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Deep-Brain Stimulation of the Subthalamic Nucleus Selectively Decreases Risky Choice in Risk-Preferring Rats

STN-DBS decreases risky decision making

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Abstract:

Deep brain stimulation of the subthalamic nucleus (STN-DBS) can improve the motor symptoms of Parkinson's disease and negate the problematic side effects of dopamine replacement therapy. Although there is concern that STN-DBS may enhance the development of gambling disorder and other impulse control disorders (ICDs) in this patient group, recent data suggest that STN-DBS may actually reduce iatrogenic ICDs, and alleviate obsessive-compulsive disorder. Here we sought to determine whether STN-DBS was beneficial or detrimental to performance of the rat gambling task (rGT), a rodent analogue of the Iowa Gambling Task (IGT) used to assess risky decision making clinically. Rats chose between four options associated with different amounts and probabilities of sugar pellet rewards versus time-out punishments. As in the IGT, the optimal approach was to favor options associated with smaller per-trial gains but lower time-out penalties. Once a stable behavioural baseline was established, electrodes were implanted bilaterally into the STN, and the effects of STN-DBS assessed on-task over 10 consecutive sessions using an A-B-A design. STN-DBS did not affect choice in optimal decision-makers that correctly favored options associated with smaller per-trial gains but also lower penalties. However, a minority (~25%) preferred the maladaptive "high-risk, high-reward" options at baseline. STN-DBS significantly and progressively improved choice in these risk-preferring rats. These data support the hypothesis that STN-DBS may be beneficial in ameliorating maladaptive decision making associated with compulsive and addiction disorders.

Key words: rat gambling task, impulsivity, dopamine replacement therapy, Parkinson's disease, obsessive compulsive disorder, addiction

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45 *Significance statement*

46 STN-DBS may constitute a relatively safe and effective alternative to pharmacotherapy, not just
47 for Parkinson's Disease, but for disorders of addiction and compulsion in which decision making
48 is compromised. However, concern remains over whether this manipulation may itself trigger
49 impulse control deficits or risky decision making, as may be predicted from rodent lesion data.
50 Here, we directly test this hypothesis, and evaluate the effects of STN-DBS in rats performing a
51 rodent gambling paradigm based on the Iowa Gambling Task used clinically. Far from inducing
52 impulsivity or exacerbating risky choice, STN-DBS selectively improved decision making in
53 animals exhibiting a risk-preferring strategy at baseline. These data suggest that STN-DBS may
54 be beneficial in the treatment of psychiatric, rather than solely neurological, conditions.

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56 *Introduction*

57 Given the limited efficacy of dopamine replacement therapies (DRT) such as L-DOPA
58 for Parkinson's Disease (PD), deep brain stimulation (DBS) is becoming more common to
59 relieve the motor symptoms of PD (Limousin et al., 1995; Benabid et al., 1998; Martinez-
60 Ramirez and Okun, 2014). In addition, the realisation that $D_{2/3}$ family agonists can lead to the *de*
61 *novo* development of serious impulse control and addiction problems, including gambling
62 disorder (GD), has made neurologists reluctant to prescribe this class of drugs, despite their
63 noted efficacy at restoring motor function (Lawrence et al., 2003; Evans and Lees, 2004;
64 Weintraub et al., 2006; Voon et al., 2011). Both the globus pallidus internal (GPi) and
65 subthalamic nucleus (STN) are common targets for DBS, and can lead to significant
66 improvements in motor function. As DBS involves invasive surgery, it is generally reserved for
67 later-stage PD patients for whom DRT has started to fail, yet there is increasing interest in
68 applying DBS at earlier stages of the disease in order to maximize therapeutic benefit (Charles et
69 al., 2012; Schuepbach et al., 2013).

70 STN-DBS can result in a more dramatic reduction in DRT dosing as compared to GPi-
71 DBS (Follett et al., 2010; Odekerken et al., 2013; Liu et al., 2014), therefore this region may be a
72 particularly valid target for those experiencing adverse reactions to DRT. However, the STN
73 influences a wide range of non-motor functions, including impulsivity and decision making
74 (Aron and Poldrack, 2005; Frank, 2006; Ballanger et al., 2009b), and rodent studies have been
75 particularly informative in showing that STN lesions can increase incentive motivation, motor
76 impulsivity, and decrease attention (Baunez et al., 1995; Baunez and Robbins, 1997; Baunez et
77 al., 2002; Winstanley et al., 2005; Uslaner and Robinson, 2006). Furthermore, STN-DBS in PD
78 patients can result in speedier, and arguably less reflective, decision making (Frank, 2006),

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transiently increase loss-chasing in a gambling simulation (Rogers et al., 2011), and may even precipitate the onset of GD (Witt et al., 2004; Smeding et al., 2007), although support for the latter is somewhat ambivalent (Halbig et al., 2009; Demetriades et al., 2011; Rodriguez-Oroz et al., 2011). Indeed, a recent meta-analysis comparing DBS of the STN and GPi in PD concluded there were no differences in psychiatric complications resulting from targeting of either area (Wang et al., 2016). The fact that the STN influences cognitive function may, in fact, be of benefit to other patient groups, in that STN-DBS has been suggested as an efficacious treatment for obsessive-compulsive disorder (OCD) and substance use disorder (SUD)(Mallet et al., 2008; Pelloux and Baunez, 2013). However, comparatively little is known regarding the effects of STN-DBS on relevant higher-order cognitive processes, particularly in the absence of PD.

The Iowa Gambling Task, in which subjects aim to maximise money or points through selecting from four decks of cards, was originally developed as a laboratory-based test of "real-world" decision making sensitive to frontal cortex damage (Bechara et al., 1994). The optimal strategy is to avoid "high-risk, high-reward" decks that are paired with disproportionately heavy penalties, and instead favor those associated with incremental yet consistent gains over time. Numerous clinical populations, including SUD, GD and OCD, exhibit impairments on the IGT, and such persistent choice of the risky options may be a cognitive endophenotype for psychiatric vulnerability (Winstanley and Clark, 2016). To address whether STN-DBS may improve or impair such decision making, we therefore evaluated the effects of this manipulation in rats performing the rodent gambling task (rGT), a behavioral paradigm based on the IGT. Given that STN-DBS may specifically impact individuals exhibiting maladaptive choice strategies, we deliberately analysed whether this manipulation differentially affected optimal decision-makers vs risk-preferring rats.

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102

103 *Material and Methods*

104 *Subjects*

105 Male Long Evans rats (n = 24; initial weight: 250-275g; Charles River, St. Constant,
106 Canada) were pair-housed with free-access to water under a reverse light cycle in a climate-
107 controlled colony. Rats were food restricted to 85% of their free-feeding weight and maintained
108 on 14 g of standard rat chow per day plus any sugar pellets earned on task (~5 g per day). All
109 experimental practices were in accordance with the Canadian Council on Animal Care, and
110 approved by the Animal Care Committee of the University of British Columbia.

111 *Behavioral apparatus*

112 Pre-operative behavioural training took place in 12 standard Med Associates five-hole
113 operant chambers housed in ventilated sound-attenuating cabinets. Each chamber featured a
114 food tray outfitted with both a stimulus light and an infrared beam for detecting nose-poke
115 inputs. Sucrose pellets (45 mg; Bio-Serv, Frenchtown, NJ, USA) could be delivered to this tray
116 from an external food hopper and a house light was positioned on the chamber wall above. An
117 array of five response apertures was located on the opposite wall, each equipped with stimulus
118 lights and infrared beams for detecting input. Four boxes were equipped with a counter-balanced
119 arm and removable roof insert to enable tethering, and post-operatively only these four boxes
120 were used for behavioral testing. It was possible to deliver bilateral DBS via programmable
121 electrical stimulators to animals within two of these latter boxes at any one time. All of the
122 operant chambers ran according to MedPC (RRID: SCR_014721) programs written by CAW,
123 and controlled by an IBM-compatible computer.

124 *Behavioural training*

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125 Subjects (n = 24) were trained to perform the rGT as described previously (Zeeb et al.,
126 2009). In the rGT, subjects sample between four options associated with different magnitudes
127 and probabilities of sugar pellet rewards versus time-out punishments in order to maximize
128 reward earned. In each 30 minute session, subjects chose between one of four options,
129 designated by illumination of response holes 1, 2, 4 and 5 (see Figure 1 for task schematic).
130 Each hole was associated with a distinct probability and magnitude of reward or timeout
131 punishments, and are subsequently identified based upon the number of potential pellets earned
132 per choice, one pellet (P1), two pellets (P2), three pellets (P3), and four pellets (P4). As in the
133 IGT, the optimal approach in the rGT was to favor options associated with smaller per-trial gains
134 but lower time-out penalties; consistent choice of the smaller reward options was advantageous
135 due to more frequent rewards, but also less frequent and shorter timeouts, with the two-pellet
136 choice (P2) resulting in the most reward earned per unit time.

137 Subjects began each trial by nose-poking in the illuminated food tray. This response
138 extinguished the tray light and resulted in a 5s inter-trial interval (ITI), during which all lights in
139 the chamber were extinguished. If subjects withheld responding during the ITI, holes 1,2,4, and 5
140 of the array were illuminated for 10s. A response in any illuminated hole turned off all stimulus
141 lights and led to either onset of the tray light and delivery of a reward, or the start of a time-out
142 'punishment' period. Rewarded trials led to illumination of the food tray and immediate delivery
143 of the appropriate number of sucrose pellets. If a trial was punished, no reward was delivered
144 and the stimulus light within the chosen hole flashed at 0.5 Hz until the punishing timeout
145 elapsed, at which point the tray light was illuminated. If rats failed to make a nose poke in one
146 of the illuminated holes within 10s, the trial was counted as an omission. Following completion
147 of any trial type, the tray light was re-illuminated and subjects could begin a new trial by nose-

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148 poking therein. As in the five-choice serial reaction time task (5CSRT; a rodent analog of the
149 continuous performance test, designed to measure visuospatial attention, motor impulsivity and
150 motivation (Carli et al., 1983; Robbins, 2002)), a response made in one of the five response holes
151 during the ITI was punished by a 5s timeout period and recorded as a premature response. These
152 premature responses serve as a well-validated index of motor impulsivity (Robbins, 2002). The
153 time-out period was marked by illumination of the house light, after which the food tray light
154 was re-illuminated and subjects could commence a new trial. Training and testing continued
155 each week day until a statistically stable baseline was observed across all variables measured (44
156 sessions).

157 *Electrode implantation*

158 Stimulating electrodes consisted of two platinum wires (EEP-1495 MS303/9-A/SPC
159 Plastics One, Roanoke) sheathed in 9mm of 22 gauge PEEK tubing, such that 0.5mm of each
160 electrode was left bare. Animals were anesthetised with 2% isoflurane in oxygen and then
161 secured in a stereotaxic frame. Once anesthetized, animals were given 5 mg/kg ketoprofen
162 subcutaneously. The incisor bar was initially set to -3.3 mm. Great care was taken to ensure the
163 skull was level prior to implanting the electrode, and the incisor bar adjusted until there was <
164 0.2mm difference in height between bregma and lambda. Using standard stereotaxic technique
165 under aseptic conditions, sterile bilateral stimulating electrodes were inserted at an angle of 5
166 degrees off vertical through bore holes made in the skull, and then secured with bone screws and
167 dental cement, according to the following stereotaxic coordinates: anteroposterior (AP) -3.8 from
168 bregma; medial/lateral (ML): ±3.1 from the midline; dorsoventral (DV) from skull: -8.4. Plastic
169 dust caps were used to protect the external electrode contacts. Animals were given a week to
170 recover in their home cage before behavioural testing resumed. Animals were then reassessed on

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171 the rGT until stable baseline performance was observed over a minimum of 3 consecutive
172 sessions.

173 *STN-DBS during rGT performance*

174 A timeline showing the phases of the behavioral experiment is provided in Figure 2. A within-
175 subjects design was used, and all animals experienced STN-DBS. The start of DBS was
176 synchronised to the start of the rGT test session, and remained on throughout the entire 30-
177 minute session. Each rat received DBS repeatedly, throughout ten successive, daily rGT test
178 sessions. Animals were divided at random into two groups. Group 1 received three "mock
179 DBS" rGT sessions, during which the electrodes were connected to the stimulators via spring-
180 loaded tethers, but stimulation was OFF, in order to acclimatise animals to being tethered. This
181 group then received STN-DBS throughout 10 consecutive rGT sessions, during which the
182 stimulators were turned ON (130Hz, 60us pulse width). Prior to the first behavioral test session,
183 the current amplitude was adjusted for each individual rat according to former studies (Rouaud et
184 al., 2010), and for each electrode, to just below that which induced the well-known hyperkinetic
185 motor effects in the contralateral paw (treading, "piano playing"). Group 2 performed the rGT as
186 per baseline training during this period. In each behavioral run of four animals, two therefore
187 received STN-DBS or mock DBS, and two did not. Once group 1 had completed the tenth STN-
188 DBS session, the conditions were switched such that group 2 then received three sessions of
189 "mock DBS, followed by ten STB-DBS sessions, and group 1 simply performed the rGT. After
190 five additional behavioral sessions, group 1 was humanely euthanised via live decapitation, the
191 brains removed and flash frozen on dry ice, and stored at -80°C. In case any effects of STN-
192 DBS persisted beyond the stimulation epoch itself, care was taken to ensure all rats completed
193 the same number of post-stimulation sessions. As such, group 2 performed an additional thirteen

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194 rGT sessions prior to euthanasia, such that data were collected from 18 post-stimulation sessions
195 for all rats.

196 *Histology*

197 The brains were emersion-fixed in 4% paraformaldehyde at 4°C for 7 days, and then
198 transferred to 30% sucrose solution. Tissue was sectioned into 30 µm sections on a cryostat set
199 to -20°C. These slices were mounted onto 2% gelatin-coated slides and stained with cresyl
200 violet. The location of electrode tips were then plotted onto standard rat brain sections (Paxinos
201 et al., 1998).

202 *Data analyses*

203 Data from each experiment were analysed using SPSS (version 24.0; SPSS, Chicago, IL,
204 USA). As per previous reports (Zeeb and Winstanley, 2011, 2013; Ferland and Winstanley,
205 2016), the following rGT variables were analysed: score (the total number of advantageous
206 choices minus the total number of disadvantageous choices: [P1 + P2]-[P3 + P4]); percent choice
207 of each option, percent premature responses, omissions, trials completed, choice- and reward
208 collection latencies. A statistically stable pattern of behavior was verified by a repeated-
209 measures analysis of variance (ANOVA) across data from at least three consecutive sessions,
210 with session (three levels) and, where appropriate, choice option (four levels: P1-P4) as within-
211 subjects factors, in which the session and session x option interactions were not significant.
212 Animals with a mean positive score at baseline were designated as "optimal decision-makers",
213 whereas rats with negative scores were classified as "risk-preferring"(Ferland and Winstanley,
214 2016). This between-subjects factor (group) was included in all analyses. To determine whether
215 risk-preferring rats differed with respect to weight gain as a result of pair-housing, body weight

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(G) data over the course of the experiment were analysed by within-subjects ANOVA with weight record (38 levels) as a within subjects factor, and group as a between-subjects factor.

The effects of mock DBS were also determined by ANOVA, by comparing data from these three sessions to three stable post-operative baseline sessions. Any effect of STN-DBS (sessions 1-3, sessions 4-6) were analysed through comparison to mock DBS. The final four DBS sessions were similarly compared to the three mock DBS sessions plus the last post-operative baseline session, in order to correctly populate the ANOVA fields with four sessions in each stimulation condition. Post-stimulation sessions were divided into three day bins, and whether any effects of STN-DBS were still evident once stimulation had ceased was again determined via ANOVA through comparison with the three mock DBS sessions. Results are expressed as mean ± standard error of the mean (SEM). Differences were considered significant at $p < 0.05$.

Results

Histology

Data from five rats were excluded from the experiment due to electrode failure (n = 1), loss of head-cap (n = 2), seizures upon stimulation (n = 1), or general ill-health (n = 1). Two additional rats were excluded from data analyses due to incorrect placement of the electrode, leaving a final n of 17 (optimal decision-makers: n = 13; risk-preferring: n = 4). The location of the electrode tips for these 17 subjects is shown in Figure 3.

Effects of STN-DBS on risky choice

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Animals became accustomed to tethering over three mock stimulation sessions prior to DBS, as indicated by stable patterns of choice across all 4 options (Figure 4A,B; session: $F_{2, 30} = 2.211$, $p = 0.127$; session x risk-preference: $F_{2, 30} = 0.066$, $p = 0.936$), and stable score values across session (Figure 4C session: $F_{2, 30} = 0.697$, $p = 0.506$). This mock DBS baseline matched the stable post-operative baseline established following electrode implantation, and is therefore a reliable representation of basal decision-making patterns in these rats (score: postop/mock: $F_{1, 15} = 0.024$, $p = 0.880$; postop/mock x risk-preference: $F_{1, 15} = 0.001$, $p = 0.976$, risk preference: $F_{1, 15} = 29.753$, $p = 0.0001$). Animals designated as risk-preferring did not differ from optimal decision-makers in terms of weight gain during pair-housing, and all animals gained weight robustly during the course of the experiment (Figure 5, weight record: $F_{37, 555} = 153.43$, $p < 0.0001$; weight record x risk-preference: $F_{37, 555} = 0.44$, $p = 0.99$; risk-preference: $F_{1, 15} = 0.11$, $p = 0.75$).

Comparing responding during the mock stimulation sessions to the first three DBS sessions, no effects of DBS on choice were apparent in either optimal-decision-makers or risk-preferring rats (choice: stimulation on/off x risk-preference x option: $F_{3, 45} = 0.524$, $p = 0.668$; score: stimulation on/off x risk-preference: $F_{1, 15} = 0.622$, $p = 0.44$). However, during DBS sessions 4-6, the risk-preferring group selectively and specifically increased choice of the best option, P2 (Figure 4; stimulation on/off x risk-preference x option: $F_{3, 45} = 3.775$, $p = 0.017$; P2: stimulation on/off vs risk-preference: $F_{1, 15} = 7.476$, $p = 0.015$). This change in choice is also reflected in a significant increase in risk-preferring rats' score (stimulation on/off x risk-preference: $F_{1, 15} = 9.426$, $p = 0.008$; risk-preferring only: stimulation on/off: $F_{1, 3} = 11.216$, $p = 0.044$; optimal decision-makers only: stimulation on/off: $F_{1, 3} = 0.707$, $p = 0.417$). This effect persisted through the subsequent DBS sessions (choice: stimulation on/off x risk-preference x

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option: $F_{3, 45}$= 2.901, p = 0.045; score: stimulation on/off x risk-preference: $F_{1, 15}$ = 5.837, p = 0.029), but was no longer evident once stimulation was discontinued: risk-preferring rats once again started to make significantly more risky choices in the three post-stimulation sessions as compared to on STN-DBS (stimulation on/post x session x risk-preference x choice: $F_{6, 90}$= 2.667, p = 0.02), and there was no significant difference in choice patterns when comparing mock stimulation to the first three post-stimulation sessions (choice: stimulation off/post x risk-preference x choice: $F_{3, 45}$= 0.612, p = 0.610; score: stimulation pre/post x risk-preference: $F_{1, 15}$ = 1.597, p = 0.226).

Effects of STN-DBS on other variables

Again, all variables measured were stable during the three mock DBS sessions, and this behavioural pattern matched that observed in the post-operative baseline (postop/mock: all Fs ≤ 1.859, p ≥ 0.193; postop/mock x risk-preference: all Fs ≤ 2.514, p ≥ 0.134). Optimal decision-makers and risk-preferring rats did not differ at baseline with respect to the level of premature responses, latency to collect reward, and omissions made (risk-preference: all Fs ≤ 0.462, p ≥ 0.507). Risk-preferring rats consistently performed fewer trials, as reported previously (Barrus et al., 2015; Ferland and Winstanley, 2016), due to the longer periods of time-out punishment resulting from such a disadvantageous choice strategy (risk preference $F_{1, 15}$ = 8.331, p = 0.011). Contrary to previous datasets, risk-preferring rats also tended to be slower to make a choice at baseline in the current experiment (risk preference F = 6.047, p = 0.027).

Comparing the first three DBS sessions to the basal stimulation off condition, there was no effect on premature responding (Figure 6A; stimulation on/off: $F_{1, 15}$ = 0.652, p = 0.432; stimulation on/off x risk-preference: $F_{1, 15}$ = 1.695, p = 0.213). A significant decrease in premature responses was nonetheless evident in the subsequent three DBS sessions, regardless of

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rats' basal decision-making strategy (stimulation on/off: $F_{1, 15} = 13.560$, $p = 0.002$; stimulation on/off x risk-preference: $F_{1, 15} = 0.338$, $p = 0.569$; risk-preference: $F_{1, 15} = 0.462$, $p = 0.507$). This effect was transient, and did not persist across the remaining DBS sessions (stimulation on/off: $F_{1, 15} = 1.016$, $p = 0.329$; stimulation on/off x risk-preference: $F_{1, 15} = 0.022$, $p = 0.884$; risk-preference: $F_{1, 15} = 1.028$, $p = 0.327$), and post-stimulation levels of premature responding were comparable to those observed pre-stimulation (stimulation off/post: $F_{1, 15}$ 1.617, $p = 0.223$; stimulation pre/post x risk-preference: $F_{1, 15} = 0.302$, $p = 0.591$).

STN-DBS significantly increased omissions in all rats, and this was evident within the first three sessions of stimulation (Figure 6B; stimulation on/off: $F_{1, 15} = 12.118$, $p = 0.003$; stimulation on/off x risk-preference: $F_{1, 15} = 0.490$, $p = 0.495$) and throughout subsequent sessions (stimulation on/off: all Fs $\geq = 29.519$, p's $= 0.0001$; stimulation on/off x risk-preference: all Fs ≤ 2.366, p's ≥ 0.145). This effect was also temporary, and resolved back to pre-stimulation levels within the first three sessions of post-stimulation testing (stimulation off/post: $F_{1, 15} = 1.0$, $p = 0.333$; stimulation pre/post x risk-preference: $F_{1, 15} = 0.480$, $p = 0.499$). STN-DBS did not affect trials completed in the first three sessions (Figure 6C stimulation on/off: $F_{1, 15} = 2.922$, $p = 0.108$; stimulation on/off x risk-preference: $F_{1, 15} = 2.621$, $p = 0.126$; risk-preference: $F_{1, 15} = 7.103$, $p = 0.018$). In the subsequent three DBS sessions, risk-preferring rats tended to increase the number of trials completed, thereby tracking the improvement in optimal choice observed in this subgroup, although they still performed fewer trials than optimal decision-makers (stimulation on/off x risk-preference: $F_{1, 15} = 4.026$, $p = 0.063$; risk-preference: $F_{1, 15} = 6.426$, $p = 0.023$). Analyses of subsequent STN-DBS trials revealed no significant difference from mock stimulation, suggesting any effect on trials completed in both risk-

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305 preferring rats is transient as well as slight (stimulation on/off x risk-preference: $F_{1, 15} = 0.880$, p
306 = 0.363; risk-preference: $F_{1, 15} = 7.770$, p = 0.014).

307 STN-DBS also increased choice latency within the first three sessions, an effect that
308 appeared to be more pronounced in optimal decision-makers, but was clearly evident in both
309 subgroups of animals (Table 1; stimulation on/off: $F_{1, 15} = 17.755$, p = 0.001; stimulation on/off
310 x risk-preference: $F_{1, 15} = 3.117$, p = 0.098; risk preference: $F_{1,15} = 0.101$, p = 0.754). This effect
311 persisted throughout the remainder of the stimulation sessions (stimulation on/off: all Fs ≥ =
312 29.750, p's < 0.0001; stimulation on/off x risk-preference: all Fs ≤ = 0.232, p's ≥ 0.637). Once
313 again, as soon as stimulation ceased, choice latencies returned to pre-stimulation levels, although
314 there was no longer a significant difference between optimal decision-makers and risk-preferring
315 rats (stimulation on/off: $F_{1, 15} = 2.432$, p = 0.242; stimulation on/off x risk-preference: $F_{1, 15}$ =
316 0.284 p = 0.602; risk-preference: $F_{1, 15} = 1.701$, p = 0.212).

317 Reward collection latency was not significantly different from mock stimulation during
318 the first three sessions of STN-DBS (Table 1; stimulation on/off: $F_{1, 15} = 1.85$, p = 0.1.94;
319 stimulation on/off x risk-preference: $F_{1, 15} = 0.288$, p = 0.60). Similar to choice latency, the time
320 taken to collect reward significantly increased throughout the next three DBS sessions
321 (stimulation on/off: $F_{1, 15} = 11.84$, p = 0.004; stimulation on/off x risk-preference: $F_{1, 15} = 0.462$,
322 p = 0.507), and this effect was likewise evident throughout subsequent stimulation sessions
323 (stimulation on/off: $F_{1, 15} = 22.67$, p = 0.0001; stimulation on/off x risk-preference: $F_{1, 15}$ =
324 0.2.83, p = 0.114). Again, once stimulation ceased, performance returned to pre-stimulation
325 levels (stimulation on/off: $F_{1, 15} = 2.23$, p = 0.16; stimulation on/off x risk-preference: $F_{1, 15}$ =
326 0.001 p = 0.99; risk-preference: $F_{1, 15} = 2.136$, p = 0.016).

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Discussion

Here, we used a rodent behavioral paradigm with strong translational validity to assess the effects of STN-DBS on risky decision making. We show, for the first time, that STN-DBS selectively improves decision making in animals classified as risk-preferring at baseline, increasing choice of a less risky and more profitable option in these animals. In contrast, optimal decision-makers did not alter their choice pattern in response to this manipulation. Although STN-DBS concomitantly increased the time both optimal decision-makers and risk-preferring rats took to make a choice and collect any reward earned, while also increasing the number of omissions made, it did not alter the total number of trials animals completed per session, or increase animals' tendency to make a premature response. Although not entirely selective for decision making, the effects of STN-DBS on choice in risk-preferring rats are therefore not easily explained as an artefact of universal changes in motivation or locomotion. Indeed, these data suggest that STN-DBS may be a viable alternative to DRT in Parkinsonian patients at risk for ICDs, and may also be an effective treatment for other neurological or psychiatric conditions hallmarked by risky decision making, such as addiction disorders.

Our data stand in contrast to a previous report which suggested that STN-DBS increased motor impulsivity in rats performing the rGT, while failing to affect decision making (Aleksandrova et al., 2013). Critically, however, STN-DBS did not take place while animals performed the rGT in this latter study- instead, stimulation was delivered for two hours prior to performance of the rGT in an unspecified location. Due to the experimental design employed, it is difficult to determine whether the tethering itself contributed to the elevated impulsivity: the animals were not habituated to tethering prior to the initiation of DBS, and there was no significant difference in the level of impulsive action observed following two hours of tethering,

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351 regardless of whether stimulation was ON or OFF. As such, the claim that STN-DBS increases
352 motor impulsivity in this experiment should be interpreted with caution.

353 Similar to the data reported here, application of STN-DBS during performance of the
354 5CSRT likewise did not affect premature responding either in rats with 6-hydroxydopamine
355 lesions to the dorsolateral striatum, a model of early PD that results in the loss of dopamine in
356 this area, or in otherwise-intact rats (Baunez et al., 2007). In this latter study, STN-DBS also
357 resulted in slower latencies to respond and increased omissions, again matching the current
358 dataset. Interestingly, in the operant chambers used in this earlier study, animals were required
359 to push a panel inwards in order to get access to the food tray, and STN-DBS significantly
360 increased the number of such panel pushes. As such, STN-DBS may increase motivation for
361 food reward (Baunez et al., 2005), similar to STN lesions (Rouaud et al., 2010). Although we
362 did not monitor repeated entries to the food tray in the current study, we found that animals were
363 slower to collect the food reward they earned, suggesting animals were not necessarily more
364 motivated to consume the sucrose pellets used as rewards in the rGT. A general boost in
365 motivation is thus unlikely to explain the decrease in risky choice observed in the current study.

366 This is the first manipulation, to our knowledge, that has selectively improved the
367 maladaptive decision-making pattern of risk-preferring rats in the rGT. The mean score value
368 for these rats increased by around 50 points due to a highly significant and selective increase in
369 choice of the best option, P2. This change in the score variable caused by STN-DBS therefore
370 does not simply reflect random choice among, or indifference to, the various options. These
371 observations may inform our understanding of the neurobiology underlying baseline differences
372 in risky choice. Due to the relatively low incidence of risk-preferring rats, the majority of studies
373 evaluating the impact of neural or pharmacological manipulations have focused instead on

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374 modifying choice of optimal decision-makers. For example, risky choice can be increased in
375 these animals by lesions to the basolateral amygdala (BLA)(Zeeb and Winstanley, 2011), and
376 also by systemic administration of the dopamine $D_{2/3}$ antagonist eticlopride (Zeeb et al., 2009;
377 Zeeb et al., 2013), although this latter effect did not replicate in subsequent studies (Paine et al.,
378 2013; Barrus and Winstanley, 2016). Disrupting connectivity between the orbitofrontal cortex
379 (OFC) and BLA slows learning of the optimal strategy, but silencing the OFC does not affect
380 choice once a stable pattern of decision making has been established (Zeeb and Winstanley,
381 2011, 2013). Whether aberrant activity in the BLA or OFC or dopamine system contributes to
382 an innate preference for the risky options, or how this could be remedied by STN-DBS, remains
383 unknown.

384 Indeed, the mechanism through which STN-DBS might precipitate cognitive-behavioural
385 change has yet to be fully clarified. Originally, STN-DBS was thought to normalise aberrant
386 activity in PD patients, locally inhibiting STN function through a depolarization block, thereby
387 restoring motor function in PD through disinhibition of the thalamus (see (Gubellini et al., 2009)
388 for review). However, DBS can also excite proximal fibres of passage, resulting in enhanced
389 neuronal firing in terminal regions, as well as increasing the firing of afferent projections (Vitek,
390 2002; McCracken and Grace, 2007; Gradinaru et al., 2009). The STN is highly interconnected
391 with the ventral pallidum, and thereby receives considerable indirect input from numerous limbic
392 structures, but the STN also receives direct input from the OFC and medial prefrontal cortex
393 (Maurice et al., 1998; Haynes and Haber, 2013). It is theoretically possible, therefore, that STN-
394 DBS may exert beneficial effects on risky choice in the rGT through altering activity in these
395 cortical regions (Ballanger et al., 2009a), a conclusion that would fit with the known contribution

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396 of these areas to choice on-task (Paine et al., 2013; Zeeb and Winstanley, 2013; Zeeb et al.,
397 2015).

398 The beneficial effects of STN-DBS were delayed, in that we did not observe significant
399 improvement in decision making within the first three treatment sessions. Similar effects have
400 been observed with regards to the effects of STN DBS on attention or motivation, when
401 significant effects could only be obtained after multiple daily sessions (Baunez et al., 2007;
402 Rouaud et al., 2010). Although this time-course may suggest that STN-DBS does not reliably
403 induce changes in decision making, the need for repeated stimulation could also be required to
404 trigger neuroplasticity which then results in cognitive change. In support of the latter, previous
405 data suggest that chronic (5 days) of STN-DBS results in dramatic inhibition of glutamatergic
406 synaptic transmission in the striatum, potentially through decreased expression of AMPA and
407 NMDA receptor expression or sensitivity (Gubellini et al., 2006). Such changes may reflect
408 neuroplastic processes, such as long-term depression, that could arise through circuit-level
409 changes in the thalamo-cortico-striatal loop as a result of repeated STN-DBS (Albin et al., 1989).
410 Chronic STN-DBS can also increase expression of brain derived neurotrophic factor (BDNF) in
411 the striatum (Spieles-Engemann et al., 2011). Whether such neuroplastic events could contribute
412 to new learning in risk-preferring rats, and therefore a shift towards more optimal decision-
413 making, remains to be empirically determined. Interestingly, deep brain stimulation of the fornix
414 increases BDNF levels in the hippocampus (Gondard et al., 2015), an effect which may be linked
415 to the ability of this manipulation to improve memory function in an experimental model of
416 dementia (Hescham et al., 2013).

417 STN-DBS has been found effective in the treatment of OCD (Mallet et al., 2002; Mallet
418 et al., 2008), a patient group that is likewise impaired on the IGT (Cavedini et al., 2010; Starcke

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419 et al., 2010; Zhang et al., 2015), and in which OFC dysfunction has long been documented
420 (Modell et al., 1989; Saxena et al., 1999; Evans et al., 2004). Although therapeutic benefit may
421 still be attributed to normalised frontal function (Le Jeune et al., 2010), recent work has
422 documented an electrophysiological signature associated with OCD in the ventromedial STN
423 that is associated with OCD symptom severity, as well as clinical benefit post-DBS (Piallat et al.,
424 2011; Welter et al., 2011; Mulders et al., 2016). Disrupted information processing at the level of
425 the STN, and its normalization, may therefore play a more fundamental role in both the
426 manifestation of OCD and its resolution following STN-DBS (Mulders et al., 2016). Whether a
427 similar aberration in activity likewise characterises, and even drives, maladaptive risky choice or
428 compulsive gambling behavior remains to be determined. Based on the current data, and
429 observations that STN-DBS may be beneficial in reducing compulsive drug use (Pelloux and
430 Baunez, 2013), such a possibility may be worthy of investigation.

431 With regards to addiction risk, some data suggest that patients who have a family history
432 of alcohol use, and are potentially more vulnerable to addictions themselves, are more likely to
433 develop impulse control problems following DRT (Voon et al., 2007). Interestingly, risk-
434 preferring rats, i.e. those who benefited from STN-DBS in the current study, are uniquely and
435 negatively affected by concurrent cocaine self-administration: their decision making becomes
436 even more risky, whereas optimal decision-makers are unaffected, despite self-administering
437 comparable amounts of cocaine (Ferland and Winstanley, 2016). Risk-preferring animals also
438 show enhanced cue-induced drug-seeking with extended time in withdrawal, a putative
439 behavioral marker of enhanced relapse vulnerability (Grimm et al., 2001). As such, risk-
440 preferring rats may constitute a useful model of addiction vulnerability. In humans, the time-
441 course across which risky decision-making is evident in SUD tracks subjective craving for drug,

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442 such that both resolve at a similar time-point following successful treatment (Wang et al., 2013).
443 Conversely, unresolved and persistent risky decision making on the IGT in SUD patients is a
444 strong predictor of treatment failure (Stevens et al., 2013). As such, a manipulation that
445 ameliorates risky choice on the rGT/IGT, such as STN-DBS, could have therapeutic efficacy for
446 treating SUD. Indeed, a growing body of preclinical and clinical data suggest that STN-DBS
447 may be useful in reducing drug use and drug craving (Baunez et al., 2005; Rouaud et al., 2010;
448 Pelloux and Baunez, 2013). Should our observation that STN-DBS improves risky decision
449 making translate to human subjects, this would suggest an additional cognitive mechanism by
450 which this manipulation improves treatment outcomes.

451 To conclude, DBS is increasingly being considered for psychiatric conditions, rather than
452 purely neurological diseases, due to the urgent need for effective treatments, and lack of
453 innovation in effective pharmacotherapeutics for mental illness. Given the invasive nature of the
454 procedure, a cautious approach is understandable, and the need for further research into the
455 potential cognitive effects of DBS, and its mechanism of actions, should not be minimised.
456 However, by making use of the considerable degree of experimental control possible when using
457 an animal model, this study strongly suggests that STN-DBS does not impair decision making
458 under uncertainty, despite fears to the contrary, but may actually ameliorate the maladaptive
459 persistence in the selection of risky options seen in a subgroup of individuals. These data add to
460 the growing body of research arguing that STN-DBS may be effective more widely in disorders
461 of compulsion and maladaptive drive.

462

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694 *Figure legends*

695 Figure 1: Task schematic of the rGT. A nose poke response in the food tray extinguished the
696 traylight and initiated a new trial. After an inter-trial-interval (ITI) of 5 s, four stimulus lights
697 were turned on in holes 1, 2, 4 and 5, each of which was associated with a different number of
698 sugar pellets (1 - 4 pellets, labelled P1-P4). The animal was required to respond at a hole within
699 10 sec. This response was then rewarded or punished depending on the reinforcement schedule
700 for that option (indicated by the probability of a win or loss in brackets). If the animal was
701 rewarded, the stimulus lights turned off and reward was delivered. If the animal "lost", the
702 stimulus light in the chosen hole flashed at a frequency of 0.5Hz for the duration of the punishing
703 time-out, and all other lights were extinguished. The order of the options from left to right was
704 counter-balanced across the cohort (version A as shown, version B: 4,1,3,2). The maximum
705 number of pellets available per 30 min session shows that P1 and P2 were better than P3 and P4.
706 The percent choice of the different options was the primary dependent variable. A score variable
707 was also calculated, as for the IGT, to determine the overall level of risky choice as follows:
708 [(P1+P2) – (P3+P4)]. A negative score indicated a preference for the risky options, and rats
709 were categorised as optimal decision-makers or risk-preferring rats accordingly. Adapted with
710 permission from (Barrus et al., 2015).

711 Figure 2: Experimental time line delineating the duration and order of each phase of the study.

712 Figure 3: Histological verification of electrode location. The location of all acceptable electrode
713 tips within the subthalamic nucleus are shown in black circles. Coordinates are relative to
714 bregma. Plates modified from (Paxinos and Watson, 1998)

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715 Figure 4: Effects of STN-DBS on decision-making variables. While STN-DBS did not alter
716 relative preference for any of the four options in optimal decision-makers (A), this manipulation
717 significantly increased optimal choice in risk-preferring rats across the last seven DBS sessions,
718 as indicated by increased choice of the best option, P2 (B) and a resulting increase in the score
719 variable (C). This effect was no longer evident once stimulation was no longer applied during
720 the rGT. Data shown are group mean ± SEM.

721 Figure 5: Weight gain throughout food restriction and pair-housing. Body weight was recorded
722 three to five days per week during the first month of food restriction, and at least once per week
723 for the duration of the experiment. As expected, all rats showed robust weight gain over time,
724 and the rate or degree of weight gain did not differ between optimal decision-makers and risk-
725 preferring rats. Data shown are group mean ± SEM

726 Figure 6: Effects of STN-DBS on non-choice variables. Regardless of baseline decision-making
727 strategy, STN-DBS transiently decreased premature responding, an effect that reached
728 significance in sessions four through six (A), and significantly increased omissions (B) across all
729 sessions in which stimulation was applied. While STN-DBS did not alter the number of trials
730 completed by optimal decision-makers, risk-preferring rats tended to complete more trials in
731 sessions 4-6 of stimulation, matching the epoch in which the most dramatic improvements in
732 decision making were observed (Figure 4). None of these effects were still evident in the three
733 sessions immediately following the final DBS session. Data shown are group mean ± SEM.

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Phase	Choice latency (s)		Reward collection latency (s)	
	Optimal	**Risk-preferring**	**Optimal**	**Risk-preferring**
Post-op BL	1.25 (0.18)	1.58 (0.21)	1.56 (0.10)	1.25 (0.17)
Mock DBS	1.27 (0.16)	1.73 (0.14)	1.61 (0.10)	1.33 (0.25)
DBS S1-3	**2.36 (0.22)**	**2.33 (0.16)**	**2.58 (0.35)**	**2.05 (0.29)**
DBS S4-6	**2.16 (0.20)**	**2.81 (0.26)**	**2.38 (0.22)**	**2.46 (0.41)**
DBS S7-10	**2.28 (0.30)**	**2.92 (0.38)**	**2.22 (0.25)**	**2.55 (0.42)**
Post DBS S1-3	1.26 (0.20)	1.79 (0.37)	1.65 (0.10)	1.45 (0.21)

Table 1: Latencies to make a choice and collect reward during the different phases of the experiment in optimal decision-makers and risk-preferring rats. Bold type signifies a significant difference ($p < 0.05$) from the mock DBS sessions. Data are mean (SEM).

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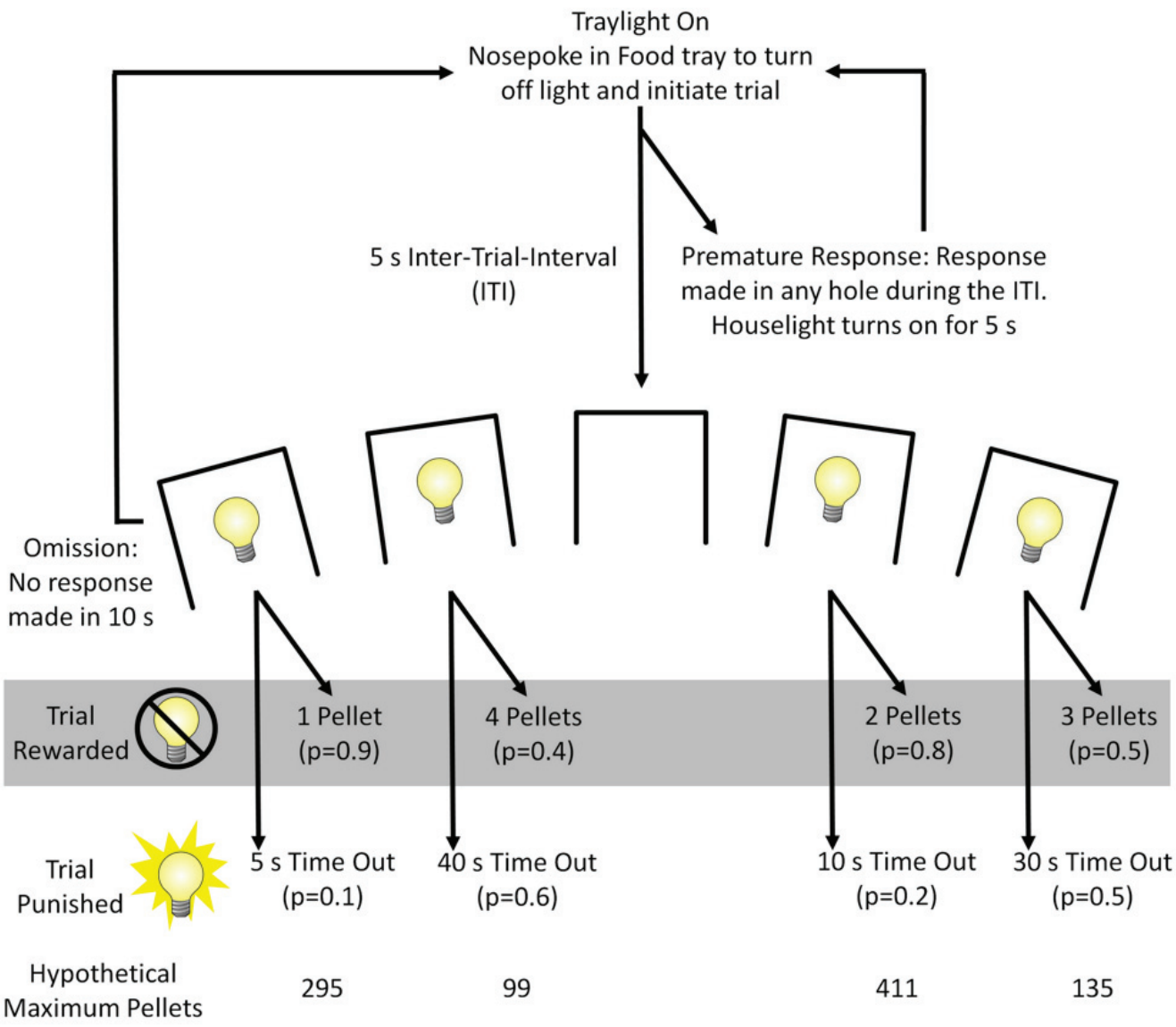

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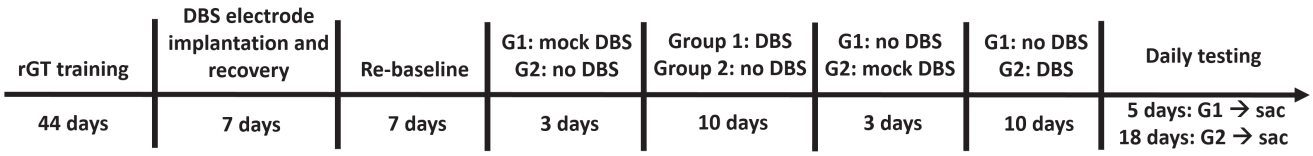

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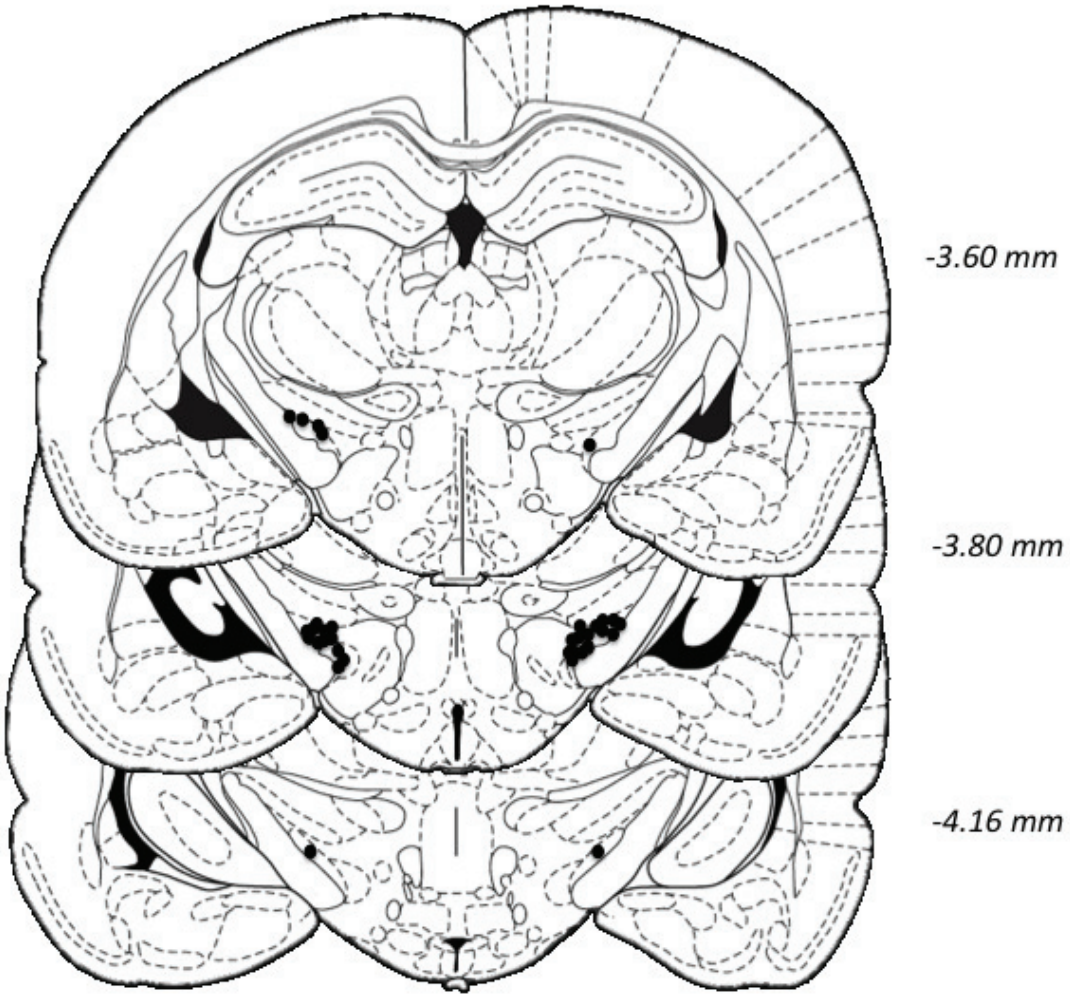

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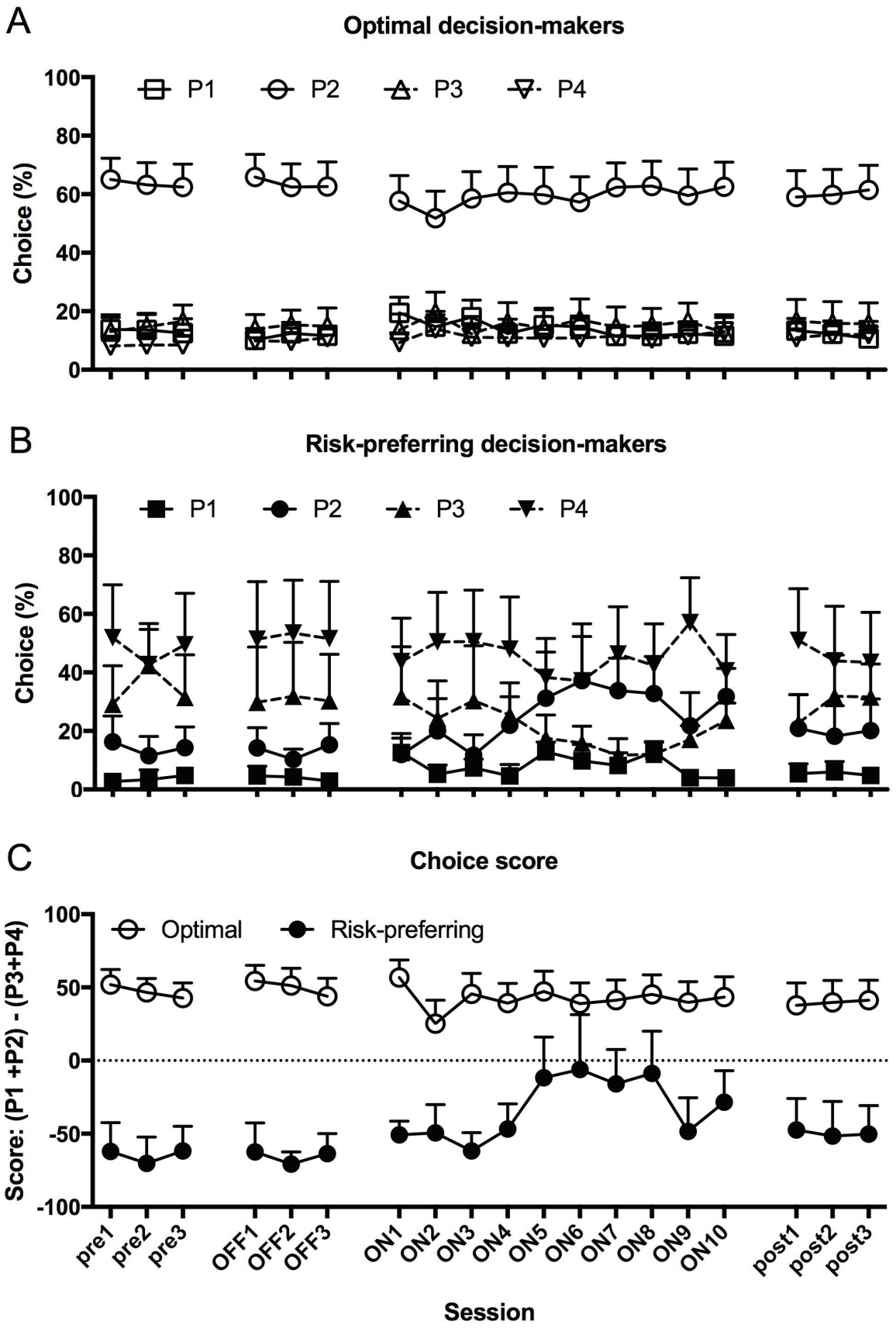

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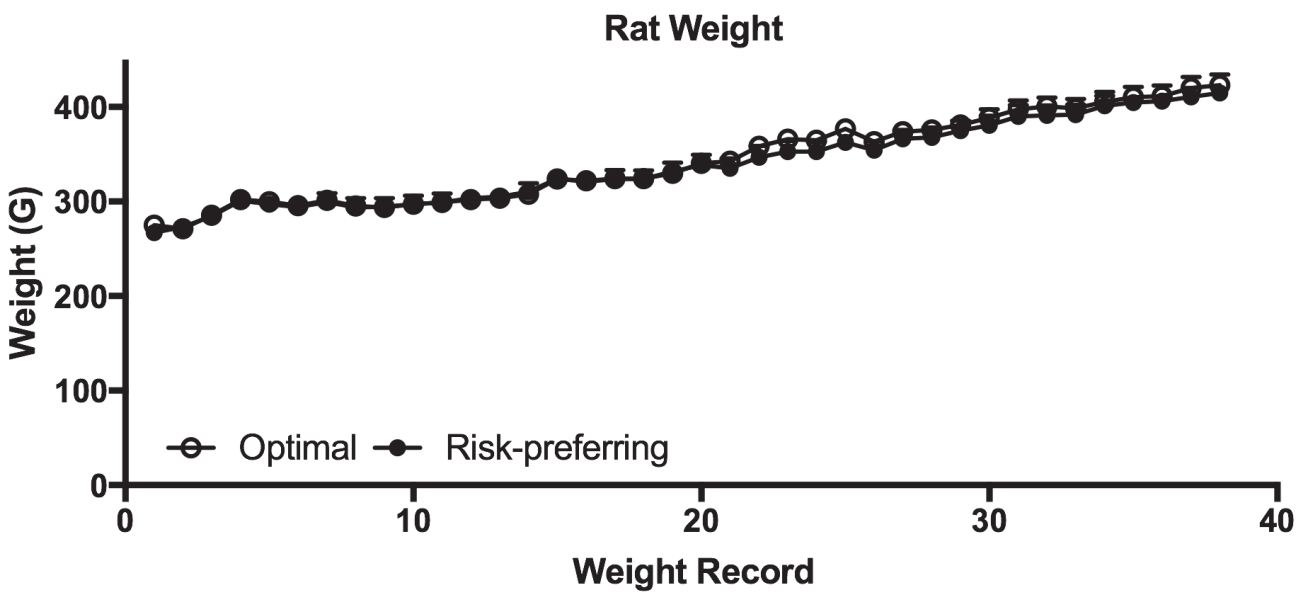
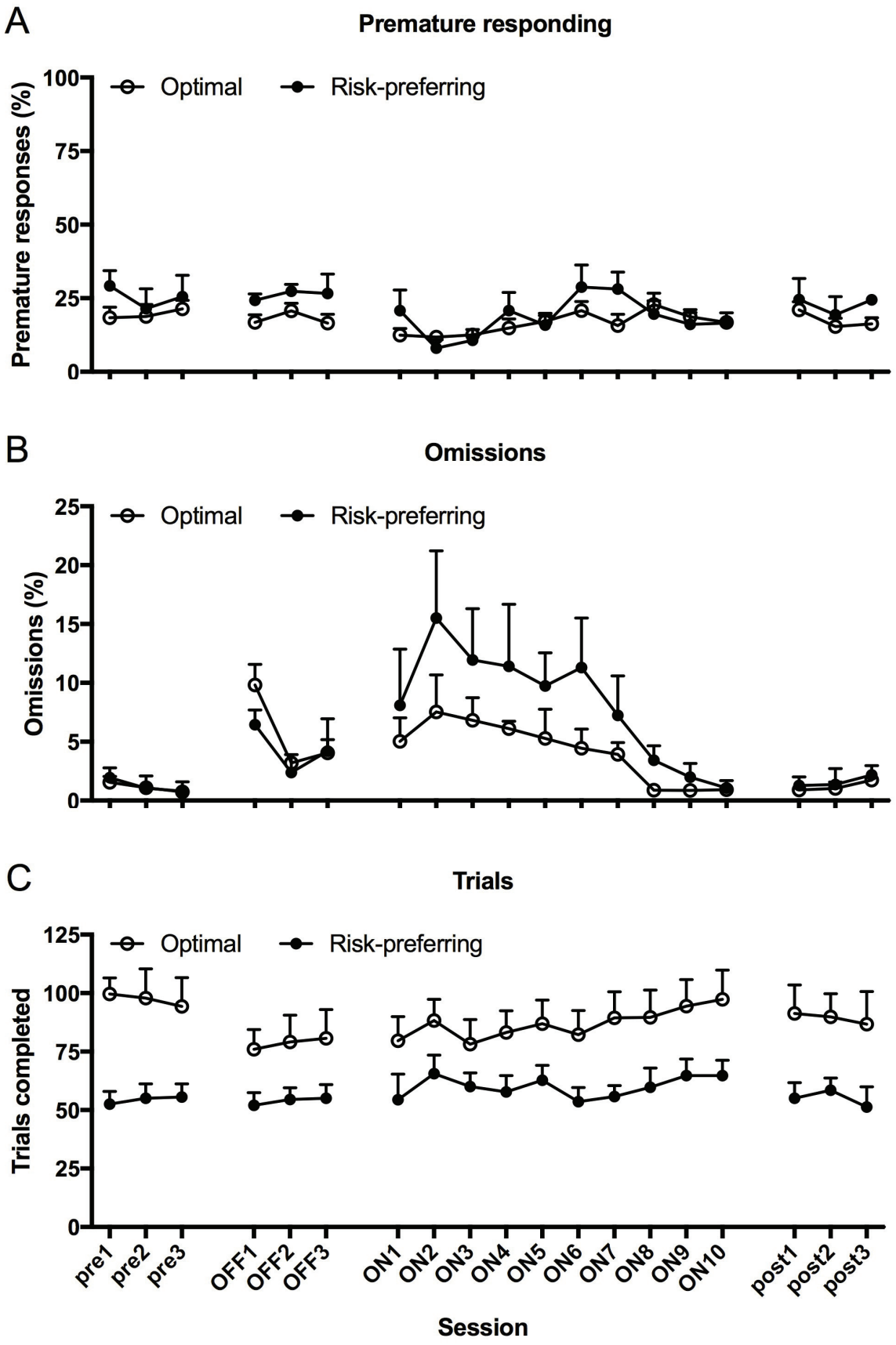
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