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# SUBTHALAMIC HIGH-FREQUENCY DEEP BRAIN STIMULATION REDUCES ADDICTION-LIKE ALCOHOL USE AND SUPPRESSES THE OVERCONSUMPTION INDUCED BY THE PEER'S PRESENCE

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1 **Title: SUBTHALAMIC HIGH-FREQUENCY DEEP BRAIN STIMULATION REDUCES**  
2 **ADDICTION-LIKE ALCOHOL USE AND SUPPRESSES THE OVERCONSUMPTION**  
3 **INDUCED BY THE PEER'S PRESENCE**

4  
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14  
15 **Abstract:**

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

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

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

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

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

33  
34 **Keyword:** alcohol, social context, subthalamic nucleus, deep brain stimulation, peer's presence

35  
36 **Main text:**

37 **Introduction**

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

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

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

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

## 74 **Materials and Methods**

### 75 **Animals**

76 32 Adult Lister-Hooded rats (~400 g, Charles River Laboratories, Saint-Germain-sur-l'Arbresle,  
77 France) were used in these behavioral experiments. Only male rats were used to avoid inter-variability  
78 of the hormonal cycle. Animals were paired housed, in Plexiglas cages with unlimited access to food  
79 and water. Temperature- and humidity-controlled environments were maintained with an inverted 12 h  
80 light/dark cycle (light -onset at 7 pm). All experiments were conducted during the dark cycle (8am-  
81 8pm). Animals were handled daily. All animal care and use were conformed to the French regulation  
82 (Decree 2013-118) and were approved by local ethic committee and the National French Agriculture  
83 Ministry (authorization #3129.01). Experimental group sizes were determined by taking into accounts  
84 the 3Rs rules to reduce the number of animals used.

### 85 **Electrode design for STN DBS**

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

### 92 **Surgery**

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

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

### 103 **Behavioral apparatus**

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

### 112 **Behavioral procedure**

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

#### 114 **1-Experiment 1: recreational ethanol self-administration**

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

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

#### 132 **2-Escalation of ethanol intake through intermittent access to alcohol (IAA)**

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

#### 143 **3- Experiment 2: Addiction-like ethanol consumption**

144 36 hours after the last session of IAA, rats were subjected to the same 10% ethanol self-administration  
145 procedure than for Experiment 1, for 10x1h other sessions: 5 consecutive sessions alone ('Alone') and  
146 5 consecutive sessions in presence of an alcohol-naive stranger peer ('With peer'). Operant chambers  
147 were the same as those used in the first procedure. The order of the conditions 'Alone' vs. 'With peer'

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

#### 154 **Deep Brain Stimulation**

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

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

#### 166 **Histology**

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

#### 172 **Statistical Analyses**

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

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

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

#### 181 **Results**

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

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

#### 190 **Experiment 1:**

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

192 To study the influence of social context and the role of STN, a three-way ANOVA was used (social  
193 context x STN DBS + session) to assess the number of rewards obtained (i.e. active lever presses outside  
194 of the timeout period). No main effects were observed for social context ( $F(1, 270)=0.015$ ;  $p=0.901$ ),

195 STN DBS ( $F(1, 270)=0.040$ ;  $p=0.842$ ) and session ( $F(4, 270)=0.649$ ;  $p=0.628$ ). The interactions of STN  
196 DBS and social context were also non-significant (STN DBS x social context ( $F(1, 270)=0.001$ ;  
197  $p=0.972$ ).

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

201 In **STN stimulated rats** ( $n=13$ ), the alcohol intake in the alone condition (*mean*  $7.60 \pm 0.25$  *rewards*)  
202 was comparable to the control group. STN DBS seems not to influence recreational alcohol use in this  
203 experiment. In presence of an alcohol-naive unfamiliar peer, STN DBS did not change significantly the  
204 ethanol consumption compared to when STN-stimulated rats were in the alone condition (*mean*  $8.09 \pm$   
205  $0.15$  *rewards*), and was similar to the control group's intake (**Fig. 2a**).

## 206 **Influence of the Alcohol Preference**

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

212 **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  
213 the sessions ( $F(4, 130)=0.759$ ;  $p=0.554$ ) nor of the interaction STN DBS x social context ( $F(1,$   
214  $130)=0.159$ ;  $p=0.691$ ), although a trend for the social context effect ( $F(1, 130)=3.518$ ;  $p=0.063$ ).  
215 Indeed, HD control rats ( $n=8$ ) had similar ethanol consumption in the alone condition (*mean*  $10.95 \pm$   
216  $0.36$  *rewards*) and in a presence of an alcohol-naive stranger peer (*mean*  $11.05 \pm 0.72$  *rewards*). STN  
217 DBS did not affect alcohol consumption in HD animals ( $n=6$ ) (*alone: mean*  $10.37 \pm 0.40$ , *with a peer:*  
218 *mean*  $9.73 \pm 0.53$  *rewards*), that was equivalent to the control group in the same circumstances.

219 **In LD rats** ( $n=14$ , **Fig. 2c**), the ANOVA analysis indicated a trend for an STN DBS effect ( $F(1,$   
220  $130)=3.669$ ;  $p=0.058$ ) and for the social context ( $F(1, 130)=3.415$ ;  $p=0.067$ ), but no significant effect of  
221 the repeated sessions ( $F(4, 130)=0.459$ ;  $p=0.766$ ), nor interaction STN DBS x social context ( $F(1,$   
222  $130)=0.356$ ;  $p=0.552$ ).

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

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

## 230 **Experiment 2: Influence of peer's presence and STN contribution following escalation of ethanol** 231 **use**

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

233 Alcohol consumption during IAA was analyzed with a two-way ANOVA with STN DBS group as  
234 between factors (control group vs. "to be stimulated group" although there is no stimulation during IAA)  
235 and sessions as within factors. During the intermittent access to alcohol, rats showed a progressive  
236 increase of their alcohol consumption (**Fig. 3a**) over the sessions ( $F(4.34, 95.43)=18.083$ ;  $p<0.0001$ ),  
237 with no difference between the control group and the "to be stimulated" group ( $F(1, 22)=1.197$ ;  $p=0.286$ )  
238 and no interaction between these two factors ( $F(4.34, 95.43)=1.749$ ;  $p=0.140$ ). Post-hoc analyses  
239 confirmed the progressive increase of alcohol intake over the sessions, reaching a level of consumption

240 during the last session ( $mean\ 3.01 \pm 0.35\ g/kg\ ethanol$ ) that was significantly higher than that of the first  
241 session ( $mean\ 1.66 \pm 0.13\ g/kg\ ethanol$ , Bonferroni's test:  $p=0.00015$ ).  
242 Two-way ANOVA (STN DBS group x sessions) of water consumption during IAA (**Fig. 3b**) revealed  
243 a main effect of session ( $F(5.40, 118.80)=7.893$ ;  $p<0.0001$ ) and no difference between the two future  
244 groups ( $F(1, 22)=0.170$ ;  $p=0.5$ ) nor the interaction between session x STN DBS ( $F(5.40, 118.80)=1.011$ ;  
245  $p=0.418$ ). The session effect is due to inter-session variability but no difference between the first ( $mean$   
246  $16.22 \pm 0.92\ g/kg\ water$ ) and the last sessions ( $mean\ 22.39 \pm 2.27\ g/kg\ water$ , Bonferroni's test,  $p=1$ )  
247 was found.  
248 As a result, both control and 'to be stimulated' groups exhibited comparable escalation and loss of  
249 control only over alcohol intake.

### 250 ***Influence of Peer's Presence and STN Contribution on Escalated Alcohol Intake***

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

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

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

270 To assess a possible gradual effect of the STN DBS on ethanol intake, we reordered the sessions in the  
271 proper sequence independently of the social conditions (i.e., the order of passage in the two social  
272 conditions were counterbalanced between animals, **Fig. 3d**). We then performed a one-way ANOVA  
273 (reordered session) to assess the effects of the STN DBS over time on alcohol intake. Our results  
274 revealed a significant effect of the reordered session ( $F(9, 109)=2.396$ ;  $p=0.008$ ), confirming that the  
275 STN DBS progressively decreased alcohol intake.

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

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

281 **For HD rats** ( $n=12$ , **Fig. 3e**), a three-way ANOVA was run to explore the influence of social context,  
282 STN DBS, and repeated sessions. While no impact of the social context ( $F(1, 95)=0.724$ ,  $p=0.397$ ) and  
283 sessions ( $F(4, 95)=0.698$ ;  $p=0.595$ ) emerged, effect of STN DBS ( $F(1, 95)=10.003$ ;  $p=0.002$ ) was  
284 significant. No interaction effects were found (STN DBS x social context:  $F(1, 95)=0.792$ ;  $p=0.376$ ),  
285 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  
286 STN DBS x social context x session:  $F(4, 95)=0.192$ ;  $p=0.942$ ).

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

296 **For LD rats** (n=12, **Fig. 3f**), the three-way ANOVA revealed a significant effect of the social context  
297 ( $F(1, 95)=10.631$ ;  $p=0.002$ ) and STN DBS ( $F(1, 95)=10.108$ ;  $p=0.002$ ), but no influence of the session  
298 ( $F(4, 95)=0.443$ ;  $p=0.778$ ). No significant interaction was found (STN DBS x social context:  $F(1,$   
299  $95)=2.919$ ;  $p=0.091$ , STN DBS x session:  $F(4, 95)=0.395$ ;  $p=0.812$ , social context x session:  $F(4,$   
300  $95)=0.317$ ;  $p=0.867$  and STN DBS x social context x session:  $F(4, 95)=0.315$ ;  $p=0.868$ ).

301 LD control animals (n=5) consumed more alcohol in presence of a peer (*mean*  $7.64 \pm 0.34$  rewards)  
302 than when they were in the alone condition (*mean*  $4.40 \pm 0.42$  rewards, Bonferroni's test,  $p=0.0006$ ).  
303 Although STN DBS (n=7) did not affect ethanol intake when rats were in the alone condition  
304 (Bonferroni's test compared to LD controls,  $p=0.366$ , *mean*  $3.74 \pm 0.45$  rewards), it prevented the  
305 overconsumption induced by the presence of a peer (*mean*  $4.86 \pm 0.47$  rewards) (lower consumption in  
306 LD STN DBS compared with LD controls, Bonferroni's test,  $p=0.005$ ). Consequently, STN DBS  
307 effectively suppressed the excessive consumption triggered by the presence of a peer in LD rats.

## 308 **Discussion**

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

317

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

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



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

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

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

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

361           During recreational alcohol use (Experiment 1), the present study showed no significant effect  
362 of STN DBS on ethanol intake. These results are consistent with a previous work showing that lesion of  
363 STN did not affect rats' alcohol intake in a forced consumption test, and in a two-bottle choice protocol  
364 (Lardeux and Baunez 2008). Moreover, similar to alcohol, STN manipulation was ineffective at  
365 decreasing recreational cocaine use (Baunez et al. 2005; Rouaud et al. 2010; Giorla et al. 2022; Vielle  
366 et al. preprint). However, while no effort was required in the present study that used continuous  
367 reinforcement, when the demand was increased, as in a progressive ratio task, STN manipulation was  
368 efficient at reducing cocaine motivation (Baunez et al. 2005; Rouaud et al. 2010). For alcohol, this effect  
369 has been shown to depend on the loss of control over ethanol intake. If rats did not undergo an IAA  
370 protocol, the effect of STN lesion depended on the rat's alcohol preference (Lardeux and Baunez 2008).  
371 After an IAA protocol, STN lesion decreased the level of ethanol motivation (Pelloux and Baunez 2017).  
372 Thus, like for cocaine, STN manipulation could blunt alcohol addiction-like criteria, without altering  
373 recreational drug use.

374           Indeed, applying DBS at high frequency to the STN after escalation of ethanol intake reduced  
375 alcohol consumption. These results are in line with previous works showing that lesion of STN  
376 prevented escalation of ethanol intake and diminished the rebound intake after abstinence (Pelloux and  
377 Baunez 2017). This has been shown for cocaine, heroin and alcohol (Pelloux and Baunez 2017; Pelloux  
378 et al. 2018; Vielle et al. preprint; Wade et al. 2016). Interestingly, in contrast to our former results with  
379 cocaine that failed to show an effect of STN DBS on the maintained escalated intake (Pelloux et al.  
380 2018), it was here reduced for alcohol. This disparity in the impact of STN DBS on escalated alcohol  
381 and cocaine consumption could potentially be attributed to the type of drug available. Cocaine is a  
382 psychostimulant, while alcohol has depressant effects. The road of administration could also explain the  
383 differences observed between alcohol and cocaine. Alcohol is consumed orally, leading to different  
384 pharmacokinetics and longer absorption time compared to intravenously administration that enters  
385 directly in the bloodstream (Robinson et al. 2002). This delay deferred the activation of the reward  
386 system and pleasurable effects (Robinson et al. 2002). Introducing a delay before obtaining a reward  
387 has been shown to decrease motivation (Jarmolowicz and Hudnall 2014). Consequently, it might thus  
388 be comparatively easier to reduce motivation for alcohol compared to cocaine with STN DBS. However,  
389 one might also consider that having a direct sensory input with alcohol in the mouth, but also its smell,

390 could lead to anticipation of ethanol effects, while intravenous injection might be less efficient at  
391 anticipating the physiological and psychoactive effects of cocaine. The differences are therefore difficult  
392 to simply explain with the mean of administration. It is interesting to note however that, although the  
393 DBS or lesion procedure did not lead to changes in sustained escalated intake of cocaine, a precise  
394 targeting of the STN using optogenetics has been shown to be efficient (Vielle et al. preprint).

395 Finally, differences in the experimental protocol would account for such differences. Indeed,  
396 cocaine escalation, and maintenance in Pelloux et al. (2018), were performed in the same context  
397 (operant cages). In the present experiment, escalation of alcohol intake occurred in different cages than  
398 the maintenance, and the access (intermittent vs. daily), and concentrations of ethanol were also different  
399 between escalation procedure and the operant measure of consumption (20 vs. 10%). Thus, in this  
400 experiment, such differences between escalation and maintenance could have facilitated STN DBS  
401 effect on the maintenance of ethanol use in comparison with the cocaine experiment (Pelloux et al.  
402 2018).

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

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

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

421 The influence of the social context was observed here in LD rats having escalated their alcohol  
422 consumption. Interestingly, in these animals, STN DBS effectively abolished the overconsumption  
423 induced by the presence of the peer. These results align with precedent findings, in which STN DBS has  
424 suppressed recreational alcohol overconsumption triggered by different types of peer (Sicre et al.,  
425 unpublished data). STN optogenetic inhibition was also found to suppress the protective effect of a peer  
426 on cocaine recreational use (Vielle et al. preprint). The STN could thus be part of the neurobiological  
427 substrate of the influence of the social context on behavior. Indeed, studies focusing on the effects of  
428 ultrasonic vocalizations (USV) playback on cocaine intake showed that STN lesion abolished the  
429 beneficial influence of positive USV emitted by a stranger rat (Montanari et al. 2018; Vielle et al. 2021).  
430 Additionally, STN lesion suppressed the rewarding effect of positive USVs when rats were pressing a  
431 lever to listen to USVs (Vielle et al. 2021). It is important to note however that the combination of social  
432 context and STN manipulation does not systematically lead to neutralization or additivity of opposite  
433 effects, nor potentiation of similar effects. For example, STN lesions could decrease further the cocaine  
434 intake in presence of a peer (Giorla et al 2022), while STN neuronal optogenetic inhibition did not  
435 potentiate the decreased cocaine intake after escalation (Vielle et al preprint). All these findings suggest  
436 that presence of a peer effects on drug use probably involves STN as a neurobiological substrate. In  
437 human studies, STN DBS has been shown to induce deficits in facial and voice emotional decoding  
438 (Biseul et al. 2005; Brück, Kreifelts, and Wildgruber 2011; Kalampokini et al. 2020; Péron et al. 2010;  
439 2013). A recent study has also shown that STN activity assessed with fMRI, was modulated by the  
440 presence of an observer during the performance of a stop-signal reaction time task by cocaine-addicted  
441 individuals (Terenzi et al. preprint). All these results converge to suggest the involvement of STN in  
442 mediating the impact of social interactions on drug-related behavior. Social interaction has been shown

443 to trigger the release of oxytocin within the brain's reward circuit (Dölen et al. 2013; Hung et al. 2017).  
444 Additionally, there are evidences suggesting that the STN possesses oxytocin receptors that can regulate  
445 locally dopamine transmission (Baracz and Cornish 2013, 2016). Furthermore the injection of oxytocin  
446 into the STN has been demonstrated to reduce methamphetamine-induced reinstatement (Baracz et al.  
447 2015). Through oxytocin release induced by social interaction, the STN activity could thus be modulated  
448 and potentially affect drug consumption behavior.

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

451

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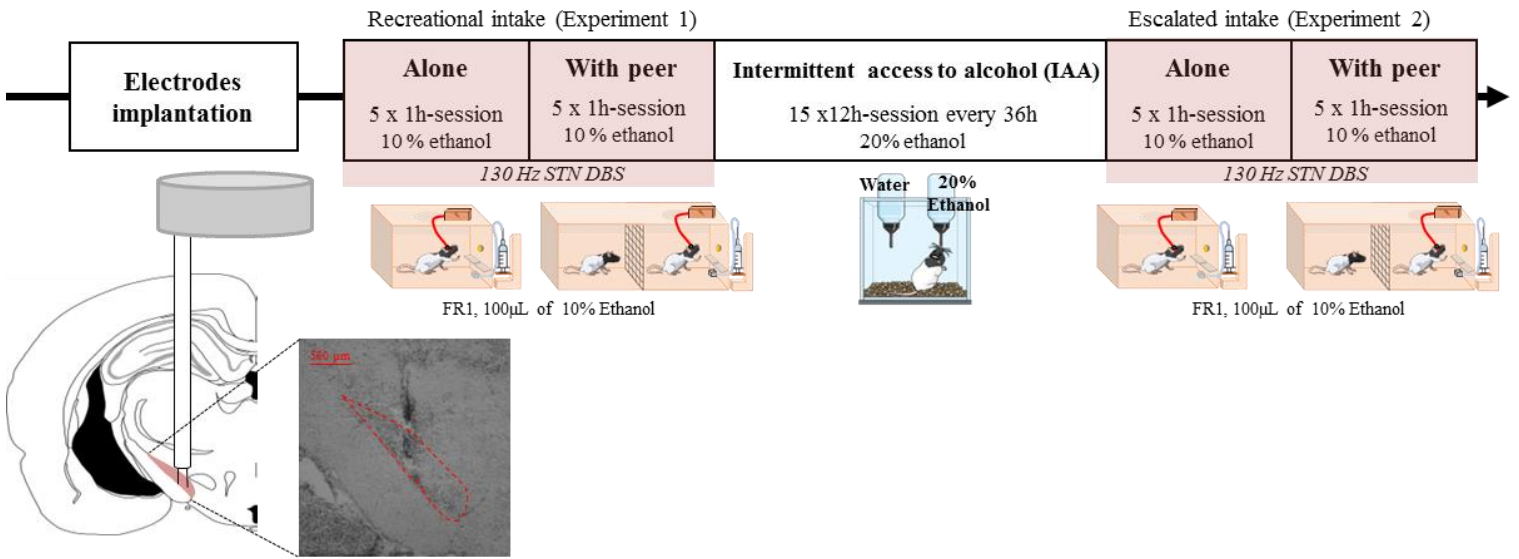
621 **Author contributions:**

622 Conceptualization: CB, CV, LV  
623 Research performance: CV, LV, MW, NM  
624 Data analyses: CV, LV  
625 Funding acquisition: CB, LV  
626 Writing – original draft: CB, CV, LV  
627 Writing – review & editing: CB, CV, LV, MD, MW, NM

628 **Competing interests:** Authors declare that they have no competing interests.

629 **Data and materials availability:** All data are available in the main text, or on request to the authors.

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631 **Fig. 1 Timeline of the behavioral experiment**

632 Top: Behavioral experiment timeline

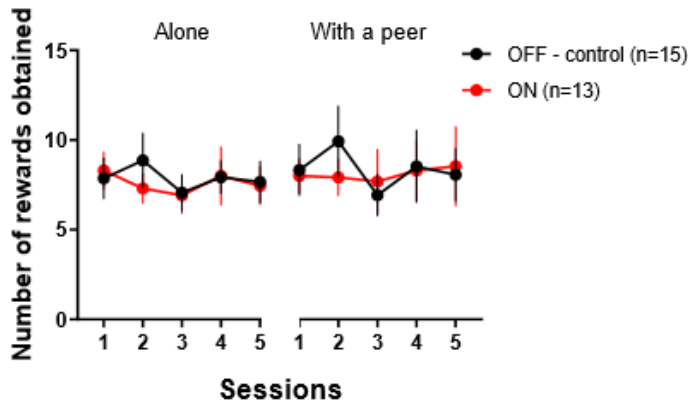
633 Down: (left) schematic representations of the electrode implanted in the STN,

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

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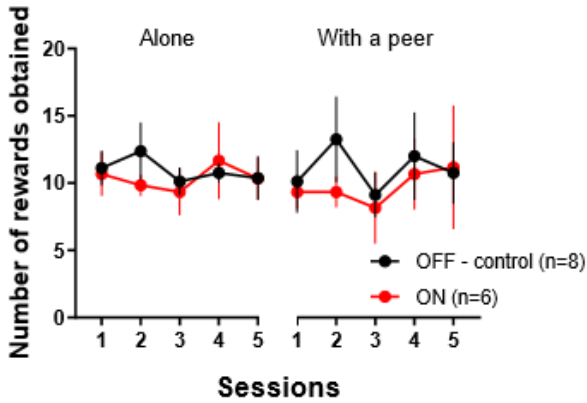
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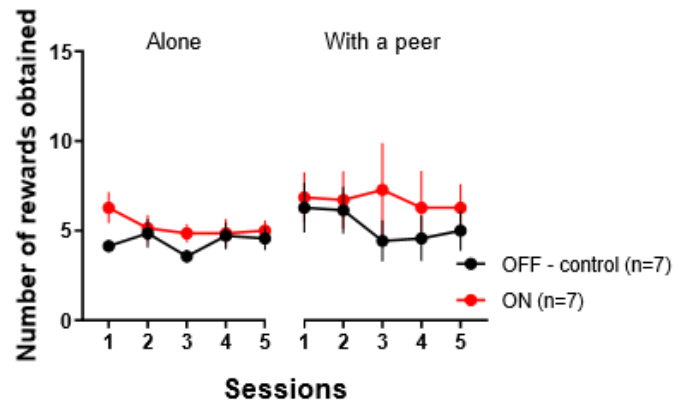
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High drinkers



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Low drinkers



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638 **Fig. 2 Neither peer's presence nor STN DBS modulate recreational ethanol intake.**639 Results are presented as mean  $\pm$  SEM number of rewards obtained (i.e. number of active lever presses)

640 per 1h-session.

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

642 (red dots – ON) groups during five sessions in the alone condition ( $7.88 \pm 0.29$  vs.  $7.60 \pm 0.25$ 643 rewards respectively) and five sessions with an alcohol-naive stranger peer ( $8.36 \pm 0.48$  vs.  $8.09 \pm$ 644  $0.15$  rewards respectively)

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

646 – ON) High drinkers in the alone condition ( $10.95 \pm 0.40$  vs.  $10.37 \pm 0.40$  rewards respectively)647 and in a presence of an alcohol-naive stranger peer ( $11.05 \pm 0.72$  vs.  $9.73 \pm 0.53$  rewards,

648 respectively)

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

650 Low drinkers in the alone condition ( $4.37 \pm 0.23$  vs.  $5.23 \pm 0.27$  rewards, respectively)651 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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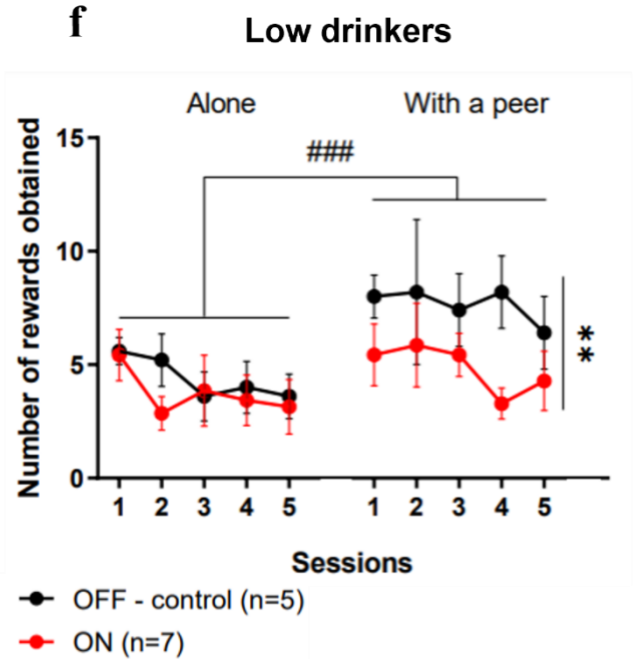
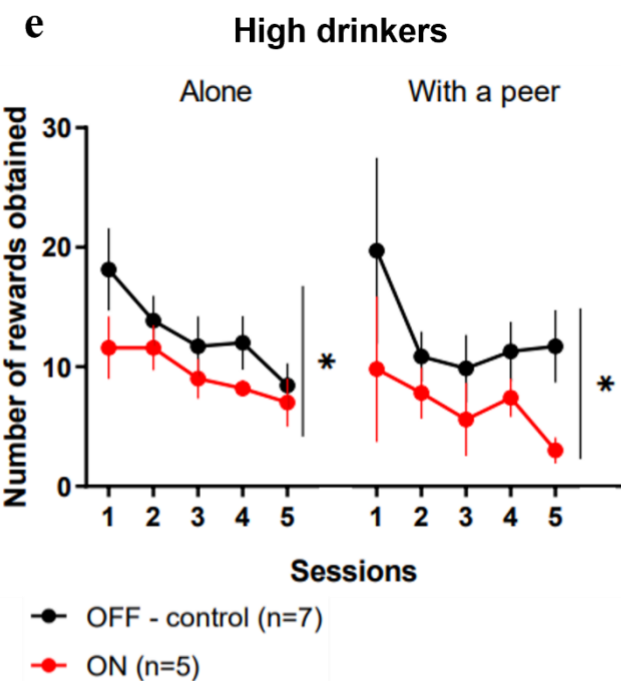
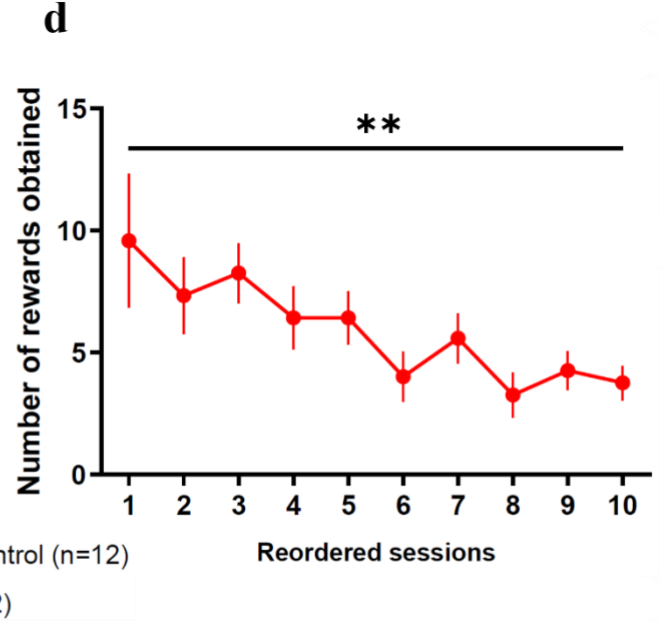
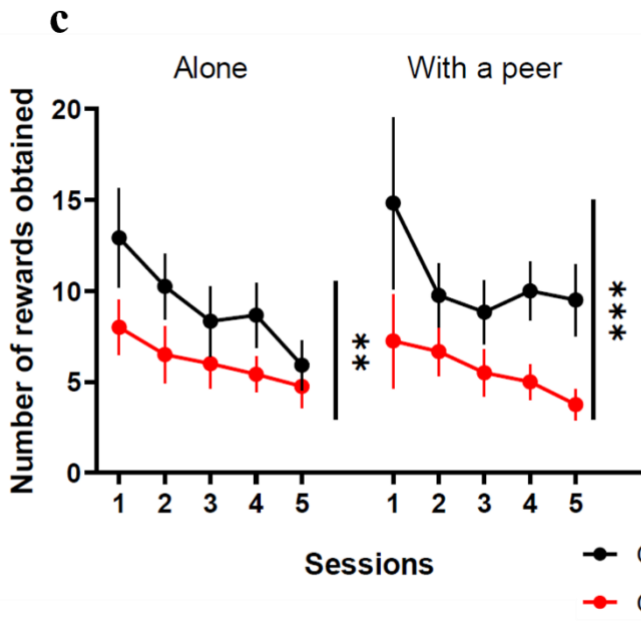
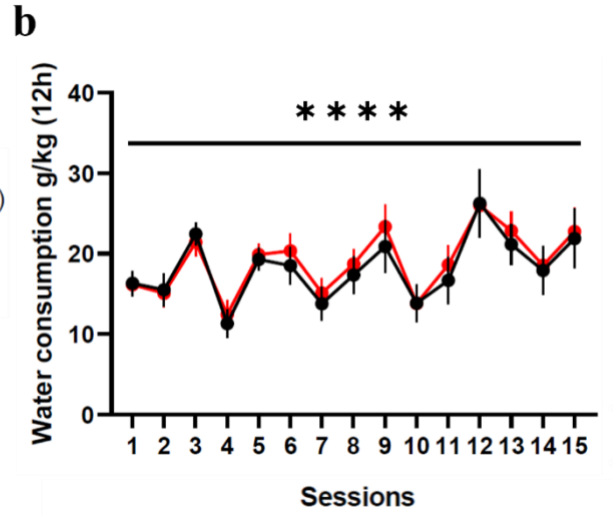
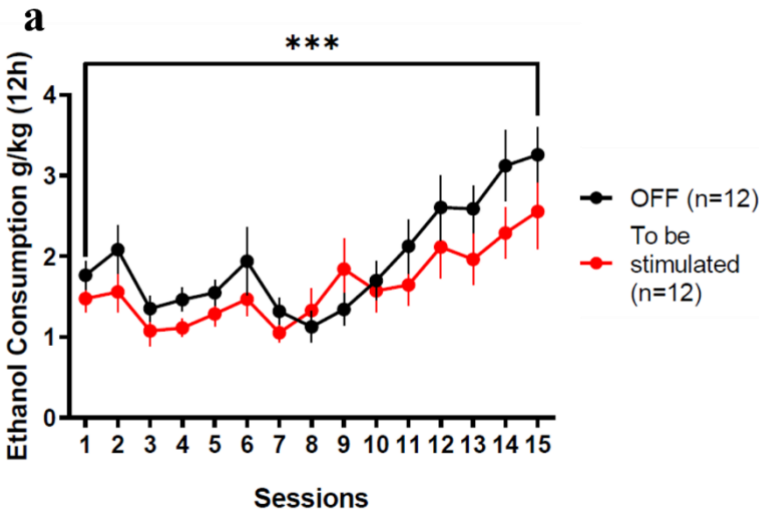
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# 3



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

Results are presented as mean  $\pm$  SEM.

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

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

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