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Peer's Presence Reverses Escalated Cocaine Intake in Rats

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1 **Title: PEER'S PRESENCE REVERSES ESCALATED COCAINE INTAKE**
2 **IN RATS**

3
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12
13 **One Sentence Summary:** The presence of a stranger peer drastically decreases cocaine intake
14 after drug escalation, as does a subthalamic optogenetic modulation.

15 **Abstract:** The immediate social context at the time of drug consumption is critical at modulating
16 it. The neurobiological substrate of such an influence is however poorly documented. The presence
17 of a stranger peer, naïve to the drug, has been shown to reduce recreational cocaine intake in rats
18 with similar results in human cocaine users. Here we assessed its influence in rats having
19 previously lost their control over drug consumption. The subthalamic nucleus (STN) has been
20 shown to play a critical role in cocaine motivation, escalation and re-escalation, as well as
21 compulsive drug seeking. We show here that after escalation of cocaine intake, the presence of a
22 stranger peer drastically reduced cocaine intake. The same effect was observed after both
23 optogenetic inhibition and high-frequency stimulation of the STN in absence of a peer. We further
24 show that the beneficial influence of social presence is mediated via the STN.

25 **Main Text:**

26 **INTRODUCTION**

27 There are currently no validated pharmacological agents for treating cocaine abuse. An alternative
28 is to use behavioral and social interventions. These therapies have been shown to be effective in
29 helping cocaine users regain the control on their drug consumption (1, 2), highlighting the key
30 influence of environmental factors on drug use and cessation. Although only few preclinical
31 studies took into account this environmental, or contextual, influence (3–5), social factors have
32 been shown to play a critical role in initiation, maintenance, attempt to quit and relapse of drug
33 use in both rodents and humans (6, 7). Positive social context in everyday life (*e.g.* parenting in
34 humans, maternal cares in rats) has a preventive effect on drug consumption (8, 9), while aversive
35 social interaction (*e.g.* children abuse in humans, repeated social-defeat in rats) or a lack of positive
36 social contact (*e.g.* loneliness in humans, isolation rearing or maternal separation in rats) leads to
37 an increasing risk to develop substance use disorders (SUD) (10–13). Proximal social factors, such
38 as the social presence during drug consumption, also affect the drug intake (14), depending on the
39 nature of the substance used (15), the relationship between the subject and the stimulus peer (16)
40 and the latter's behavior (*i.e.* self-administering or not; 15). In both rats and humans, the presence
41 of a drug-naïve stranger peer seems to represent the situation that decreases the most the

42 recreational cocaine intake(16). However, the influence of the peer's presence on addiction-like
43 behaviors, such as after a loss of control over drug consumption, remains to be investigated in rats,
44 as well as its neurobiological substrate.

45
46 Recent studies have suggested that the beneficial influence of proximal social factors on
47 recreational drug use could involve the subthalamic nucleus (STN) (18–20). Given its involvement
48 in inhibitory control (21–24) and motivation processes (25–27), the STN appears as a promising
49 target for the treatment of cocaine addiction (28). Rodent studies revealed that STN lesion or high-
50 frequency (HF) deep brain stimulation (DBS) both decreases motivation for cocaine and increases
51 motivation for sweet food in rats (27, 29). STN HF-DBS was also shown to prevent the
52 development of escalation and to further reduce re-escalation of cocaine or heroin intake (30, 31).
53 STN oscillatory activity would serve as a predictive biomarker of vulnerability to addiction. In
54 fact, manipulating STN activity with DBS bi-directionally influences compulsive-like cocaine
55 seeking (32). Although the neural effects of STN DBS remain to be clarified, it seems legitimate
56 to consider STN as a potential target to treat addiction.

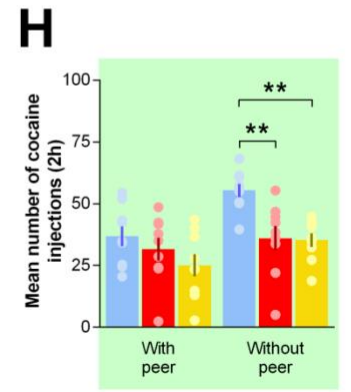
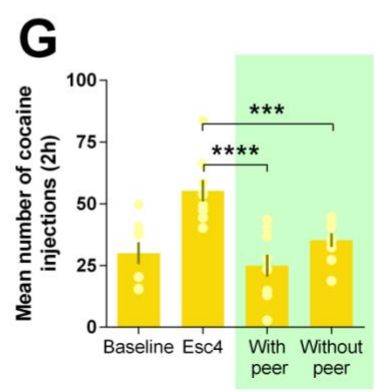
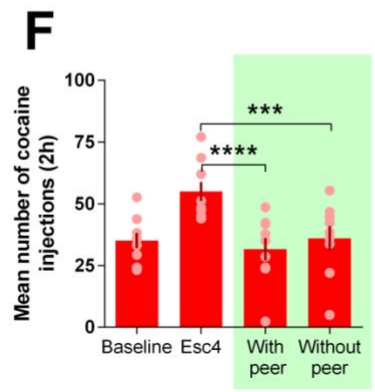
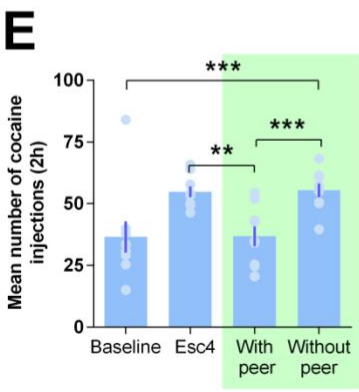
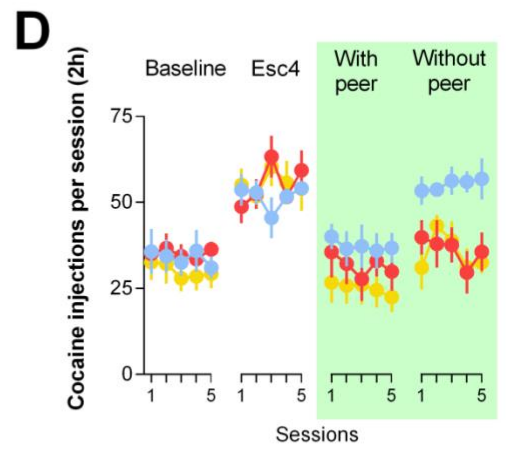
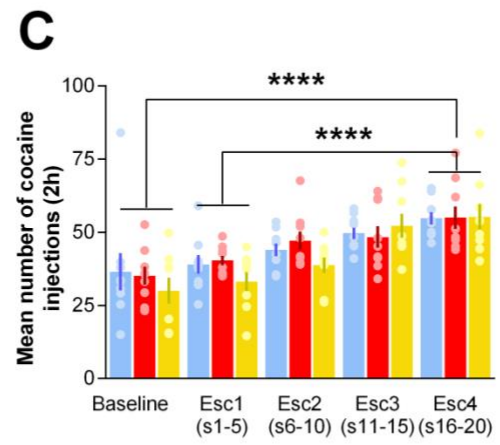
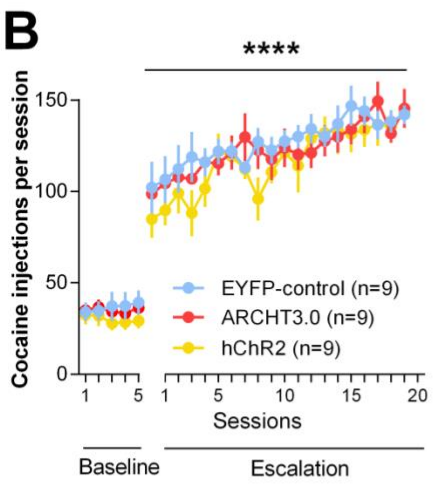
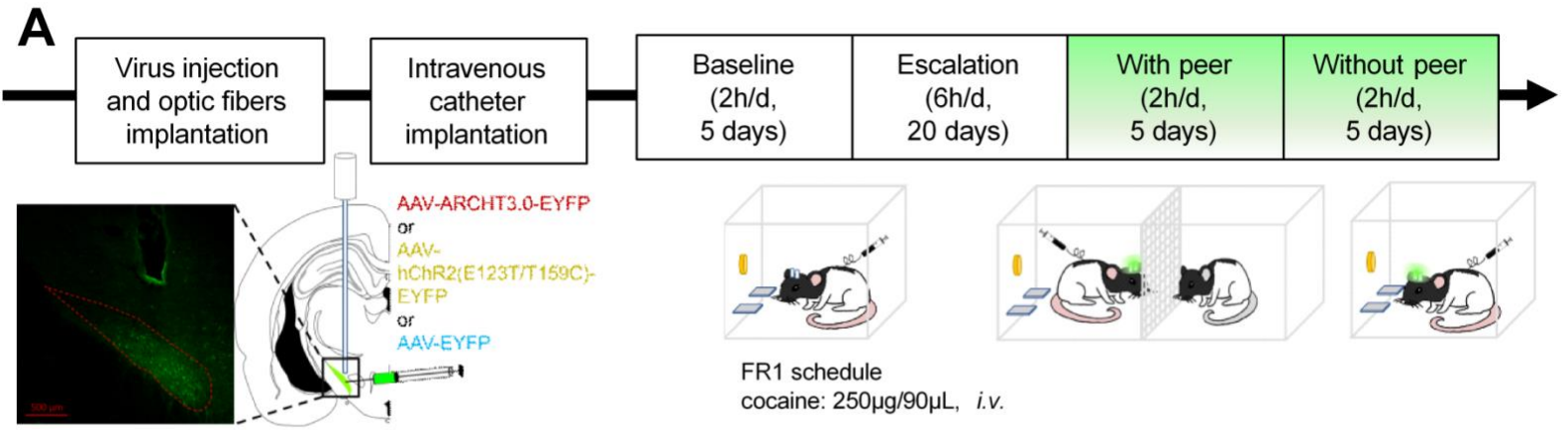
57
58 Here, we assessed whether the presence of a stranger peer, naïve to the drug can reduce cocaine
59 intake in rats having lost their control over cocaine intake. Following a cocaine escalation
60 procedure, we investigated how the presence of a peer affects cocaine intake. We further examined
61 the potential contribution of the STN in this social influence, using optogenetic to selectively
62 modulate its neuronal activity in presence or absence of the peer.

63

64 RESULTS

65 27 rats received bilateral injections of AAV5-CaMKII-EYFP (n=9, EYFP-control group), AAV5-
66 CaMKII-ArchT3.0-p2A-EYFP-WPRE (n=9, ARCHT3.0 group) or AAV5-CaMKII-
67 hChR2(E123T/T159C)-p2A-EYFP-WPRE (n=9, hChR2 group) into the STN, with optic fibers
68 implanted 0.4 mm above each injection site. They were trained to self-administer cocaine
69 (250µg/90µL, *i.v.* injections) under a fixed ratio 1 (FR1) schedule of reinforcement, with a f2h-
70 daily access to the drug. After stabilization of their basal cocaine intake (<25% variation for 5
71 consecutive days), animals were then subjected to an escalation procedure, consisting in a daily
72 6h-session of extended access to the drug during 20 days. Finally, they were tested for 2h self-
73 administration sessions in presence of a drug-naïve stranger peer for 5 consecutive days ('*With*
74 *peer*' condition). They were also allowed to self-administer cocaine for 5 consecutive days without
75 the presence of a peer ('*Without peer*' condition). The order of '*With peer*' and '*Without peer*'
76 conditions were counterbalanced between animals (Fig. 1A). The photo-modulation of STN
77 activity was only delivered during these 2h-sessions.

78



80 **Fig. 1 Peer's presence or STN optogenetic modulations reduce cocaine intake following drug**
81 **escalation.**

82 (A) Timeline of the behavioral experiment (upper part). Representative native fluorescence
83 emitted by transfected STN neurons and implanted optic fiber trace, with schematic coronal
84 section of the rat brain at the level of the STN, and schematic apparatus (bottom part). (B) Number
85 of cocaine injections received by EYFP-control (n=9, blue), ARCHT3.0 (n=9, red) and hChR2
86 (n=9, yellow) expressing animals during the five 2-h sessions of the baseline and the twenty 6-h
87 sessions of escalation (****: sessions effect during escalation) with the laser OFF. (C) Mean
88 number of cocaine injections received during the two first hours of the sessions in blocks of 5-
89 sessions (baseline, escalation: 'Esc1', 'Esc2', 'Esc3' and 'Esc4', corresponding respectively to
90 sessions 1-5, 6-10, 11-15 and 16-20). (D) Cocaine injections received during the two hours of the
91 baseline, the first two hours of 'Esc4', and the two hours sessions with the laser activated: 'With
92 peer' and 'Without peer'. (E,F,G) Mean number of cocaine injections received during the two first
93 hours of the sessions in 5-sessions blocks (baseline, 'Esc4', 'With peer', 'Without peer')
94 respectively in EYFP-control (E), ARCHT3.0 (F) and hChR2 (G) animals. (H) Mean number of
95 cocaine injections received during the two first hours of the sessions with the laser activated 'With
96 peer' and 'Without peer' in EYFP-control, ARCHT3.0 and hChR2 rats. In A, D-H, the green areas
97 correspond to the sessions with activation of the laser. In C,E,F,G: Each dot represents an
98 individual mean per block of 5 sessions. **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$

99 **All rats escalated cocaine consumption**

100 In absence of laser activation, all animals showed a stable baseline of cocaine intake (mixed 2-way
101 ANOVA, sessions effect: $F_{(4,96)}=2.058$, $p=0.5001$) and drastically escalated their consumption
102 during the 6h sessions of extended access to the drug ($F_{(19,456)}=12.59$, $p<0.0001$) (**Fig. 1B**). The
103 three groups took similar amount of cocaine during both the baseline (group effect: $F_{(2,24)}=0.4996$,
104 $p=0.6129$) and the 6h sessions of extended access to the drug ($F_{(2,24)}=0.6492$, $p=0.5314$). These
105 results were further confirmed by analyzing the mean number of cocaine injections took during
106 the two first hours of each session per block of 5 sessions (**Fig. 1C**; baseline, escalation: ‘Esc1’,
107 ‘Esc2’, ‘Esc3’, ‘Esc4’, groups effect: $F_{(2,24)}=0.6225$, $p=0.545$, 5-sessions blocks effect:
108 $F_{(4,96)}=25.15$, $p<0.0001$). Tukey’s post-hoc comparisons confirmed that rats consumed more
109 cocaine during ‘Esc4’ than during the baseline ($p<0.0001$), ‘Esc1’ ($p<0.0001$) and ‘Esc2’
110 ($p<0.0001$). We also controlled the fact that escalation of drug intake was due to the extended
111 access procedure by maintaining other animals (EYFP-control, $n=7$ and ARCHT3.0, $n=6$) in a
112 short access (2h) to cocaine during 20 days (same timeline used in the ‘escalation’ protocol, see
113 Supplemental). Only rats that had a long access to the drug escalated their cocaine intake during
114 the two first hours of the sessions (mixed 2-way ANOVA, long/short access x session interaction:
115 $F_{(4,91,132,65)}=3.37$, $p<0.007$, **Fig. S1A, Table S1-2**).

116 To assess the effect of the peer’s presence and the STN photo-modulation on cocaine intake, we
117 compared the number of cocaine injections took by 3 groups during the sessions of the baseline,
118 ‘Esc4’ (2 first hours), ‘With peer’ and ‘Without peer’ (**Fig. S1B**; mixed 3-way ANOVA). No effect
119 of sessions was found (results reported in **Table S3-4**). We thus averaged the sessions in blocks of
120 five sessions, corresponding to these various conditions. The results confirmed that the opsins
121 expression modulates cocaine intake depending on the conditions (mixed 2-way ANOVA; group
122 x condition interaction: $F_{(6,72)}=2.524$, $p=0.0284$). Similar results were found in animals maintained
123 in short access (condition x optogenetic group $F_{(3,33)}=5.781$, $p=0.0027$) (**Fig. S1B**). In contrast, the
124 number of errors or perseverations made by the animals remained unchanged during the entire
125 course of the experiment for all groups (**Fig. S2, Table S5-6**), suggesting that these conditions and
126 the STN photo-modulations specifically affected the responses towards the drug without side-
127 effects.

128 **Peer’s presence decreases escalated cocaine intake...**

129 In EYFP-control rats, the presence of a peer drastically reduced cocaine self-administration after
130 drug escalation (**Fig. 1E**; Tukey’s post-hoc analysis: $p=0.0014$, ‘With peer’ compared with
131 ‘Esc4’), similar to their basal level of consumption ($p>0.9999$ compared with baseline). In EYFP-
132 control animals maintained in short access, peer’s presence not only reduced cocaine intake
133 compared with ‘Esc4’ ($p=0.0009$), but also compared with the baseline ($p=0.0046$) (**Fig. S1C**).

134 **... Like the subthalamic nucleus optogenetic inhibition...**

135 The laser activation did not affect cocaine intake in EYFP-control animals ‘Without peer’, which
136 displayed an escalated-like level of cocaine intake ($p=0.9993$ ‘Without peer’ compared with
137 ‘Esc4’), consuming significantly more drug than during their baseline ($p=0.0009$).

138 In contrast, the STN photo-inhibition induced a drastic decrease in drug intake in ARCHT3.0 rats
139 ‘Without peer’ (**Fig. 1F**; $p=0.0007$ vs. ‘Esc4’ and $p=0.9973$ vs. baseline). Cocaine intake was
140 significantly lower in ARCHT3.0 rats than in EYFP-control ones in the ‘Without peer’ condition

141 (Fig. 1H; Sidak's post-hoc analysis: $p=0.0027$), confirming this beneficial effect of the STN photo-
142 inhibition.

143 In contrast, the STN photo-inhibition did not reduce cocaine use in ARCHT3.0 animals maintained
144 in short access sessions (Fig. S1D; $p=0.9808$, 'Without peer' compared to 'Esc4'). These rats
145 consumed similar amount of drug than EYFP-control animals 'Without peer', despite the laser
146 activation (Fig. S1E; $p>0.9999$). In line with previous reports (27, 29, 30), these results show that
147 the STN neuromodulation affects cocaine abuse, but not its recreational use.

148 ... Or its optogenetic HF-stimulation

149 Interestingly, the STN optogenetic HF-stimulation also reduced cocaine intake in hChR2
150 transfected rats 'Without peer' (Fig. 1G; $p=0.0003$ vs. 'Esc4' and $p=0.6759$ vs. baseline). These
151 animals also consumed less drug than EYFP-control rats 'Without peer' ($p=0.0018$). This results
152 shows that optogenetic HF-stimulation induces a similar behavioral effect than optogenetic
153 inhibition.

154 STN photo-modulations contribute to the beneficial effect of peer's presence

155 The presence of a peer also drastically reduced cocaine consumption in photo-activated
156 ARCHT3.0 ($p<0.0001$ vs. 'Esc4' and $p=0.8739$ vs. baseline), as well as in hChR2-transfected rats
157 ($p<0.0001$ vs. 'Esc4' and $p=0.7119$ vs. baseline). However, their level of consumption was not
158 lower than EYFP-control rats in similar condition ($p=0.5768$ vs. ARCHT3.0 and $p=0.0861$ vs.
159 hChR2). There was no significant difference between 'With peer' and 'Without peer' conditions
160 for both ARCHT3.0 ($p=0.7769$) and hChR2-transfected ($p=0.1361$) rats, in contrast to EYFP-
161 control ones ($p=0.0009$), confirming the lack of additivity in the effects of the STN photo-
162 modulations and the peer's presence. This indicates that of the reduction in cocaine intake observed
163 with STN photo-modulations or the peer's presence occluded each other.

164 Interestingly, the presence of a peer combined with STN photo-inhibition did not reduce cocaine
165 intake in ARCHT3.0 rats maintained in short access ($p>0.9999$ vs. 'Esc4' and $p=0.9996$ vs.
166 'Without peer'). These animals consumed significantly more cocaine than the EYFP-control rats
167 'With peer' ($p=0.0494$), suggesting that STN photo-inhibition blocked the beneficial effects of
168 social presence, for animals that had not escalated their cocaine intake.

169 These results suggest that the beneficial influence of the peer's presence is mediated via the STN.
170 Nevertheless, in social context, the STN neuromodulation interferes in a different manner with
171 recreational (*i.e.* suppression of social influence) and escalated drug use (*i.e.* occlusion of social
172 influence).

173

174 Electrophysiological assessment of STN photo-inhibition

175 To assess the efficacy of our optogenetic manipulations on STN neuronal activity, we performed
176 *in vivo* recordings in anesthetized animals and *ex vivo* patch-clamp recordings on brain slices. 30
177 naïve adult rats (not used for the behavioral experiment) were injected with AAV5-CaMKII-EYFP
178 ($n=3$), AAV5-CaMKII-ArchT3.0-p2A-EYFP-WPRE ($n=13$) or AAV5-CaMKII-
179 hChR2(E123T/T159C)-p2A-EYFP-WPRE ($n=14$). Recordings were performed 3-4 weeks
180 following the opsins injection.

181 Opsins expression did not deeply change the electrophysiological properties of the STN neurons,
182 as resting membrane potential (Kruskall-Wallis: $p=0.8214$), cell capacitance ($p=0.0644$),

183 membrane resistance ($p=0.7397$), access resistance ($p=0.3158$) and firing rate (mixed 2-way
184 ANOVA, Frequency x Group interaction: $F_{(30,390)}=0.2480$, $p>0.9999$) were equivalent between
185 EYFP-control ($n=3$ animals; $n=8$ cells), ARCHT3.0 ($n=7$ animals; $n=11$ cells) and hChR2 groups
186 ($n=5$ animals; $n=10$ cells) (**Fig. S3**). To confirm the efficacy of the optogenetic modulation, we
187 first applied discrete light pulses on STN neurons (**Fig. S4**). Longer pulse-width duration and
188 higher light intensity elicited higher inhibitory currents in ARCHT3.0 positive cells (At 5mW,
189 effect of pulse duration; $\chi^2(5)=51.88$, $p<0.0001$, Dunn's post-hoc test: $p<0.0100$ vs. 1s pulse and
190 $p<0.0010$ vs. 10s, 15s or 20s pulse). Consistent with previous reports (33), our these results suggest
191 that higher laser activation (*i.e.* increased pulse duration and brighter illumination) leads to higher
192 activation of opsins and increases the transmission through a larger volume of tissue, thereby
193 recruiting a larger pool of neurons. To further assess the effect of optogenetic inhibition, electrical
194 stimuli (10Hz, injected current: rheobase + 20-130pA) were delivered to STN neurons, to evoke
195 actions potentials before applying photo-inhibition (**Fig. 2A**). A 15s light-pulse delivered to
196 ARCHT3.0-expressing neurons successfully inhibited neuronal firing (**Fig. 2B**, $p=0.0006$). We
197 then applied the same light pattern than during the behavioral experiments (*i.e.* alternation of a 15s
198 period ON followed by a 5s period OFF, for 5min) on other ARCHT3.0-transfected cells ($n=2$ rats,
199 $n=7$ cells) (**Fig. 2C**). Photo-inhibition of STN neurons leads to reduced firing rate of STN neurons
200 (**Fig. 2D**; Dunn's post-hoc test: $p=0.0323$ vs. baseline), which was resumed when the laser was
201 stopped ($p=0.9999$). This confirmed that our photo-inhibition protocols were efficiently at
202 inhibiting STN neurons.

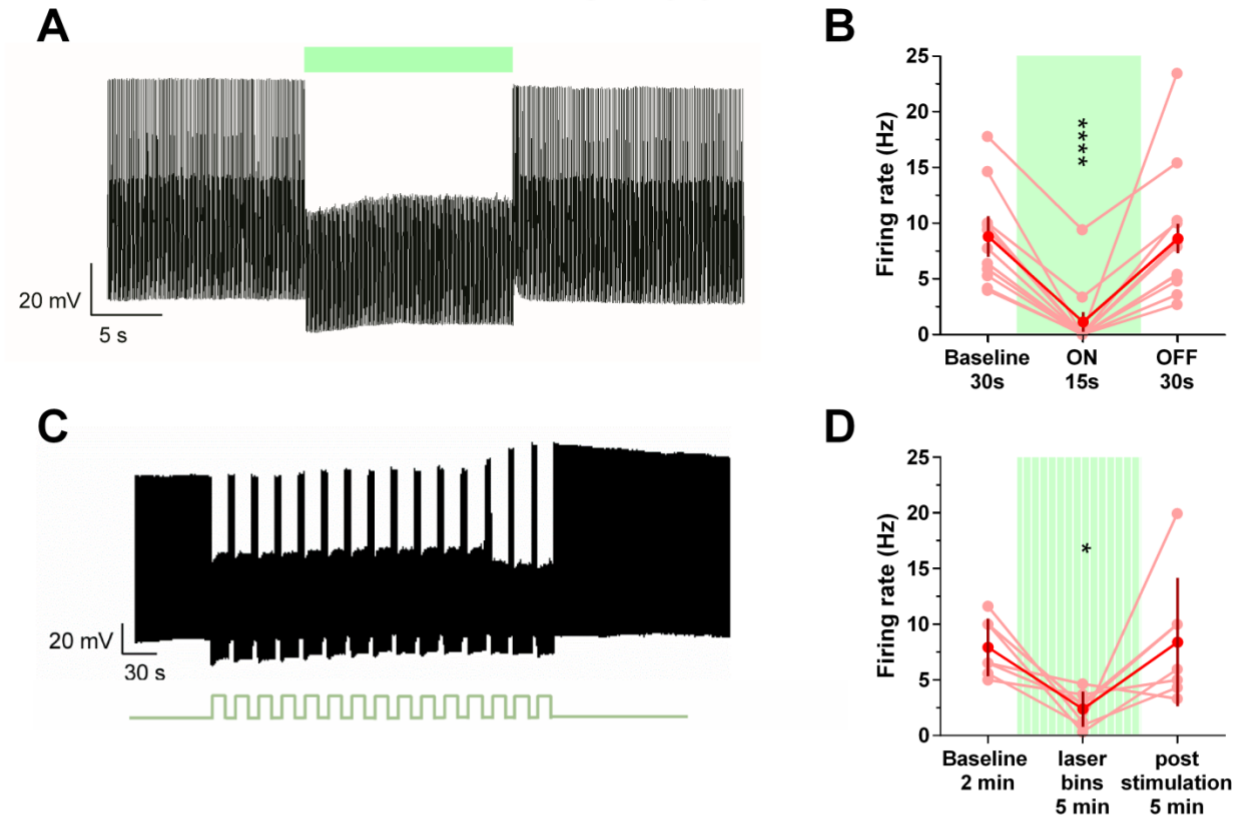
203 To control the effects of the STN photo-inhibition in *in vivo* conditions, we performed extracellular
204 recordings in ($n=4$) anesthetized animals, which STN neurons had been transfected with
205 ARCHT3.0-AAV. To estimate the population response, the neuronal firing of STN neurons was
206 normalized to the 20s baseline prior photo-modulation. In ARCHT3.0 transfected rats, a 15s light-
207 pulse (5 mW) successfully inhibited neuronal firing in STN neurons (**Fig. 2E,F**, Dunn's post-hoc
208 test: $p<0.0001$ vs. baseline, $n=16$ cells) but did not impact neuronal activity during the intermittent
209 5s OFF periods ($p=0.959$), as observed in our ex vivo preparations. As a result, the normalized
210 firing rate frequency in ARCHT3.0-transfected neurons significantly diminished during the 180s
211 of laser bins (composed of alternation of 15s ON/5s OFF periods) compared with their baseline
212 activity (**Fig. 2G**; $p<0.0001$ vs. baseline) . STN firing activity during the 20s following the laser
213 bins was similar to the baseline ($p>0.9999$).

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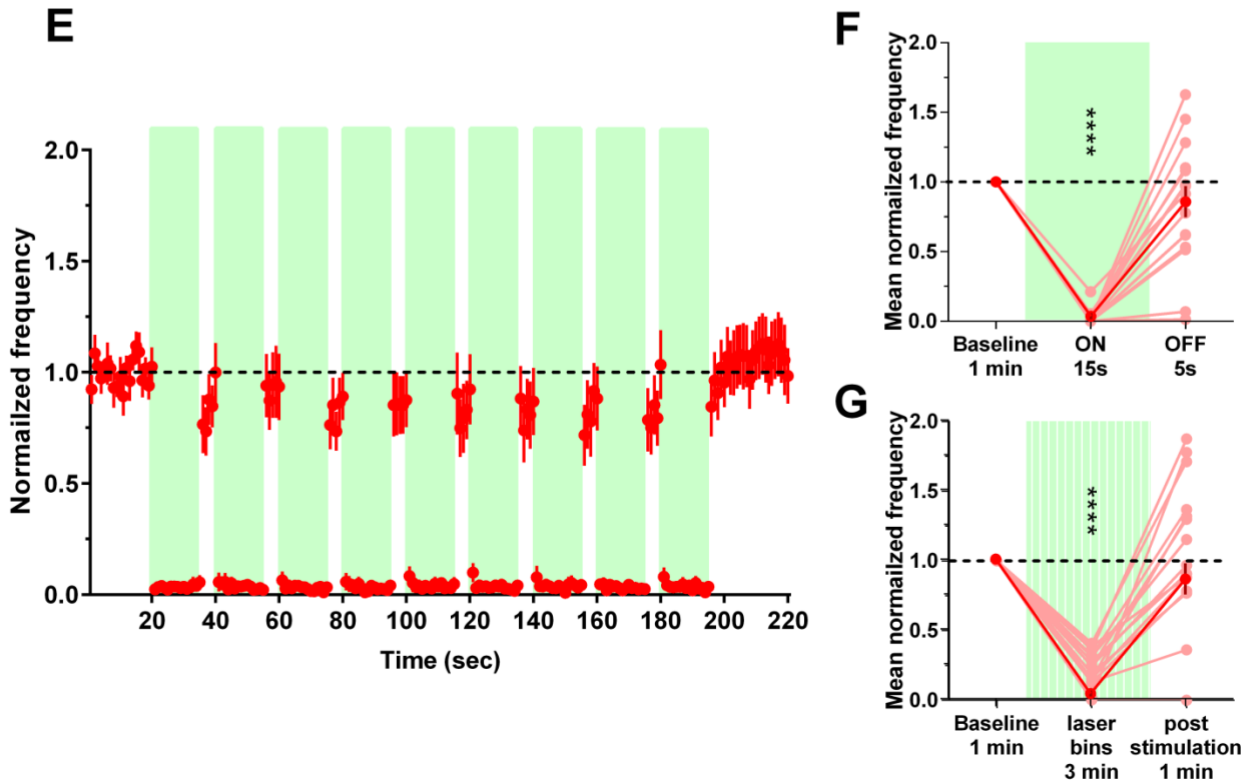
216 **Fig. 2 Electrophysiological assessment of STN optogenetic inhibition.**
217 (A) Typical response recorded in one STN neuron expressing ARCHT3.0 driven at a 10Hz
218 frequency undergoing 15s of photo-inhibition (green line: laser ON). (B) Firing rate in ARCHT3.0-
219 expressing STN neurons was reduced by a single 15s light pulse (n=11 cells). (C) Example of
220 response for an ARCHT3.0-transfected STN neuron during 5 min of laser activation applied with
221 the same pattern as during behavioral experiments (*i.e.* alternations of 15s ON, interleaved with 5s
222 OFF, for 5min). (D) Firing rate in STN neurons expressing ARCHT3.0 was reduced by 5min of
223 laser application at this pattern (n =7 cells). (E) Normalized frequency in ARCHT3.0-transfected
224 STN neurons during 20-s of baseline recording, followed by 180-s of laser activation with the
225 same pattern and 20s post stimulation (n=16 cells). (F) 15s laser activation (ON-15s), but not 5s
226 of obscurity (OFF-5s) reduced the mean normalized frequency in ARCHT3.0-transfected STN
227 neurons, compared with their baseline activity (n=16 cells). (G) 180-s of laser bins diminished the
228 mean normalized frequency in STN neurons, compared with their baseline activity. Following
229 180-s of laser bins, these cells returned to their baseline level of activity. Full green area
230 corresponds to continuous laser activation. Hatched green area corresponds to laser bins. In
231 **B,D,F,G**: Each light red dot and line represents an individual value. Dark red dot and lines
232 correspond to the mean and SEM.
233 *: $p < 0.05$, ****: $p < 0.0001$.

234

Ex vivo photo-inhibition of STN neurons transfected with ARCHT3.0



In vivo photo-inhibition of STN neurons transfected with ARCHT3.0



236 Electrophysiological assessment of STN optogenetic HF-stimulation

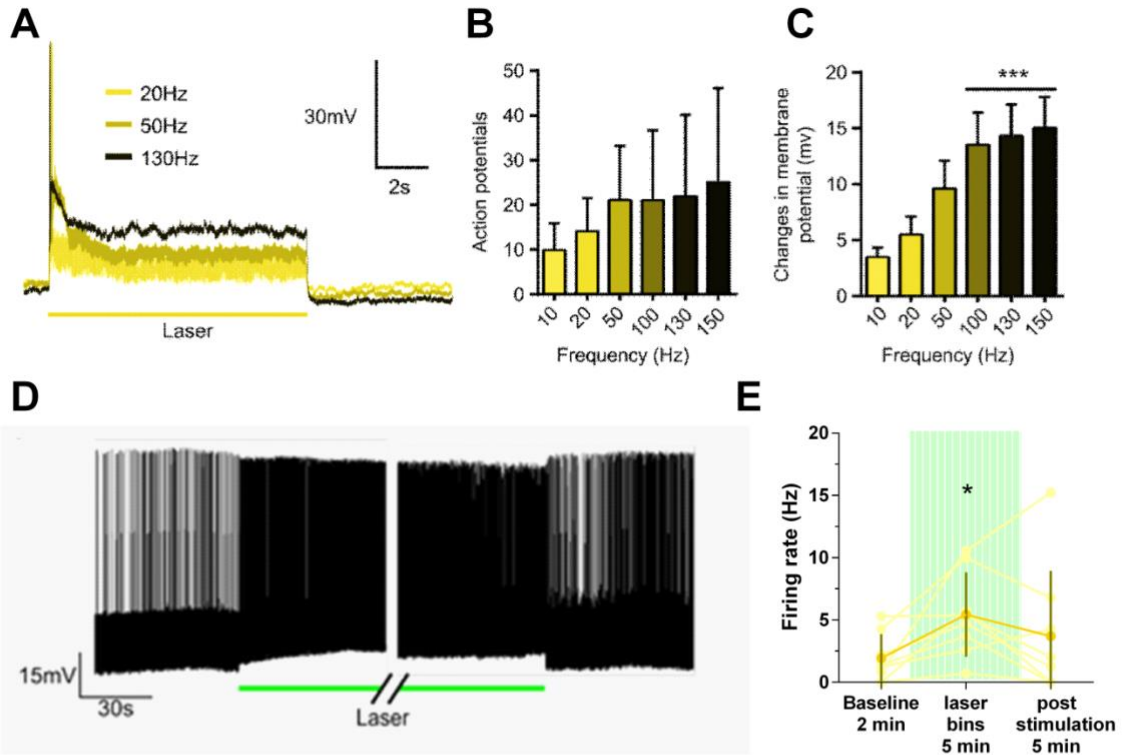
237 When discrete light pulses were applied *ex vivo* in (n=10) hChR2-expressing STN neurons, longer
238 pulse-width duration and higher light intensity elicited higher depolarizing currents (intensity set
239 at 10mW, effect of pulse duration: $\chi^2(5)=46.00$, $p<0.0001$, Dunn's post-hoc test: 0.5ms pulse
240 $p<0.001$ vs. 4ms pulse and vs. 5ms pulse; at 1s pulse duration, effect of light intensity: $\chi^2(3)=28.92$,
241 $p<0.0001$, 2.5mW $p<0.01$ vs. 10 mW and $p<0.001$ vs. 20mW, **Fig. S4D-G**). The effects of
242 optogenetic stimulation were assessed in STN neurons with 10s of laser illumination at various
243 frequencies (**Fig. 3A**). Interestingly, higher frequencies of laser stimulation did not change the
244 number of action potentials compared to lower frequencies (**Fig. 3B**). However, higher frequencies
245 significantly increased membrane potential ($p<0.001$ for 100-, 130- and 150-Hz vs. 10-Hz; **Fig.**
246 **3C**), suggesting that this pattern increased the excitability of STN neurons. To test this hypothesis,
247 we applied a 10Hz electrical stimulation in other hChR2-transfected STN neurons (n=2 rats, n=8
248 cells) (injected current: Rheobase +0-50pA) to evoke a few action potentials. We then applied
249 130Hz laser stimulation for 5min (**Fig. 3D**), which significantly increased the firing rate of STN
250 neurons ($p<0.0351$, **Fig. 3E**). Following cessation of the photo-stimulation, the firing rate was no
251 longer different from the baseline period ($p>0.05$). This suggests that 130Hz optogenetic
252 stimulation is unlikely to induce action potentials on its own but increases STN neurons
253 excitability.

254 In a set of hChR2-transfected rats (n=7 animals; n=16 cells), the impact of STN HF-stimulation
255 (130 Hz during 3 min) was also assessed *in vivo*. To estimate the population response, the neuronal
256 firing of STN neurons was normalized to the 1 min baseline prior to photo-modulation. Although
257 the overall population increased its firing rate during light application (**Fig. 3F,G**), about half of
258 the cells (n=7) did not modify their firing rate (non-responding cells; $p>0.9999$ baseline vs. laser
259 bins). In contrast, the impact of STN HF photo-stimulation was strongly marked in 9 neurons
260 (responding cells; $p=0.0019$ compared with baseline). These cells returned to their basal level of
261 activity when the photo-stimulation was turned OFF ($p>0.9999$ compared with baseline).

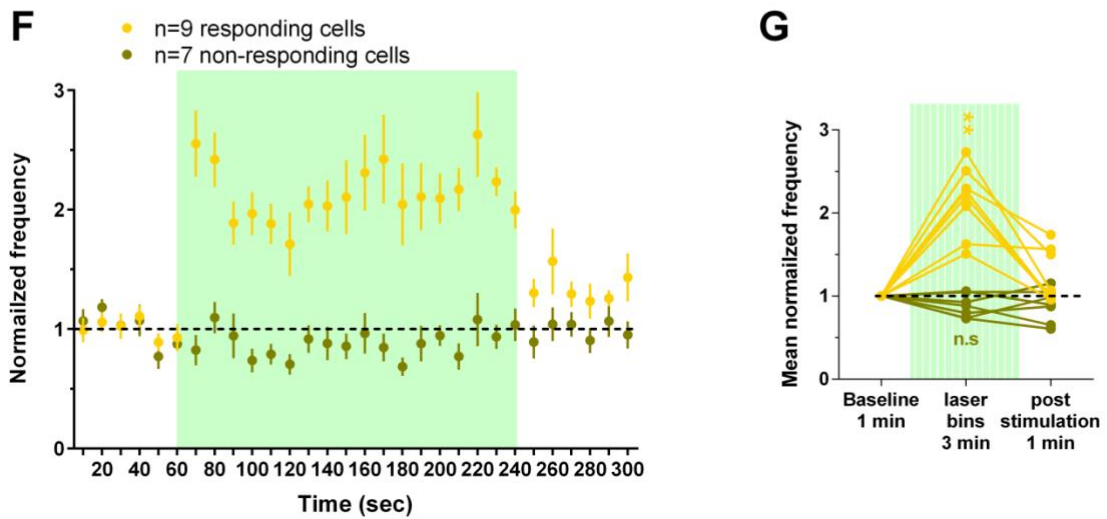
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263 **Fig. 3 Electrophysiological assessment of STN optogenetic HF-stimulation.**
264 (A) Typical excitatory response recorded in current-clamp for a STN neuron expressing hChR2
265 and facing 10s of laser stimulation at various frequencies: 20 (light yellow), 50 (dark yellow) and
266 130Hz (black), eliciting a few action potentials but increasing membrane potential. (B) Number of
267 action potentials elicited during 10s of photo-stimulation (n=10 cells). (C) Variation of membrane
268 potential caused by the 10s optogenetic stimulation at various frequencies (n=10 cells). (D)
269 Example of response in hChR2 positive STN neuron at onset (left panel) and offset (right panel)
270 of 5min laser stimulation at 130Hz (green line) used during behavioral testing. (E): Average
271 changes in firing rate induced by 5 min of 130Hz laser stimulation (n=8 cells). Light dot and lines
272 represent individual values. Dark line and dot correspond to the mean and SEM. (F) Normalized
273 frequency in responding (light yellow; n=9) and non-responding (dark yellow; n=7) hChR2-
274 expressing STN neurons during 1min of baseline recording, followed by 180s of HF photo-
275 stimulation (at 130Hz) and 1 min post stimulation. (G) Mean normalized frequency during
276 baseline, HF photo-stimulation and post-stimulation in responding and non-responding cells.
277 Full green area corresponds to 130Hz laser stimulation.
278 *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Ex vivo HF photo-stimulation of STN neurons transfected with hChR2



In vivo HF photo-stimulation of STN neurons transfected with hChR2



280 DISCUSSION

281 Here, we showed that the presence of a stranger peer, naïve to the drug, leads to a drastic reduction
282 of cocaine consumption in rats after they had previously lost the control over their drug intake
283 during cocaine escalation. In these animals, although the duration of the sessions was then reduced
284 (from 6 to 2h sessions), cocaine intake remained higher than for animals not exposed to escalation
285 procedure, in line with Ahmed et Koob (34). Laser activation, with various parameters, had no
286 effect in EYFP-control, indicating that laser light did not influence cocaine self-administration *per*
287 *se*. In contrast, both STN optogenetic inhibition and HF-stimulation reduced cocaine consumption
288 after escalation, in line with electric DBS former study (30). This reduction was however not
289 further modulated by the presence of a peer.

290 Expanding upon our former results showing that the presence of a drug-naïve stranger observer
291 could reduce cocaine intake in rats only exposed to short access sessions (16), we showed here a
292 similar effect, even after they had lost the control over their drug consumption in the escalation
293 procedure. In this present experiment, the stranger peer has been changed every day, preventing a
294 possible habituation effect, as confirmed by the statistical analysis showing no changes across the
295 five repeated sessions. This lack of familiarity with the peer present during drug consumption
296 could be responsible for the beneficial influence of the presence of a peer. Social novelty has
297 indeed been shown to be highly rewarding in laboratory rats (16, 35). Of note, we only tested male
298 individuals, mainly because they are known to be more sensitive to social context (35). To fully
299 address the influence of social context and gender differences on drug use, female subjects would
300 have to be included in future investigations. Indeed, female rats acquire self- administration
301 behavior more rapidly (36), and escalate their drug intake (37) quicker than male rat, a feature also
302 observed in human drug users (38). Nevertheless, from our results, the presence of a stranger
303 individual, not consuming the drug, would have a beneficial effect against SUD, in favor of the
304 wider implementation of consumption rooms and socially based SUD therapeutics.

305 However, the presence of a peer does not always play a protective role on drug use. It was shown
306 that when two rats learn to take drug together, the peer's presence facilitates the acquisition of
307 drug self-administration (14, 39). Similarly, when cocaine availability has been paired with the
308 presence of an observing congener, the latter can later induce drug craving and relapse (40).
309 Altogether, these findings indicate that the presence of a peer differentially influences drug intake,
310 depending on the contingency between social contact and drug use, but also depending on the
311 observer's behavior (*e.g.* also self-administering drug or not) and its relationship with the focal rat
312 (*e.g.* familiarity or dominancy). Like others (4, 41), we thus argue here that considering the social
313 context in animal models of SUD is necessary to address the translational crisis in addiction
314 research, and would, ultimately, lead to the development of effective treatments for SUD.

315 STN photo-inhibition and HF photo-stimulation drastically reduced cocaine consumption after a
316 loss of control over drug intake. This result is somewhat surprising, because we previously showed
317 that electric STN HF-DBS reduced cocaine intake after escalation only after a protracted
318 abstinence period (35 days), but not when applied immediately after drug escalation (30). Yet, a
319 key finding from Pelloux et al., (30) study was the wider development of low frequency neuronal
320 oscillations in the STN during the process of cocaine escalation. These oscillations are known to
321 drive abnormally synchronized oscillations in the basal ganglia network of parkinsonian patients,
322 as well as parkinsonian-like rats (42) and are further suppressed by STN pharmacological lesion
323 or reduced by its electrical HF-DBS (43, 44). A recent computational study (45) showed that both
324 STN optogenetic HF-stimulation and inhibition are more efficient than its electrical HF-DBS to

325 suppress this abnormal synchronized oscillatory activity in basal ganglia. Here, the fact that STN
326 optogenetic photo-modulations drastically decreased cocaine consumption immediately after drug
327 escalation could thus rely on this higher efficiency at suppressing STN-driving low frequency
328 oscillatory activity in the basal ganglia network. Nonetheless, from a translational point of view,
329 our results confirm the beneficial effect of STN neuromodulations as a potential treatment for
330 SUD, as suggested previously (27–32, 46, 47).

331 Surprisingly, photo-inhibition and photo-activation of STN neurons in ARCHT3.0 and hChR2
332 groups, respectively, both reduce the cocaine intake of animals that had previously escalated their
333 cocaine intake. Of note, our behavioral experiment relies on the use of home-made self-
334 administration chambers and control system. This latter did not allow us to discriminate rats’
335 behaviors during the laser bins (*i.e.* 5min ON and OFF periods). Such kind of analysis would allow
336 us to better understand the similar effect induced by these opposite STN neuromodulations. Yet,
337 it has already been shown that chemically-induced inhibition of the STN or its electrical HF
338 stimulation both reduce motivation to work for cocaine (see for instance 24, 26). This was
339 explained by the fact that HF-DBS is consensually thought to inactivate the cell bodies, while
340 stimulating the passing fibers. On the other hand, our electrophysiological recordings of STN
341 neuronal activity confirmed the efficacy of the opsins used in the behavioral experiment and
342 showed inhibition of STN neurons activity in ARCHT3.0 and neuronal activation in hChR2
343 groups, even when the stimulation was applied at 130 Hz. A general side-effect such as tissue
344 heating due to long-lasting laser activation (48) in behavioral experiments seems unlikely since
345 the different patterns of laser activation had no effect in the control group. Nevertheless, in a study
346 using different parameters of laser stimulation, repetitive optogenetic stimulation of CHETA-
347 transfected amygdala inputs to the prefrontal cortex was shown to induce a long-lasting synaptic
348 depression (49). Further electrophysiological recordings of the STN-related network efferent
349 structures would be necessary to highlight their possible inhibition by STN optogenetic HF-
350 stimulation. For example, it is plausible that photo-activation of STN neurons would stimulate
351 GABAergic neurons of the external Globus Pallidus, which would in turn increase their inhibitory
352 tone on STN neurons, thus mimicking the effects of photo-inhibition of STN neurons.
353 Alternatively, both STN optogenetic HF-stimulation and inhibition may effectively suppress
354 abnormal low frequency oscillations (40) associated with cocaine escalation (27), through different
355 mechanisms of action, thereby reversing the loss of control over drug abuse.

356

357 In both ARCHT3.0 and hChR2 groups, cocaine intake was reduced in such manner that it could
358 not be further diminished by the presence of a peer. This could be due to a floor effect: the STN
359 optogenetic modulation by itself could indeed have reduced cocaine consumption at its maximum.
360 Indeed, in the control group, the presence of a peer diminished the drug intake to its baseline level,
361 whereas the laser activation similarly reduced it in the ‘Without peer’ condition in both STN
362 optogenetic HF-stimulation and inhibition groups. At such a low level of drug use, it is therefore
363 possible that any additional protective factor would not reduce further drug consumption.
364 Nevertheless, the fact that peer’s presence decreased recreational cocaine consumption (in those
365 animals remaining in short access sessions with no escalation; see Supplemental) only in EYFP-
366 control, but not in ARCHT3.0 rats, makes it unlikely. Thus, the fact that STN optogenetic
367 manipulations and peer’s presence induce a similar effect without potentiating each other strongly
368 suggests an interaction between these manipulations, implying that the influence of social contact
369 on drug use relies on a neurobiological network involving the STN. It is noteworthy that in Giorla

370 et al. (16), STN-lesioned rats only exposed to short access sessions of cocaine self-administration
371 reduced their recreational cocaine intake in presence of a peer, like sham-control animals. This is
372 different to what is reported here when STN neurons were inhibited in the short access group. This
373 discrepancy can be explained by the fact that our experimental designs were drastically different
374 (e.g. same stranger observer for 5 days vs. novel stranger every day). Notably, it is possible that
375 the STN lesions induced compensatory mechanisms in the STN network, that are not observed
376 during its acute optogenetic inhibition.

377 Finally, further studies are needed to unravel the role of the STN in the influence of social contact
378 on drug use, as well as the cellular mechanisms involved. It has been shown that social reward
379 induces an oxytocin release in the brain reward system in mice (50, 51), highlighting an overlap
380 between social and drug rewards neural circuitry (52). Interestingly, oxytocin also acts within the
381 STN to locally regulate dopaminergic neurotransmission in rats (53). An acute intra-ventricular
382 injection of oxytocin was shown to be sufficient to normalize cocaine-induced *c-fos* activity in the
383 STN, and to prevent reinstatement of cocaine seeking (54). Oxytocin transmission within the STN
384 may thus play a critical role in the results obtained in the present study.

385

386 **MATERIALS AND METHODS**

387 **Study design**

388 This study aims at assessing whether the presence of a peer and the modulation of STN neuronal
389 activity can modulate cocaine intake in rats having lost their control over cocaine intake. Animals
390 were thus injected AVV in their STN and implanted with optic fiber to allow the pho-modulation
391 of STN activity. For the all behavioral experiment, hChR2 and ARCHT3.0 groups were
392 interleaved with EYFP-control ones. Group assignment for viral injections was also randomly
393 assigned, such as animals were randomized by cage during the all experiment. In case of missing
394 data for an animal in a given session (due, for instance, to catheter disconnection), the average of
395 the two closest days of cocaine injections in the same condition was used. Animals were excluded
396 from the study after histological assessments (see section Histology) by an experimenter
397 blinded to the experimental conditions. Experimental group sizes were determined by taking into
398 account historical accuracy within our group for stereotactic targeting of a given brain region.

399 **Animals**

400 72 male Lister Hooded rats (Charles River Laboratories, Saint-Germain-sur-l'Arbresle, France)
401 weighing ~320 g at their arrival were used in the behavioral experiment. Only male rats were used
402 in this study, because social interaction has been reported to be more rewarding for them than for
403 females (35). Animals were housed in pairs with unlimited access to water and food (Scientific
404 Animal Food and Engineering, Augy, France). They were maintained in a temperature-controlled
405 room, under a 12-hour inverted light/dark cycle, with all experiments conducted during the dark
406 cycle (7am-7pm). Rats used as observer peer and electrophysiological recordings lived in the same
407 conditions and had similar age and weight. Animals were handled daily. All animal care and use
408 were conformed to the French regulation (Decree 2010-118) and approved by the local ethic
409 committee and the French Ministry of Agriculture under the license #3129.01 and followed the 3R
410 European rules.

411 **Virus**

412 To transfect STN neurons, we used AAV5 with the recombinant protein expression under
413 CamKIIa-promoter control (UNC Vector Core, Chapel Hill, USA). The EYFP-control,
414 ARCHT3.0 and hChR2 groups received respectively the following AAV5 constructs: AAV5-
415 CaMKII-EYFP, AAV5-CaMKII-ArchT3.0-p2A-EYFP-WPRE and AAV5-CaMKII-
416 hChR2(E123T/T159C)-p2A-EYFP-WPRE.

417 **Surgeries**

418 Once rats reached ~400g, they were anesthetized with ketamine (Imalgene, Merial, 100 mg/kg,
419 *i.p.*) and medetomidine (Domitor, Janssen 30 mg/kg, *i.p.*), reversed at the end of the surgical
420 procedure with an injection of atipamezole (Antisedan, Janssen, 0.15 mg/kg, *i.m.*). They also
421 received an antibiotic treatment with amoxicillin (Duphamox, LA, Pfizer, 100 mg/kg, *s.c.*) and
422 were administered meloxicam (Metacam, Boehringer Ingelheim, 1 mg/kg, *s.c.*) for analgesia.
423 Animals were then placed in the stereotaxic frame (David Kopf apparatus) for 0.45 μ L bilateral
424 injections of virus into the STN (with tooth bar set at -3.3 mm), at the following coordinates :
425 anterior/posterior = -3.7 mm ; lateral = \pm 2.4 mm from bregma ; dorsoventral = -8.35 mm from
426 skull; from Paxinos & Watson, (55). For behavioral tests, optic fibers were implanted 0.4 mm
427 above each injection site and maintained within a head-cap made of dental cement anchored on
428 the skull.

429 After a week, rats assigned to behavioral testing were also subjected to intra-jugular implantation
430 of a catheter. Using standard surgical procedures (27) and the same anesthetic procedure than for
431 the stereotaxic surgery, silicon catheters were inserted into the right jugular vein and exited
432 dorsally between the scapulae. The catheters were then flushed daily with a sterile saline solution
433 containing heparin (Heparin Sodium, Sanofi, 3g/L) and enroflorilexine (Baytril, Bayer, 8g/L)
434 during all the experiment to maintain their patency and to reduce infection risk. Rats were then
435 allowed 10 days for recovery.

436 At the end of the experiment or after a session in case of doubt, catheters were tested with propofol
437 (Propovet, Abbott, 10 mg/ml) to confirm their patency.

438

439 **1 - Behavioral experiment**

440 **Apparatus**

441 Homemade self-administration chambers (60x30x35cm) divided into two compartments separated
442 by a metallic grid were used in this experiment. The wall of one compartment per cage was
443 equipped with two levers and a central light. All the chambers described above were controlled by
444 a custom-built interface and associated software (built and written by Y. Pelloux).

445 **Experimental procedure of cocaine self-administration**

446 Before the start of the session, catheters of rats were connected to cocaine syringes positioned on
447 motorized pumps (Razel Scientific Instruments, St-Albans, VT, USA), via infusion lines and liquid
448 swivels. The cocaine injection was assigned to one of the two levers (“active lever”) and
449 counterbalanced between rats. An FR1 schedule of reinforcement was used, implying that each
450 lever pressing on the active lever delivered an intravenous infusion of cocaine (250 μ g per 90 μ l
451 infusion in 5s) and switched ON the cue-light during cocaine delivery. Each injection was followed
452 by a 20-s time-out period, during which any further lever press on the active lever was recorded as

453 perseveration but had no consequence. Pressing on the other lever (“inactive lever”) was recorded
454 but had no consequence.

455 Rats were first trained to self-administer cocaine for 2-h daily sessions. Once consumption became
456 stable (<25% of variability in the number of cocaine injections for 5 consecutive days) –
457 considered here as the baseline consumption - they were exposed to 6-h daily sessions of cocaine
458 self-administration for 20 days. Starting at day 10, rats’ optics fibers were connected to the optic
459 coupler, with the laser OFF, during the 2 first hours of the sessions, for habituation to the cables.

460 After completion of the escalation, rats were exposed to 10 others 2-h sessions of cocaine self-
461 administration, with laser stimulation (ON). This condition was composed of two blocks of 5 five
462 consecutive days, during which rats would self-administer cocaine alone or in presence of an
463 observer peer, placed in the other compartment of the cage. Because we already showed that STN
464 optogenetic modulations alter social recognition memory (Vielle et al., unpublished), the observer
465 peer was different every day. The orders of the conditions ‘Without peer’ vs ‘With peer’ and the
466 presentation of the observers (5 individuals, in total) were counterbalanced between rats.

467 **Optogenetic manipulation during behavioral testing**

468 Homemade optic fibers (230 μ m, Thorlabs) were connected to a 200mW 532nm DPSS laser via an
469 optic coupler (FCMM625-50A, Thorlabs). Light pulses were generated under the control of a
470 signal generator (DS8000 Digital Stimulator, World Precision Instruments) at the following
471 parameters: 2ms light pulse at 130Hz pulse train for STN HF-stimulation and 15s light pulse at
472 0.2Hz pulse train for STN inhibition. During the experiment, the light pulses were discontinuous,
473 with 5-min bins of light ON, interleaved with 5-min bins of light OFF. Before experiments, light
474 power at fiber tip was set, using a power meter (PM20A, Thorlabs), at 10mW for STN HF-
475 stimulation and 5mW for inhibition. Control rats were randomly assigned to one light stimulation
476 condition for the whole experiment. The effects of these light delivery parameters on the STN
477 neurons firing pattern were tested in vitro and in anesthetized animals (see above).

478

479 **2 – Intracellular *ex vivo* recordings of STN neuronal activity**

480 Animals were anesthetized with intraperitoneal injection of ketamine (Imalgene, Merial, 200
481 mg/kg) and medetomidine (Domitor, Janssen 60 mg/kg) and perfused intra-cardiacally with ice-
482 cold artificial cerebrospinal fluid (ACSF). 200 μ m coronal slices containing the STN were
483 prepared in ice-cold ACSF with a vibratome (1200S, Leica). After being cut, the slices were
484 maintained for 10 minutes at 33°C and then transferred to holding ACSF at room temperature.
485 ACSF used for perfusion, cutting, and recovery contained NMDG as a sodium substitute and
486 contained, in mM: 92 NMDG, 2.5 KCl, 1.25 NaH₂PO₄, 30 NaHCO₃, 20 HEPES, 25 glucose, 2
487 thiourea, 5 Na-ascorbate, 3 Napyruvate, 0.5 CaCl₂ and 10 MgSO₄-7H₂O (pH: 7.35). ACSF used
488 for holding slices prior to recording was identical but contained 92 mM NaCl instead of NMDG
489 and contained 1 mM MgCl and 2 mM CaCl₂. ACSF used to perfuse slices during recording was
490 maintained at 31°C and contained, in mM, 125 NaCl, 2.5 KCl, 1.25 NaHPO₄, 1 MgCl, 2.4 CaCl,
491 26 NaHCO₃ and 11 glucose. All ACSF preparations were saturated with 95% O₂ and 5% CO₂.
492 Cells were patched using glass pipets with resistance 3.5-5.0M Ω , filled with internal solution
493 containing, in mM, 140 potassium gluconate, 5 NaCl, 2 MgCl₂, 10 HEPES, 0.5 EGTA, 2 ATP,
494 0.4 GTP (pH: 7.35). Series resistance was monitored during experiment with 10mV
495 hyperpolarizing pulses and maintained below 20M Ω , or cells were discarded. Firing pattern of

496 STN neurons was determined by injecting depolarizing currents during 500ms with 20pA
497 increment steps.

498 Cells were visualized on an upright microscope with infrared differential interference contrast and
499 fluorescence microscopy (Olympus, BX51WI). Recordings were made with pClamp 10.3 software
500 using a MultiClamp 700B amplifier set with 4 kHz low-pass Bessel filter and 10 kHz digitization
501 (Molecular Devices, Sunnydale, CA). The light beam of the same laser was directed at the
502 preparation using an 200 μ m optic fiber submerged into the bath with light beam aimed at the STN.
503 Laser intensities were adjusted to match those used in behavioral experiments.

504 Cells were imposed a given rhythm through current injection. Cells expressing inhibitory opsins
505 ARCHT3.0 were driven at 10Hz, with injected current intensity corresponding to rheobase + 20-
506 130pA in order to induce stable and robust firing pattern. Cells expressing excitatory opsins hChR2
507 were driven at 10Hz, intensity set at +0-50pA to elicit a few action potentials in a stable pattern.
508 Stability of the excitation was assessed through a 2min baseline recording, then we applied the laser
509 patterns used for behavioral experiments for 5min and the cells were monitored for another 5min
510 with the laser OFF.

511 For experiments testing the influence of light intensity and pulse width, cells were held at -60mV
512 in current clamp configuration and discrete light pulses were applied. When testing the influence
513 of light intensity, pulse duration was set to 15s and 1s for inhibition and stimulation groups,
514 respectively. Testing the influence of the pulse duration was performed at constant light intensity:
515 10mW (Stimulation) and 5mW (Inhibition).

516

517 **3 - Extracellular *in vivo* recordings of STN neuronal activity**

518 After at least 3 weeks of recovery following viral injection, *in vivo* electrophysiological
519 recordings were performed in 11 rats (n = 4, ARCHT3.0 group and n = 7, hChR2) to assess the
520 impact of STN optogenetic modulation on STN neurons. Briefly, rats were anesthetized with a
521 mixture of ketamine/xylazine (100/10 mg/kg, *i.p.* supplemented as needed during the recording
522 session) and mounted in a stereotaxic head frame (Horsley-Clarke apparatus; Unimécanique,
523 Epinay-sur-Seine, France). Body temperature was maintained at 36.5°C with a homeothermic
524 blanket controlled by a rectal probe (Harvard Apparatus, Holliston, MA). Single-unit activity of
525 neurons in the STN was recorded extracellularly using glass micropipettes (25-35 M Ω) filled with
526 a 0.5 M sodium chloride solution. Action potentials were recorded using the active bridge mode
527 of an Axoclamp-2B amplifier (Molecular Devices, San Jose, CA), amplified, and filtered with an
528 AC/DC amplifier (DAM 50; World Precision Instruments). Data were sampled on-line at 10 kHz
529 rate on a computer connected to a CED 1401 interface and off-line analyzed using Spike2 software
530 (Cambridge Electronic Design, Cambridge, UK). Optical fiber (230 μ m-Thorlabs) was inserted
531 with a 15° angle and the fiber tip was lowered just above the STN and connected to a 200mW
532 532nm DPSS laser. The entry point had the following coordinates: AP: -3.7 mm, ML: +1.0 mm.
533 The fiber tip was at a depth of 7.3 mm from the cortical surface.

534 The pattern of STN neurons activity was analyzed at least 20s before, 180s during and 20s after
535 photo-modulation. The parameters of light stimulation were the same than those used in behavioral
536 experiments: rats expressing ARCHT3.0 opsin were subjected to bins laser stimulation of 15s ON,
537 followed by 5s OFF (corresponding to 9 consecutive bins for 180 s), with the light power at the

538 tip of optical fiber at 5 mW ($\pm 10\%$). Rats expressing hChR2 opsin were subjected to bins laser
539 stimulation at 130 Hz, with 2 ms width, with the light power set up at 10mW ($\pm 10\%$).

540 **Histology**

541 At the end of the experiments, rats were deeply anesthetized via an injection (through their catheter
542 for animals subjected to behavioral testing or *i.p.* for those subjected to in vivo electrophysiologic
543 recordings), with ketamine (Imalgene, Merial, 200 mg/kg) and medetomidine (Domitor, Janssen
544 60 mg/kg). Then, they were perfused intra-cardiacally with 4% paraformaldehyde dissolved in
545 PBS. Brains were extracted and after cryo-protection in 30% sucrose, they were frozen into liquid
546 isopentane (-80°C), and finally cut in $40\mu\text{m}$ coronal slices with a cryostat.

547 In hChR2 rats, native fluorescence, while present, required immuno-staining to control the exact
548 boundaries of viral expression. After PBS rehydration (3 x 5 min), brain sections underwent a 90
549 min permeation step (PBS, 1% bovine serum albumin (BSA) 2% normal goat serum (NGS), 0.4%
550 TritonX-100), PBS washes (3 x 5 min) and incubation with primary antibody (mouse anti-GFP,
551 A11120, Life technologies; 1:200, in PBS 1% BSA, 2% NGS, 0.2% TritonX-100) at 4°C
552 overnight. Sections were then washed with PBS (3 x 5 min), followed by 2h incubation at room
553 temperature with secondary antibody (Goat anti-mouse Alexa 488, A11011, Life technologies,
554 1:400 in PBS 1% BSA, 2% NGS) and finally washed with PBS (3 x 5 min).

555 Brain sections of all animals were then mounted on to glass slides with homemade mounting
556 medium and examined with an epifluorescence microscope (Zeiss, Imager.z2). Animals with no
557 fluorescence in the STN, or with fluorescence partially or totally out of the STN were excluded
558 from the results, as well as rats presenting optic fibers misplacement (n=15 in total).

559 Representative correct optic fibers' location and fluorescence expression are illustrated in **Fig. 1A**.

560 **Statistical analysis**

561 All variables are expressed as mean number \pm SEM, statistical tests were two-tailed, and the p-
562 value threshold was set at $\alpha=0.05$. Statistical tests and graph were performed using GraphPad
563 Prism 6 (version 6.07).

564 1 - Behavioral analyses

565 Mixed 3- or 2-way ANOVA, followed by Tuckey's or Dunnett's post hoc, were used, when
566 appropriate, with optogenetic groups (ARCHT3.0, hChR2 and EYFP-control) as between factors,
567 and sessions or conditions (baseline, escalation: 'Esc1', 'Esc2', 'Esc3', 'Esc4', 'With peer' and in
568 'Without peer') as within factors. For the cocaine escalation only, we compared the mean number
569 of cocaine injections during 6h sessions. To compare cocaine consumption between blocks of
570 escalation and others blocks, we used the number of drug injections received during the two first
571 hours of escalation, since cocaine escalation has an effect from the beginning of drug long access
572 sessions (34).

573 2 – *ex vivo* and *in vivo* electrophysiological data analyses

574 Electrophysiological data were analyzed with Friedman test followed by Dunn's post-hoc test
575 within groups. Variations in cells properties were analyzed with Kruskal-Wallis test or mixed
576 ANOVA.

577

578

579 **Supplementary Materials**

580 We controlled the effects of the escalation on other EYFP-control (n=7) and ARCHT3.0 (n=6)
581 animals, subjected to the same protocol, except for the 20 days of escalation procedure, during
582 which they were maintained in short access (2h) sessions (results are illustrated in **Fig. S1**). We
583 compared their baseline consumption and cocaine intake during the two first hours of the following
584 20 sessions using 3-way mixed ANOVA, with access duration ('long access'; 6h and 'short
585 access'; 2h) and optogenetic groups (ARCHT3.0 and EYFP-control) as between factors and
586 sessions as within factor. Results of the 3-way ANOVA for the baseline and escalation are
587 respectively shown in **Table S1** and **Table S2**. Then, we compared cocaine intake in rats
588 maintained in short access sessions, using mixed 3- or 2-way ANOVA, followed by Tuckey's or
589 Sidak's post hoc, with optogenetic groups (ARCHT3.0, hChR2 and EYFP-control) as between
590 factors, and sessions or conditions (baseline, 'Esc4', 'With peer' and 'Without peer') as within
591 factors. Results of the three-way analysis are shown in **Table S4**.

592 To check whether or not the presence of a peer and the optogenetic modulation of the STN
593 specifically modulate responses towards the drug, with limited side-effects, we analyzed the
594 number of perseverations (*i.e.* presses on the active lever during the 20-s time-out period; reflective
595 of impulsive behavior) and errors (*i.e.* presses on the inactive lever; reflecting a possible aspecific
596 general hyperactivity that is not goal directed towards the drug) performed by the animals during
597 the main behavioral experiment (see **Fig. S2**) using mixed 3-way ANOVA, with conditions
598 (baseline, 'Esc4', 'With peer' and 'Without peer') and sessions as within factors, and optogenetic
599 groups as between factors. Results of the statistical analysis for the perseverations and errors are
600 respectively shown in **Table S5** and **Table S6**.

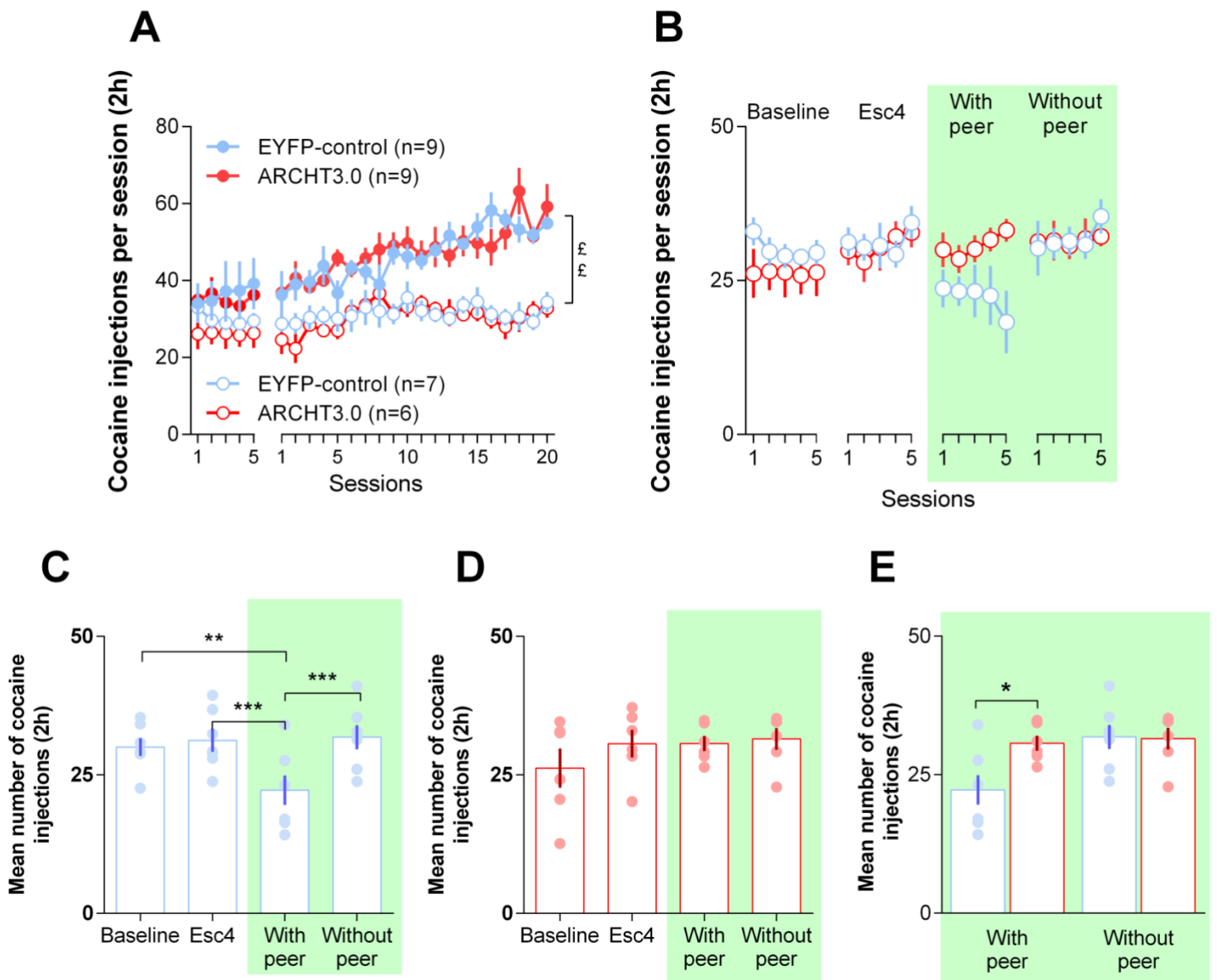
601

602 **Supplementary figures**

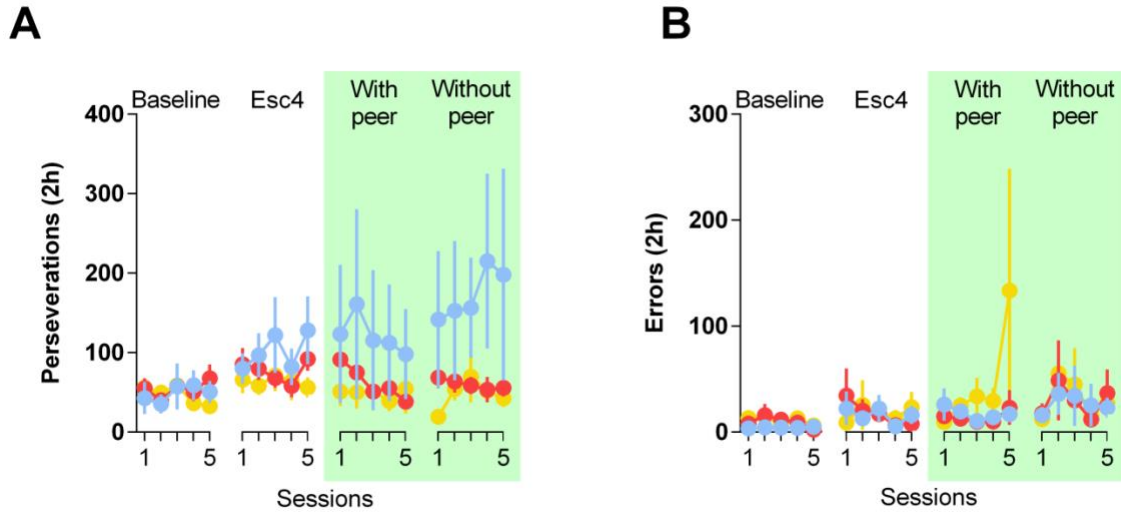
603 **Fig. S1. Peer's presence reduces recreational cocaine intake; an effect suppressed by STN**
 604 **photo-inhibition.**

605 (A) Mean number of cocaine injections received during the two first hours of the baseline and the twenty long (6h;
 606 n=9 ARCHT3.0; plain red dots and n=9 EYFP-control; plain blue dots) or short (2h; n=6 ARCHT3.0; red empty dots
 607 and n=7 EYFP-control; blue empty dots) access sessions access to the drug. (B) Cocaine injections received during
 608 the two hours of the baseline, 'Esc4', and with the laser activated (in green): 'With peer' and 'Without peer'.
 609 (C,D) Mean number of cocaine injections received during the two hours of the sessions in 5-sessions blocks (baseline,
 610 'Esc4', 'With peer', 'Without Peer') respectively in EYFP-control and ARCHT3.0 animals. (E) Mean number of
 611 cocaine injections received during the two first hours of the sessions with the laser activated 'With peer' and 'Without
 612 peer' in EYFP-control and ARCHT3.0 rats. Each dot represents individual mean per block of 5 sessions in C,D,E.
 613 Green area: laser ON. ££: $p < 0.01$ compared with long access group. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

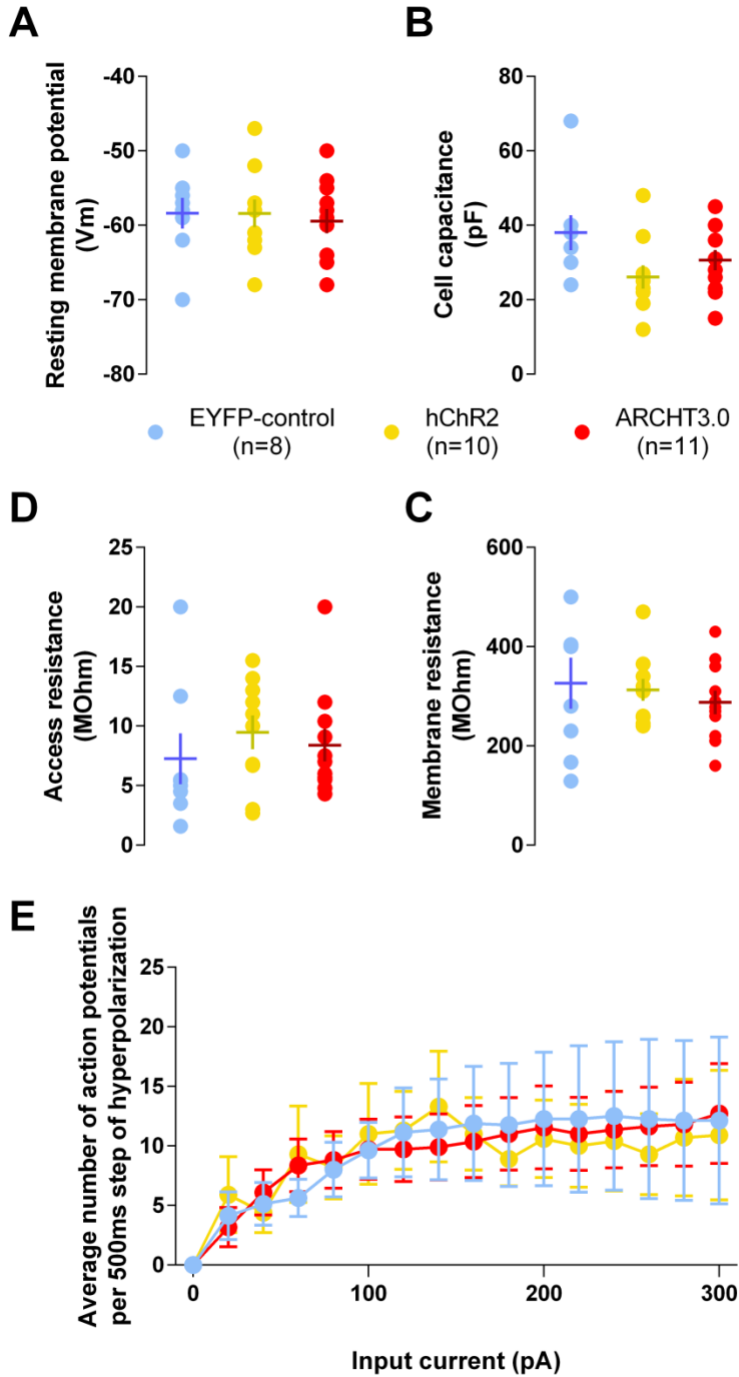
614



615 **Fig. S2. Peer's presence and STN optogenetic modulations modulated neither errors nor**
616 **perseverations.**
617 Number of perseverations (A) and errors (B) performed by EYFP-control (n=9, blue), ARCHT3.0 (n=9, red) and
618 hChR2 (n=9, yellow) rats within the two first hours of sessions during the baseline, the end of the escalation ('Esc4'),
619 and during laser activation (in green) 'With peer' and 'Without peer'.
620



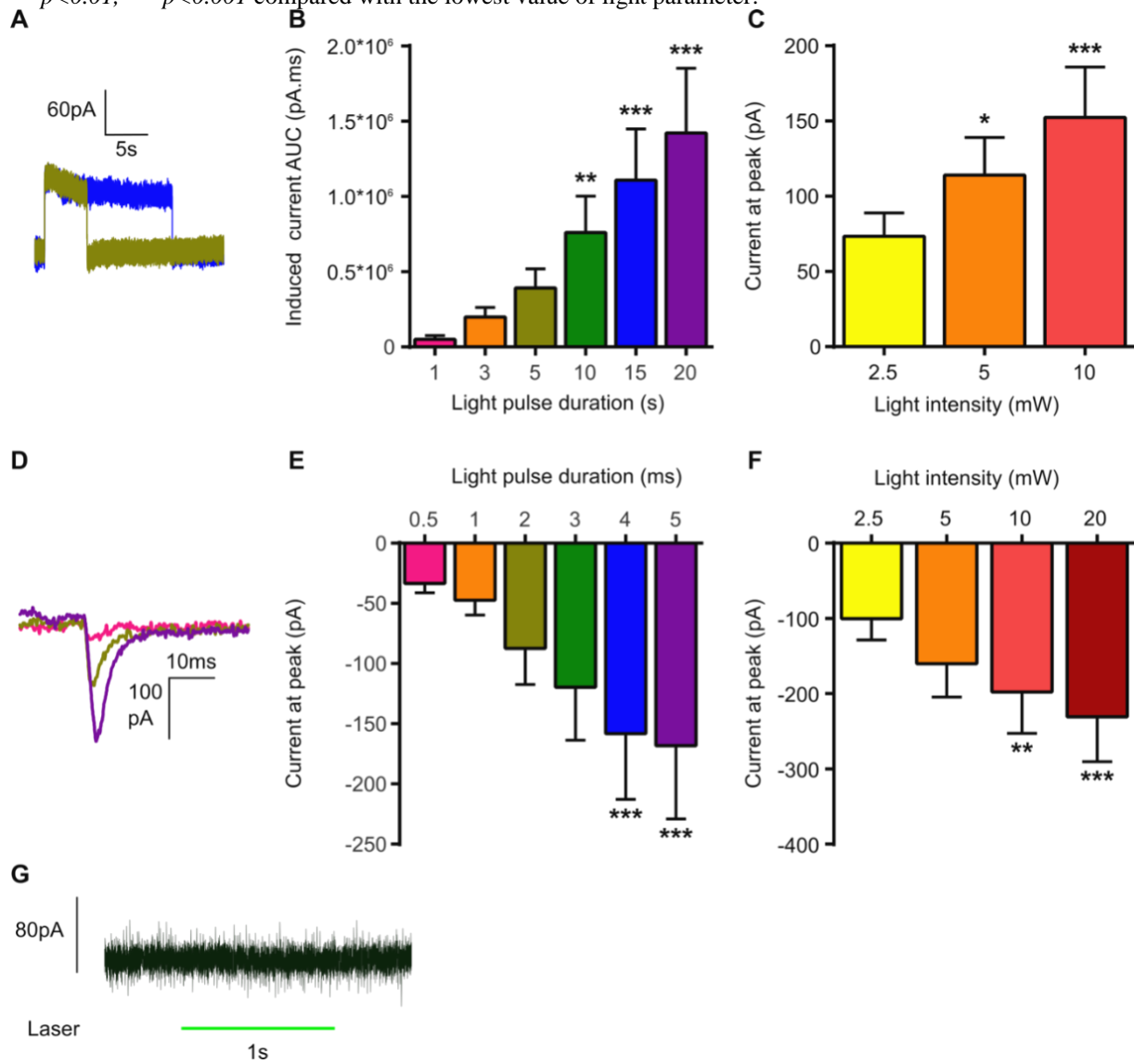
621 **Fig. S3. Cells properties of STN neurons after viral infection recorded in whole cell**
 622 **configuration.**
 623 Cell resting membrane potential (A), cell capacitance (B), membrane resistance (C), access resistance (D)
 624 and average number of action potentials (APs) elicited by a 500ms step of hyperpolarization (E) for controls EYFP-
 625 control (n=8, blue), hChR2 (n=10, yellow) and ARCHT3.0 (n=11, red) cells.



626

627 **Fig. S4. Evaluation of light stimulation parameters in STN neurons after viral infection.**

628 Example of light induced inhibitory currents in one STN neuron expressing ARCHT3.0 by a 5s (brown) and 15s (blue)
 629 pulse (A). Average area under the curve (AUC) calculated for different durations of light pulses with intensity set at
 630 5mW in ARCHT3.0 cells (n=11) (B). Average current induced in ARCHT3.0 cells by a single 15s pulse applied with
 631 different light intensities (C). Example of induced depolarizing current in hChR2 cells induced by a 0.5ms (pink), 2ms
 632 (brown) or 5ms (purple) light pulse (D). Average induced current in hChR2 cells (n=10) depending on the duration of
 633 the light pulse with intensity set at 10mW (E). Induced current in hChR2 cells by a 1s light pulse as a function of light
 634 intensity (F). Typical response of a neuron expressing EYFP-control facing a 1s laser pulse at 20mW (G). * $p < 0.05$,
 635 ** $p < 0.01$, *** $p < 0.001$ compared with the lowest value of light parameter.



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Supplementary tables:

Table S1. Results of the mixed 3-way ANOVA on the number of cocaine injections during baseline consumption with duration of access to the drug (long; 6h and short 2h access) and optogenetic groups (ARCT3.0 and EYFP-control) as between factors and sessions as within factors.

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(1,27)}=0.136$	0.716
access duration	$F_{(1,27)}=3.512$	0.088
sessions	$F_{(1.62, 43.61)}=0.490$	0.576
optogenetic groups x access duration	$F_{(1,27)}=0.558$	0.462
optogenetic groups x sessions	$F_{(1.62, 43.61)}=0.736$	0.457
access duration x sessions	$F_{(1.62, 43.61)}=3.37$	0.812
optogenetic groups x access duration x sessions	$F_{(1.62, 43.61)}=0.415$	0.620

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Table S2. Results of the mixed 3-way ANOVA on the number of cocaine injections during the 20 following sessions with duration of access to the drug (long; 6h and short 2h access) and optogenetic groups (ARCT3.0 and EYFP-control) as between factors and sessions as within factors.

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(1,27)}=0.0001$	0.993
access duration	$F_{(1,27)}=62.638$	<0.0001
sessions	$F_{(4.91, 132.65)}=6.22$	<0.0001
optogenetic groups x access duration	$F_{(1,27)}=0.199$	0.659
optogenetic groups x sessions	$F_{(4.91, 132.65)}=1.038$	0.398
access duration x sessions	$F_{(4.91, 132.65)}=3.37$	0.007
optogenetic groups x access duration x sessions	$F_{(4.91, 132.65)}=0.768$	0.572

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Table S3. Results of the mixed 3-way ANOVA on the number of cocaine injections with conditions (baseline, 'Esc4', 'With peer', 'Without peer') and sessions as within factors and optogenetic groups as between factors.

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(2,24)}=2.605$	0.095
conditions	$F_{(3,72)}=31.582$	<0.0001
sessions	$F_{(4,96)}=1.062$	0.380
optogenetic groups x conditions	$F_{(6,72)}=2.524$	0.028
optogenetic groups x sessions	$F_{(8,96)}=0.549$	0.817
conditions x sessions	$F_{(12,288)}=1.258$	0.283
optogenetic groups x conditions x sessions	$F_{(24,288)}=1.317$	0.220

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654 **Table S4. Results of the mixed 3-way ANOVA on the number of cocaine injections in rats**
 655 **maintained in short access with conditions (baseline, ‘Esc4’, ‘With peer’, ‘Without peer’)**
 656 **and sessions as within factors and optogenetic groups as between factors.**

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(1,11)}=0.127$	0.728
conditions	$F_{(3,33)}=0.698$	0.006
sessions	$F_{(4,44)}=0.553$	0.698
optogenetic groups x conditions	$F_{(3,33)}=5.781$	0.003
optogenetic groups x sessions	$F_{(4,44)}=0.460$	0.765
conditions x sessions	$F_{(12,132)}=0.568$	0.864
optogenetic groups x conditions x sessions	$F_{(12,62)}=0.777$	0.674

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659 **Table S5. Results of the mixed 3-way ANOVA on the number of perseverations with**
 660 **conditions (baseline, ‘Esc4’, ‘With peer’, ‘Without peer’)** and sessions as within factors and
 661 **optogenetic groups as between factors.**

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(2,24)}=1.155$	0.332
conditions	$F_{(3,72)}=1.165$	0.300
sessions	$F_{(4,96)}=0.168$	0.905
optogenetic groups x conditions	$F_{(6,72)}=1.028$	0.382
optogenetic groups x sessions	$F_{(8,96)}=0.996$	0.431
conditions x sessions	$F_{(12,288)}=1.427$	0.241
optogenetic groups x conditions x sessions	$F_{(24,288)}=0.889$	0.511

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663 **Table S6. Results of the mixed 3-way ANOVA on the number of errors with conditions**
 664 **(baseline, ‘Esc4’, ‘With peer’, ‘Without peer’)** and sessions as within factors and optogenetic
 665 **groups as between factors.**

Effect	F(DFn,DFd)	p-value
optogenetic groups	$F_{(2,24)}=0.536$	0.592
conditions	$F_{(3,72)}=3.119$	0.050
sessions	$F_{(4,96)}=1.145$	0.319
optogenetic groups x conditions	$F_{(6,72)}=0.780$	0.549
optogenetic groups x sessions	$F_{(8,96)}=0.760$	0.532
conditions x sessions	$F_{(12,288)}=1.214$	0.307
optogenetic groups x conditions x sessions	$F_{(24,288)}=0.680$	0.615

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669 **References and Notes**

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814 Analytic tools: FP, CBr, YP

815 Research performance: CV, LV, ATC, NM.

816 Data analyses: CV, ATC, NM

817 Funding acquisition: CBa

818 Writing – original draft: ATC, CBa, CV

819 Writing – review & editing: CBa, CV, MD, NM, YP

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823