picture from a representative electrode implanted in the STN (delineated by the red dashed line)

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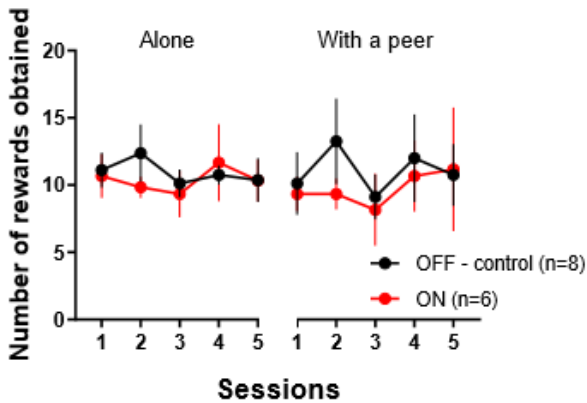
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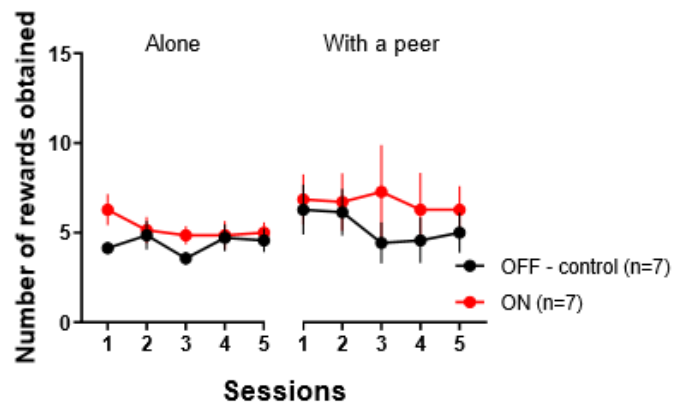
b

High drinkers



c

Low drinkers



665

666

667 **Fig. 2 Neither peer's presence nor STN DBS modulate recreational ethanol intake.**668 Results are presented as mean  $\pm$  SEM number of rewards obtained (i.e. number of active lever presses)

669 per 1h-session.

670 (a) Number of rewards obtained for non-STN-stimulated (black dots – OFF - control) and stimulated

671 (red dots – ON) groups during five sessions in the alone condition ( $7.88 \pm 0.29$  vs.  $7.60 \pm 0.25$ 672 *rewards* respectively) and five sessions with an alcohol-naive stranger peer ( $8.36 \pm 0.48$  vs.  $8.09 \pm$ 673  $0.15$  *rewards* respectively)

674 (b) Number of rewards obtained in control (black dots – OFF - control) and STN-stimulated (red dots

675 – ON) High drinkers in the alone condition ( $10.95 \pm 0.40$  vs.  $10.37 \pm 0.40$  *rewards* respectively)676 and in a presence of an alcohol-naive stranger peer ( $11.05 \pm 0.72$  vs.  $9.73 \pm 0.53$  *rewards*,

677 respectively)

678 (c) Number of rewards obtained in control (black dots – OFF - control) and stimulated (red dots - ON)

679 Low drinkers in the alone condition ( $4.37 \pm 0.23$  vs.  $5.23 \pm 0.27$  *rewards*, respectively)680 and in a presence of an alcohol-naive stranger peer ( $5.29 \pm 0.39$  vs.  $6.69 \pm 0.19$  *rewards*, respectively)

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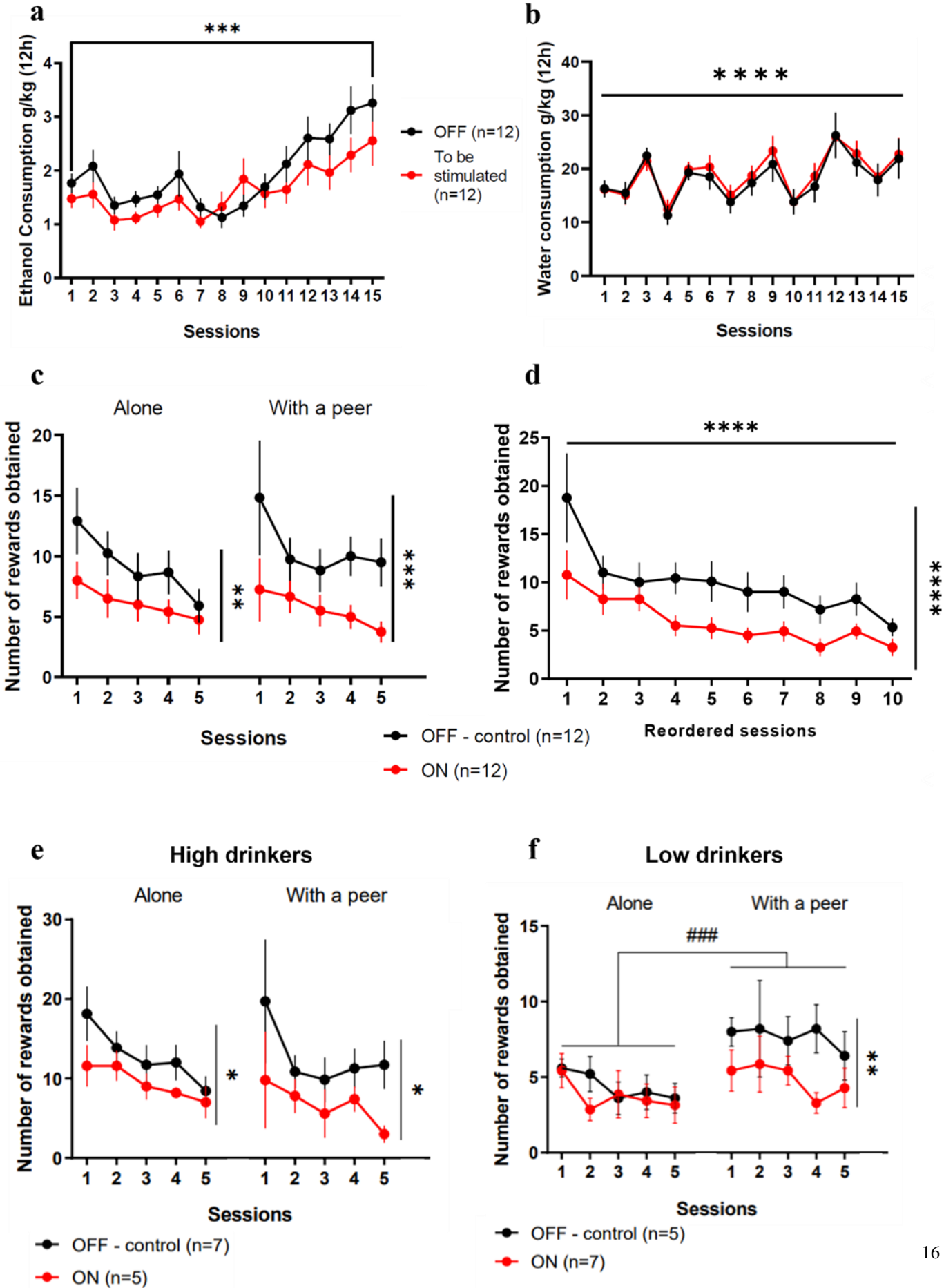
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# 3



689 **Fig. 3 STN DBS reduces the escalated intake of alcohol and suppresses the increased consumption**  
690 **induced by the peer's presence.**

691 Results are presented as mean  $\pm$  SEM.

- 692 (a) Ethanol intake in control (black dots - OFF) and "to be stimulated" (red dots - ON) groups across  
693 the 15 sessions of intermittent access to 20% ethanol. Both groups increased their consumption  
694 from session 1 ( $1.66 \pm 0.13$  g/kg ethanol) to session 15 ( $3.01 \pm 0.35$  g/kg ethanol).
- 695 (b) Water intake in OFF (black dots - OFF) and "to be stimulated" (red dots - ON) groups across the  
696 15 sessions of intermittent access to 20% ethanol. Both groups consumed the same amount of water  
697 between session 1 ( $16.22 \pm 0.92$  g/kg water) and session 15 ( $22.39 \pm 2.27$  g/kg water).
- 698 (c) Number of rewards obtained after the loss of control of alcohol intake for non-stimulated (black  
699 dots - OFF - control) and STN-stimulated rats (red dots - ON) during five 1h-sessions in the alone  
700 condition ( $9.30 \pm 1.10$  vs.  $6.13 \pm 0.55$  rewards, respectively) and five 1h-sessions with an alcohol-  
701 naive stranger peer ( $10.58 \pm 1.08$  vs.  $5.63 \pm 0.62$  rewards, respectively)
- 702 (d) Number of rewards obtained by the non-stimulated group and stimulated rats after reordering the  
703 sessions in the proper sequence irrespective of the social context. ANOVA revealed a general  
704 session and a group effect.
- 705 (e) Number of rewards obtained in control (black dots - OFF - control) and STN-stimulated (red dots  
706 - ON) High Drinkers after a loss of control, in the alone condition ( $12.83 \pm 1.59$  vs.  $9.48 \pm 0.92$   
707 rewards respectively) and in a presence of an alcohol-naive stranger peer ( $12.69 \pm 1.78$  vs.  $6.72 \pm$   
708  $1.15$  rewards, respectively)
- 709 (f) Number of rewards obtained in control (black dots - OFF - control) and stimulated (red dots - ON)  
710 Low Drinkers after a loss of control, in the alone condition ( $4.40 \pm 0.42$  vs.  $3.74 \pm 0.45$  rewards,  
711 respectively) and in a presence of an alcohol-naive stranger peer ( $7.64 \pm 0.34$  vs.  $4.86 \pm 0.48$   
712 rewards, respectively)

713

714 \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ; \*\*\*\*  $p < 0.0001$

715 ###  $p < 0.001$  between "alone" and "with peer" conditions in the non-stimulated (OFF - control) group

716