

1 INTER-INDIVIDUAL AND INTER-STRAIN DIFFERENCES IN  
2 COGNITIVE AND SOCIAL ABILITIES OF DARK AGOUTI AND WISTAR  
3 HAN RATS.

4 Lucille Alonso<sup>a,b</sup>, Polina Peeva<sup>c</sup>, Arnau Ramos-Prats<sup>d</sup>, Natalia Alenina<sup>c,e</sup>, York Winter<sup>a,b</sup>,  
5 Marion Rivalan<sup>a,b\*</sup>

6

7

8 <sup>a</sup> Humboldt University, Berlin, Germany

9 <sup>b</sup> Charité University Medicine, Berlin, Germany

10 <sup>c</sup> Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany

11 <sup>d</sup> Department of Pharmacology, Innsbruck Medical University, Innsbruck, Austria

12 <sup>e</sup> Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg,  
13 Russia

14 \* Corresponding author: E-mail address: [marion.rivalan@charite.de](mailto:marion.rivalan@charite.de).

15 Postal address: Charité - Universitätsmedizin Berlin, Exzellenzcluster NeuroCure, Animal

16 Outcome Core Facility - Behavioural Phenotyping, CharitéCrossOver, Virchowweg 6, 10117

17 Berlin, Germany

18 **Abstract**

19 **Background:** Healthy animals showing extreme behaviours spontaneously that resemble  
20 human psychiatric symptoms are relevant models to study the natural psychobiological  
21 processes of maladapted behaviours. Healthy poor decision makers (PDMs) identified using a  
22 Rat Gambling Task, co-express a combination of cognitive and reward-based characteristics  
23 similar to symptoms observed in human patients with impulse-control disorders. The main  
24 goals of this study were to 1) confirm the existence of PDMs and their unique behavioural  
25 phenotypes in the Dark Agouti (DA) and Wistar Han (WH), 2) to extend the behavioural  
26 profile of the PDMs to probability-based decision-making and social behaviours and 3) to  
27 discuss how the key traits of each strain could be relevant for biomedical research. **Methods:**  
28 We compared cognitive abilities, natural behaviours and physiological responses in DA and  
29 WH rats using several tests. We analysed the results at the strain and the individual level.  
30 **Results:** Previous findings in WH rats were reproduced and could be generalized to DA. Each  
31 PDM of either strain displayed a similar, naturally occurring, combination of behavioural  
32 traits, including possibly higher social rank, but no deficits in probability-based decision-  
33 making. A Random forest analysis revealed interesting discriminating traits between WH and  
34 DA. **Conclusion:** The reproducibility and conservation of the socio-cognitive and behavioural  
35 phenotypes of GDM (good decision maker) and PDM individuals in the two genetically  
36 different strains of WH and DA support a good translational validity of these phenotypes.  
37 Both DA and WH rat strains present large phenotypic variations in behaviour pertinent for the  
38 study of the underlying mechanisms of poor decision making and associated disorders.

39

40

41

42

43

## 44 **1. Introduction**

45 Inter-individual variability in behaviour is a natural phenomenon that applies to all  
46 behavioural dimensions. In the laboratory, however, these phenotypic variations are often  
47 perceived as inconvenient and are usually masked by averaging of the data. Considering the  
48 spectrum nature of brain disorders, most psychiatric symptoms can be conceptualized as  
49 extreme manifestations of different behavioural traits [1]. Thus, the identification of animals  
50 spontaneously exhibiting extreme behaviours that resemble human psychiatric symptoms  
51 offers the opportunity to study the natural psychobiological processes underlying maladapted  
52 behaviours [2,3].

53 Utilizing this dimensional approach to the analysis of the Rat Gambling Task (RGT), a rat  
54 version of the human Iowa Gambling task, we and others have consistently identified three  
55 types of decision makers spontaneously existent in healthy groups of Wistar Han (WH) and  
56 Sprague Dawley rats [4–8]. Whereas the majority of rats develop a strong preference for the  
57 most advantageous options in the RGT (good decision makers [GDMs]), a smaller group  
58 prefer the least advantageous options (poor decision makers [PDMs]) and some show no clear  
59 preference (intermediate phenotype [INT]) [6].

60 Compared to GDMs, healthy PDMs were found to co-express several cognitive impairments  
61 and reward-based deficits similar to symptoms observed in human patients with substance  
62 abuse disorder, pathological gambling disorder, attention-deficit hyperactivity-disorder  
63 (ADHD) or suicidal behaviour [6,8,9]. Healthy PDMs were more prone to take risks in  
64 potentially dangerous environments, showed higher motivation to obtain a reward and greater  
65 anticipatory (motor) impulsive responses, were more inflexible and chose less advantageously  
66 in the RGT due to their over-valuation of the high-reward/high-risk options compared with  
67 GDMs [8]. Their social abilities and spontaneous level of activity (e.g. arousal) are, however,  
68 still unknown [10,11]. At the biological level, PDMs also presented a particular profile  
69 compared to GDMs. PDMs showed different use of distinct regions of the prefrontal cortex

70 (PFC) to solve the RGT [7], a decreased c-Fos activation in the PFC-subcortical network  
71 normally used by the GDMs [5] and an opposite pattern of serotonin turnover compared to  
72 GDMs, with higher turnover rate in the PFC (i.e. infralimbic cortex) but lower turnover rate in  
73 subcortical areas (i.e. basolateral amygdala) [5].

74 Among other candidates, the serotonergic system appears to be a promising pathway that  
75 could be responsible for the co-expression of the traits constitutive of the PDM  
76 psychobiological profile. Indeed, serotonin plays a critical role in executive functioning  
77 (decision making, impulse control, flexibility, attention), mood control, sociality and  
78 emotional state [9,12–19], and is a privileged therapeutic target for treating pathologies  
79 associated with poor decision making such as substance abuse, ADHD, suicidal behaviour,  
80 impulsive control disorders (i.e., eating disorders, gambling), psychopathy and other  
81 aggression related disorders [20–22]. Although more than one behavioural domain was rarely  
82 tested in the same individual, other studies have reported equivalent deleterious effects of the  
83 dietary, genetic or pharmacological reductions of central serotonin function on group (*vs.*  
84 inter-individual) performance in decision making [23,24], motor impulsivity [25] and  
85 cognitive inflexibility [26], but also in social recognition [27], aggression [28] and social  
86 hierarchy [29,30].

87 In order to evaluate the functional role of the serotonergic system in the expression of the  
88 vulnerable behavioural profile in rats, we plan to use an animal model of congenital central  
89 serotonin depletion [31]. The background strain of this newly created rat line is the Dark  
90 Agouti (DA) strain. However, historically, DA rats have been mainly used in physiological  
91 studies, and have only rarely been tested for their cognitive abilities [32] and never for their  
92 social skills. We also wanted to confirm that this inbred strain of rats naturally displayed  
93 comparable behavioural phenotypic variability to WH [33].

94 Therefore, the goal of this study was to evaluate the conservation of the GDM and PDM  
95 profiles between the WH and DA strains by establishing the bio-behavioural profile of the DA

96 rats, examining the same behavioural traits naturally exhibited by the WH rats. We also used  
97 this opportunity to test the reproducibility of previous results obtained from a different  
98 laboratory with the WH strain, and to extend the behavioural profile of the PDMs to  
99 serotonin-sensitive tasks such as probability based decision making and social behaviours. We  
100 compared cognitive abilities, natural behaviours and physiological responses in DA and WH  
101 rats using several tests. These tests included the RGT, the reversed-RGT, the Delay  
102 discounting task (DDT), the Probability discounting task (PDT), the Fixed-interval and  
103 Extinction schedule of reinforcement (FI-EXT), a semi-automated version of the Visible  
104 Burrow System (VBS), the Social Recognition test (SRt) and the Elevated Plus maze (EPM).  
105 The results were analysed at both the group (strain) and individual (within strain) levels.  
106 Finally, by performing a random forest analysis, we were able to highlight key traits to  
107 discriminate one strain from the other and discuss the relevance of using each strain in  
108 different types of studies.

109

## 110 **2. Material and Methods**

### 111 **2.1. Animals**

112 In this study, we used 42 male WH rats (Charles River, Germany) and 42 male DA rats (Max  
113 Delbrück Center for Molecular Medicine, Berlin). They arrived at our animal facility at  
114 between six and nine weeks of age. Rats of the same strain were housed in pairs in standard  
115 rat cages (Eurostandard Type IV, 38 cm x 59 cm) in two temperature-controlled rooms (22°C  
116 and 50% humidity) with inverted 12-hour light cycles (lights on at 20:00 in room 1 or 01:00  
117 in room 2). The two different light cycles allowed us to maximize the use of four operant  
118 cages with two groups of 12 animals tested either in the morning or in the afternoon (i.e. 24  
119 animals per day). To habituate the animals to their new environment, they were left  
120 undisturbed for at least a week after arrival. Thereafter, they were handled daily by the  
121 experimenter. Two weeks before the beginning of the training phase, rats were marked

122 subcutaneously with a radio-frequency identification (RFID) chip (glass transponder 3 mm,  
123 Euro I.D.) under short isoflurane anaesthesia. Rats were between 9 and 12 weeks of age when  
124 first trained in the operant cages. Rats had *ad libitum* access to food and water. During  
125 operant training and testing, rats were maintained at 95% of free-feeding weight by food  
126 restriction. One DA rat was excluded from the RGT and reversed-RGT analysis since it did  
127 not show sampling behaviour at the start of the test and a strong side bias over the entire  
128 duration of the tests. One DA extreme outlier ( $< \text{mean} - 2 \times \text{SD}$ ) was excluded from the weight  
129 analysis after VBS housing.

130

## 131 **2.2. Ethics**

132 All procedures followed national regulations in accordance with the European Communities  
133 Council Directive 2010/63/EU. The protocols were approved by the local animal care and use  
134 committee and run under the supervision of the animal welfare officer of the animal facility of  
135 the Charité University Medicine.

136

## 137 **2.3. Behavioural tests**

138 Training and testing started 1 h after the beginning of the dark phase. Animals were  
139 habituated to the experimental room conditions for 30 min. The order of the tests and inter-  
140 test pauses was chosen to minimize any interference of one test on another (Fig. 1A). One  
141 group of 12 WH rats performed the DDT before the VBS housing. Not all animals underwent  
142 all tests (as can be seen from the different numbers of animals in the figures).

143

### 144 **2.3.1. Operant system and tests**

145 All operant training and testing was done in four operant cages (Imetronic, Pessac, France)  
146 controlled by a computer. The operant cages contained a curved wall on one side equipped  
147 with one to four nose-poke holes, depending on the test. On the opposite wall, a food

148 magazine was connected to an outside pellet dispenser. 45 mg sweet pellets (5TUL, TestDiet,  
149 USA) were used. A clear partition with a central opening was placed in the middle of the  
150 cage, ensuring an equal distance to all nose-poke holes from the central opening.

151

### 152 **2.3.1.1. Complex decision making in the RGT**

153 The training and testing procedures have been described previously [6]. The operant cages  
154 had four nose-poke holes on the operant wall. Training 1 started with the four nose-poke holes  
155 lit; a single nose poke by the rat led to the delivery of one pellet, and the lights in the non-  
156 selected holes were then turned off until the food magazine was visited and all holes were lit  
157 again. Daily training continued until rats obtained 100 pellets in a 30 min session (cut-off  
158 criteria). During Training 2, two consecutive nose pokes at the same hole were required to  
159 obtain one pellet; this training continued until rats obtained 100 pellets in a 30 min session.  
160 After Training 2 and for all subsequent testing phases, rats always had to make two  
161 consecutive nose pokes at the same hole for a valid choice. Training 3 was a single 15 min  
162 session in which two pellets were delivered after a choice was made, up to a maximum of 30  
163 pellets. A forced training (Training 4) was given to counter any side preferences developed  
164 during the training procedure. This training was given when a rat had chosen the holes of one  
165 side of the operant wall in more than 60% of choices during the last session of Training 2.  
166 During the first phase of Training 4, only the two nose-poke holes on the non-preferred side  
167 were lit, and choosing one of them led to the delivery of one pellet. After the collection of the  
168 first 15 pellets, the second phase of Training 4 started with all four holes lit. Choosing one  
169 hole from the side preferred in Training 2 was rewarded (with one pellet) in only 20% of the  
170 cases, whereas choosing from the other (least-preferred) side was rewarded in 80% of the  
171 cases. The cut-off criterion was set at a maximum of 50 pellets or 30 min. This training phase  
172 usually took between five and seven days, and the RGT was performed the next day.

173 During the test, the four nose-poke holes were lit and each hole was associated with an  
174 amount of reward and a possible penalty (time-out). Two holes on one side were rewarded  
175 with two pellets and associated with unpredictable long time-outs (222 s or 444 s; probability  
176 of occurrence 50% and 25%, respectively); over the long term, these options were  
177 disadvantageous. Two holes on the other side were rewarded with one pellet and associated  
178 with unpredictable short time-outs (6 s or 12 s; probability of occurrence 50% and 25%,  
179 respectively); over the long term, these options were advantageous. The theoretical gain of  
180 pellets for the advantageous options was five times higher than for the disadvantageous  
181 options at the end of the test (i.e., 60 min; [6] see Supplement 1). After a choice, the reward  
182 was delivered and the selected hole remained lit until a visit to the magazine or for the  
183 duration of the time-out. During this time, all the nose-poke holes were inactive. The cut-off  
184 criterion was 250 pellets.

185 The percentage of advantageous choices during the last 20 min of the RGT was used to  
186 identify GDMs and PDMs. GDMs were defined as choosing >70% advantageous options and  
187 PDMs as choosing <30% advantageous options. Intermediate animals (INTs) chose between  
188 30% and 70% advantageous options and did not show a steady preference for only one type of  
189 option at the end of the test. To visualize progression of preference during the RGT,  
190 advantageous choices were plotted for 10 min time intervals. In a previous study, fast and  
191 slow GDMs were described based on how rapidly they developed a preference for the  
192 advantageous options [5]. Fast GDMs chose >70% advantageous options during the first 20  
193 min of the test, whereas slow GDMs stayed < 70%. The motivation to obtain a reward  
194 (reward sensitivity) was indicated by the mean latency to visit the feeder after a choice.

195

### 196 **2.3.1.2. Cognitive flexibility in the reversed-RGT**

197 Animals were tested in the reversed-RGT 48 h after performing the RGT [6]. For this test, the  
198 contingencies associated with the four holes during the RGT were spatially reversed by



199 switching the sides for the advantageous and disadvantageous options. A test was 60 min (or a  
200 cut-off of 250 pellets).

201 A flexibility score was calculated as the preference for the same preferred options during the  
202 reversed-RGT and the RGT, which meant choosing holes at the location of the non-preferred  
203 option during the RGT. For INTs and GDMs, the flexibility score was determined from the  
204 percent of advantageous choices during the last 20 min. For PDMs, the flexibility score was  
205 determined from the percent of disadvantageous choices during the last 20 min.

206 Flexible rats had flexibility scores  $> 60\%$ , undecided rats had flexibility scores between  $60\%$   
207 and  $40\%$ , and inflexible rats had flexibility scores  $< 40\%$ .

208

### 209 **2.3.1.3. Cognitive impulsivity in the DDT**

210 For this task, the two outside nose-poke holes (25 cm apart) were used. The operant cages  
211 were otherwise identical to the other tests. During the DDT, one nose-poke hole (NP1) was  
212 associated with a small immediate reward (one pellet); the second nose-poke hole (NP5) was  
213 associated with a large delayed reward (five pellets). The protocol was adapted from Rivalan  
214 et al. [8], in which levers were used instead of nose-poke holes.

215 During training, the large reward was delivered immediately after the choice (0 s delay),  
216 which allowed the rats to develop a preference for NP5. After a choice, the selected hole  
217 stayed lit for 1 s. The magazine and house lights were turned on during a 60 s time-out. A  
218 session lasted for 30 min or until 100 pellets were delivered. A  $> 70\%$  preference for the large  
219 reward option on two consecutive sessions with  $\leq 15\%$  difference was required to start the  
220 test. At least three training sessions were performed. During the test, choosing NP5 induced  
221 the delivery of the large reward after a fixed delay, and NP5 stayed lit for the duration of the  
222 delay. After the delivery of the large reward, the magazine and the house lights were turned  
223 on for a time-out (60 s minus the duration of the delay). The delay was fixed for one day, but  
224 increased by 10 s from 0 s to 40 s after a stability criterion ( $\leq 10\%$  variation of choice of the

225 large reward during two consecutive sessions) was met. The test sessions lasted for 60 min or  
226 until 100 pellets were delivered. The preference for the large delayed reward was calculated  
227 as the mean percentage of NP5 choices during the two stable sessions. Individual area under  
228 the curve (AUC) was measured to estimate the cognitive impulsivity. The choices for the  
229 large delayed reward were normalized to the choice for the large delayed reward during the  
230 training phase (0 s delay) and plotted against the normalized delays on the x-axis (from 0 to  
231 1). The AUC was calculated as the sum of the areas of the trapezoids formed by the individual  
232 data points and the x-axis following the formula  $(x_2-x_1)[(y_1+y_2)/2]$ , [34]. The total number  
233 of nose pokes during the last training session was used as an index of the activity during this  
234 test.

235

#### 236 **2.3.1.4. Cognitive risk-taking in the PDT**

237 For this task, the two outside nose-poke holes (25 cm apart) were used. The operant cages  
238 were otherwise identical to the other tests. During the PDT, one hole (NP1) was associated  
239 with a small and certain reward (one pellet) and the second hole (NP5) was associated with a  
240 large but uncertain reward (five pellets) [24].

241 During training, choosing NP5 always delivered the large reward (probability  $P=100\%$ ). This  
242 allowed rats to develop a preference for NP5. NP1 always delivered one pellet. The reward  
243 was delivered 4 s after a choice was made in one of the nose-poke holes, and the hole stayed  
244 lit until pellet collection. The reward delivery was followed by a 15 s time-out during which  
245 the magazine light was on. A session lasted 25 min or until 200 pellets were delivered. A  $\geq$   
246 70% preference for the large reward was required to start the test. At least three training  
247 sessions were performed. During the test, the delivery of the large reward was associated with  
248 a set probability ( $P = 80\%, 66\%, 50\%, 33\%, 25\%, 20\%, 17\%, 14\%, 11\%$ , or  $9\%$ ). The  
249 probability was fixed for one day and decreased every day. A session lasted 25 min or until  
250 200 pellets were delivered. For each individual, the AUC was calculated as in the DDT. The

251 preference for the large reward was normalized to the preference during training and plotted  
252 against the probability values expressed as odds, with  $\text{odds} = (1/P)-1$  and normalized (x-axis  
253 from 0 to 1) [35].

254

### 255 **2.3.1.5. Motor impulsivity in the FI-EXT schedule of reinforcement**

256 For this task, only the central nose-poke hole was used. The operant cages were otherwise  
257 identical to the other tests. The FI consists of two phases: a fixed time interval during which  
258 choices are not rewarded, followed by a phase where a choice can be rewarded [8]. The EXT  
259 is a longer, fixed time interval during which no choices are rewarded. Both FI and EXT are  
260 conditions that cause frustration in the animal. A session consisted of seven FI of variable  
261 duration depending on the session and one EXT of 5 min; this pattern was repeated two times  
262 within a single session. The maximum number of pellets was 14 during a single session. FI  
263 lasted 30 s for the first four sessions, 1 min for the next four sessions, 2 min for the next three  
264 sessions and 1 min for the final four sessions. The final four sessions with a 1 min FI were the  
265 actual test. During the FI, the house light was on and the central nose-poke hole was inactive.  
266 At the end of the FI, the house light turned off and the central nose-poke was lit and became  
267 active; two consecutive nose-pokes induced the delivery of one pellet, the central nose-poke  
268 light was turned off and the tray light was lit. A visit to the tray induced the start of the next  
269 FI. After seven consecutive FI, the EXT period started, with all lights off and no  
270 consequences associated with nose poking. The mean number of nose pokes was measured  
271 for each FI and EXT period. We summed nose pokes for 10 s intervals during FI to visualize  
272 the anticipatory activity of the rats. Likewise, we summed nose pokes for 1 min intervals  
273 during EXT to visualize the perseverative activity. As described earlier [36], the data from the  
274 first FI of the session and the first FI after the first EXT were excluded because they deviated  
275 from the other intervals.

276

### 277 **2.3.2. Social behaviour in the VBS**

278 The VBS consisted of an open area (2000P, 61x43 cm, Tecniplast, Italy) extended to the top  
279 by high Forex PVC foam and Plexiglas (Modulor, Germany) walls and connected through  
280 two transparent tunnels to a burrow system placed into a second Type IV cage  
281 (Supplementary Fig. 5I). The burrow system was made of infrared transparent black plastic  
282 and consisted of a large chamber, a small chamber and a tunnel system (25 cm x 53 cm).  
283 Throughout the test, the burrow system remained in the dark. Food and water were available  
284 in the open area. A grid of 32 RFID detectors (PhenoSys, Berlin, GmbH) was placed below  
285 the VBS in order to automatically determine individual animal positions using the program  
286 PhenoSoft (PhenoSys Berlin, GmbH). An infrared camera (IP-Camera NC-230WF HD 720p,  
287 TriVision Tech, USA) above the VBS recorded a 30 s video every 10 min (CamUniversal,  
288 CrazyPixels, Germany). The software PhenoSoft ColonyCage (PhenoSys Berlin, GmbH) was  
289 used to identify individuals in the videos. Six rats were housed in the VBS for seven days in a  
290 humidity- and temperature-controlled room (temperature 22°C to 24°C, humidity 45% to  
291 50%). The behaviours expressed by the animals were scored on the videos of the last two days  
292 of the VBS during the first 4 h of each dark and light phase (100 videos) using a scan  
293 sampling method [37]. Four classes of behaviours were scored: affiliative, aggressive,  
294 defensive and maintenance (details in Table 1). The behaviours with a median of < 5  
295 occurrences per strain were grouped for the analysis. The body weight of the animals was  
296 measured before and after the VBS housing. Although wounds were rarely observed during  
297 this study, they were counted and documented at the end of the VBS housing. The activity  
298 (distance travelled) and the place preference were extracted using the software PhenoSoft  
299 analytics (PhenoSys Berlin, GmbH). The time spent in the open area of the VBS was  
300 measured using the data collected from the grid of detectors.

301

302

303 **Table 1. Ethogram of the behaviours scored during the VBS housing.** Based on Burman  
304 et al., Rademacher et al., and Whishaw, Ian Q and Kolb Bryan [38–40].  
305

Category	Behaviour	Definition
Affiliative	Allogrooming	Gentle grooming of another rat which is not pinned on its back
Affiliative	Attending	Orienting the head, ears and possibly the whole body toward another rat
Affiliative	Huddle	Lying in contact with another rat
Aggressive	Aggressive grooming	Vigorous grooming of another rat while pinning it
Aggressive	Attack bite	Sudden bite toward neck and back of another rat
Aggressive	Attack jump	Sudden jump toward another rat
Aggressive	Following	Rat runs after another one
Aggressive	Fight	Rough-and-tumble of two animals
Aggressive	Lateral attack	Arched-back posture oriented towards another rat, often including shoving and piloerection
Aggressive	Mutual upright posture	Both rats are standing in front of each other with vertical movements of the forepaw
Aggressive	Pinning	Being above another rat and maintaining it with the forepaw usually lying on its back
Aggressive	Struggle at feeder	Rats are pushing each other to have the place at the feeder
Aggressive	Struggle in tunnels	Rats are pushing each other to pass in the tunnel, struggling with the paws.
Defensive	Flight	Rapid movement away from another rat
Defensive	Freezing	Being immobile or maintaining a specific posture (crouching)
Defensive	Lateral defence	Exposing the flank to another rat.
Defensive	Supine posture	Lying on the back (exposure of the belly) because of another rat
Defensive	Upright defence	Exposing the belly to another rat in a half-erect posture
Maintenance	Drinking	Drinking water
Maintenance	Eating	Eating food
Maintenance	Grooming	Self-grooming, when a rat is cleaning itself with rapid little nibbles

306

### 307 **2.3.3. Faeces collection for corticosterone measurements**

308 Faeces collection took place one day before and immediately after VBS housing. At the same  
309 time of the day, all rats were simultaneously housed in individual cages with food, water and  
310 clean bedding. They spent up to 4 h in their cages. Every 30 minutes, faeces produced were

311 collected in microtubes and stored at -20°C until corticosterone extraction. Next, the samples  
312 were thawed and 0.1 g of faeces was added to 0.9 ml of 90% methanol, agitated for 30 min  
313 and centrifuged at 3000 rpm for 15 min. A 0.5 ml aliquot of the supernatant was added to 0.5  
314 ml water; this extract was stored at -20°C. Corticosterone measurements were done with an  
315 enzyme immunoassay (EIA) following the method of Lepschy et al., [41] in the laboratory of  
316 Dr. Dehnhard at the Leibniz Institute of Zoo and Wildlife Research, Berlin. The antibody was  
317 purchased from Rupert Palme (University of Veterinary Medicine, Vienna, Austria), and has  
318 been described in detail in [42]. Briefly, a double antibody technique was used in association  
319 with a peroxidase conjugate, generating a signal quantitatively measurable by photometry.  
320 The concentration of corticosterone was expressed in µg per g of faecal material as an  
321 indicator of stress level in an individual. The change in corticosterone level (%) was  
322 calculated from the values obtained before and after the VBS.

323

#### 324 **2.3.4. Social preference and recognition in the SRt**

325 The protocol was adapted from Shaha-Gold et al., [43]. The test took place in a square open  
326 field (50 cm), with a small cage placed in one corner (Supplementary Fig. 6A). The intruder  
327 animals were older WH rats with a prior habituation to the procedure. A video camera placed  
328 above the open field was used to record the experiment. Each rat was tested on two  
329 consecutive days. On the first day, the subject was placed in the open field containing the  
330 empty small cage in a corner for a habituation period of 15 min (Hab). The intruder was then  
331 placed in the small cage, and the subject could freely explore the open field for 5 min (E1).  
332 Subsequently, the small cage with the intruder was removed from the open field, and the  
333 subject remained alone in the open field for 10 min. The encounter procedure was repeated  
334 two more times with the same intruder (E2, E3). On the second day, the first 15 min of  
335 habituation were followed by a fourth encounter (E4) of 5 min with the same intruder as on  
336 day 1. After this encounter, a break of 30 min took place, during which the subject remained

337 alone in the open field. The last encounter then took place with an unfamiliar intruder placed  
338 in the same small cage for 5 min (Enew). The time spent in close interaction, including when  
339 the subject's head was in contact with the grid or within 1 cm of the grid and the nose directed  
340 to the grid, was measured for each encounter (E1, E2, E3, E4 and Enew) and for the first 5  
341 min of Hab. The social preference was calculated as the ratio of the interaction time in E1 and  
342 the interaction time during Hab. The short-term social recognition memory was calculated as  
343 the ratio of the interaction time in E1 and the interaction time in E3. The long-term social  
344 recognition memory was calculated by dividing the interaction time in Enew by the  
345 interaction time in E4.

346

### 347 **2.3.5. Exploration in the EPM**

348 The apparatus (made of black painted wood) consisted of two open arms (50 cm x 15 cm),  
349 alternating at right angles with two closed arms enclosed by 40 cm high walls. The four arms  
350 opened onto a central area (15 cm x 15 cm). There was a small ridge along the edge of the  
351 open arms (1 cm wide). The whole maze was elevated 60 cm from the ground. A video  
352 camera mounted above the maze and connected to a computer outside the experimental room  
353 was used to observe and record animal's behaviour. Light intensity in the open arms was 15  
354 Lux.

355 The experimenter placed a rat in the central area of the maze facing a closed arm. The rat was  
356 allowed to freely explore the maze for 10 min. The time spent and entries in the open and  
357 closed arms were measured. Risk taking was evaluated as time and number of visits in the last  
358 third of the open arms, constituting the more risky areas [6].

359

### 360 **2.4. Statistical analysis**

361 R (3.5.1) and R studio (1.1.456) free softwares were used for the statistical analyses [44]. For  
362 each test, two levels of analysis were considered: first, the inter-strain comparison, where

363 whole populations of WH vs. DA were compared, including INT animals; and second, the  
364 intra-strain comparison, where GDMs vs. PDMs were compared within each strain (excluding  
365 the INT animals).

366 Several non-parametric tests were used: a) the Fisher's exact test was used to compare the  
367 number of GDM and PDM in WH and DA groups; b) the Wilcoxon sign test  
368 (RVAidememoire package) [45] was used to compare the performance of the animals to the  
369 indifference level (DDT, PDT and SRT); c) the Wilcoxon rank sum test was used to compare  
370 groups of animals (DA vs. WH, GDM vs. PDM, and cluster groups between them), and  
371 whenever appropriate a continuity correction was applied to the data with the Wilcoxon rank  
372 sum test; and d) the non-parametric ANOVA with permutation for repeated measures  
373 (ImPerm package) [46] was used to compare groups of animals along different time points.  
374 The one sample t-test was used to compare the performances with the indifference level in the  
375 RGT. For the global discrimination between strains, we used a random forest (RF)  
376 classification with leave-one out validation (randomForest package) [47]. The traits included  
377 in this analysis were the variables from the different tests. Seventeen traits were used:  
378 percentage of advantageous choices during the last 20 min (RGT score); flexibility score;  
379 mean latency to visit the feeder after a choice (latency RGT); AUC in DDT; activity in DDT;  
380 AUC in PDT; mean number of responses in FI; mean number of responses in EXT; activity in  
381 VBS housing; time open VBS; number of aggressive, affiliative and maintenance behaviours  
382 in VBS test; weight variation in VBS housing; corticosterone variation in VBS housing;  
383 social preference ratio; and short-term recognition ratio. Missing values (NA) were not  
384 tolerated by the model; therefore, some animals and variables had to be excluded from the  
385 analysis (for example, two animals did not produce faeces during faeces collection and the  
386 EPM was not included). n = 22 WH and n = 24 DA were included in the RF analysis.

387

### 388 **3. Results**



### 389 **3.1. Cognitive and social abilities in DA and WH rats**

#### 390 **3.1.1. Decision-making abilities in the RGT**

391 At the beginning of the test (first 10 min), rats of both strains chose the advantageous and  
392 disadvantageous options equally (Fig. 1B). After 10 min and until the end of the test, the  
393 average performance of the DA rats moved toward the most advantageous options (20 min:  
394 one sample t-test for DA: 0.95 CI [55, 76.6],  $p = 0.005$ ), while the average performance of the  
395 WH rats remained at chance level for the entire duration of the test. However, at the end of  
396 the test (the last 20 min), large individual differences in choice became clear (Fig. 1C). In  
397 both strains, a majority of the rats preferred the most advantageous options at the end of the  
398 test ( $> 70\%$  advantageous choices during the last 20 min of test; good decision makers or  
399 GDMs); a smaller proportion preferred the most disadvantageous options ( $< 30\%$   
400 advantageous choices; poor decision makers or PDMs) and a minority of the animals showed  
401 intermediate performance (INTs). Of the DA rats, 79% were GDMs ( $n = 31$ ), 19% were  
402 PDMs ( $n = 8$ ) and 5% were INTs ( $n = 2$ ); of the WH rats, 50% were GDMs ( $n = 15$ ), 40%  
403 were PDMs ( $n = 12$ ) and 10% were INTs ( $n = 3$ ). The proportion of GDMs, INTs and PDMs  
404 between strains were not statistically different (Fisher's exact test,  $p=0.081$ ), only the  
405 proportion of GDMs vs. non-GDMs (INTs and PDMs) was higher in the DA than the WH  
406 (Fisher's exact test,  $p=0.04321$ ). These observations could explain why the average  
407 performance of the DA rats was above the 50% indifference level while the WH rats were not.  
408 The development of choice preferences during the test of the GDMs on one hand and of  
409 PDMs on the other hand were similar between strains (Supplementary Fig. 1A).

410 In both strains, "fast" and "slow" GDMs could be identified (Supplementary Fig. 1B). In the  
411 DA rats, the majority of the GDMs were the "fast" type (76%;  $n = 23/30$ ), choosing  
412 significantly and consistently the advantageous options at 20 min of testing. In the WH rats,  
413 only half of the GDMs were the "fast" type (53%,  $n = 8/15$ ).

### 415 **3.1.2. Motivation for reward in the RGT**

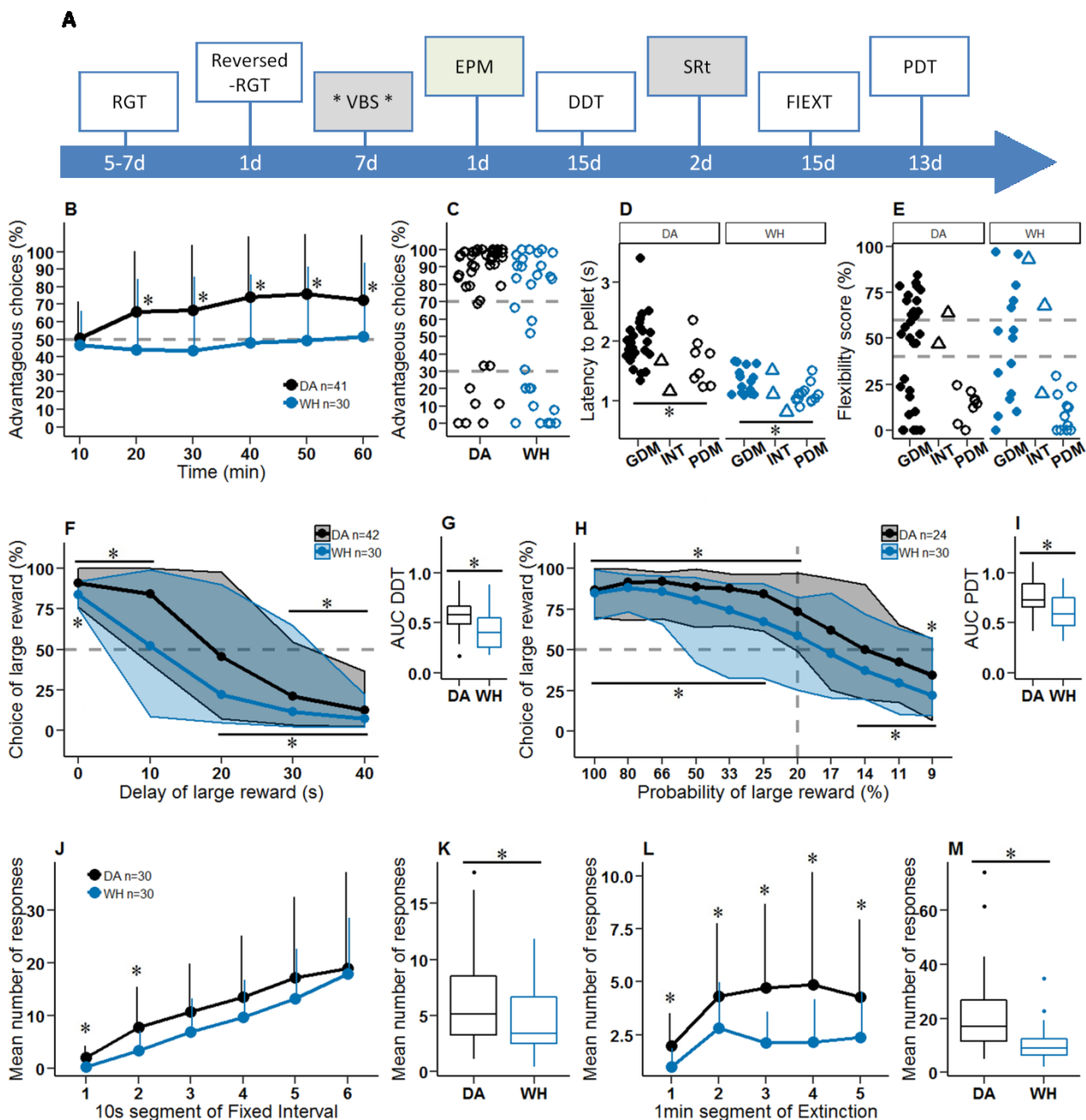
416 The latency to collect a reward after making a choice in the RGT was shorter in the WH rats  
417 (median 1.1 s) than in the DA rats (median 1.8 s; Fig. 1D, Wilcoxon rank sum test,  $W = 1151$ ,  
418  $p < 0.001$ ). This difference was not due to the different proportions of GDMs and PDMs. In  
419 both strains, the PDM rats were faster than the GDM rats at collecting the reward (Fig. 1D,  
420 Wilcoxon rank sum test, WH:  $W = 147$ ,  $p = 0.004$ ; DA:  $W = 181$ ,  $p = 0.047$ ). Interestingly,  
421 the WH GDMs had the same latency as the DA PDMs (Fig. 1D).

422

### 423 **3.1.3. Cognitive flexibility in the reversed-RGT**

424 The flexibility score indicates the propensity of an individual in the reversed-RGT to keep  
425 choosing (inflexibility) the same outcome as in the previous RGT or not choosing it  
426 (flexibility). All animals considered, DA and WH rats presented similar levels of cognitive  
427 flexibility (Fig. 1E; median 29% and 18% for DA and WH, respectively). In both strains and  
428 as expected for WH, all PDMs made highly inflexible choices in the reversed-RGT (low  
429 flexibility score; Fig. 1E). PDM rats kept choosing the hole(s) previously preferred (in the  
430 RGT), despite the outcomes of these choices now being different than in the RGT  
431 (Supplementary Fig. 2). In both strains, GDM rats had either high, intermediate or low  
432 flexibility scores (Fig. 1E). The proportion of GDMs with a high flexibility score (flexible  
433 GDMs) was 39% in DA and 33% in WH. Flexible GDMs progressively (trial after trial)  
434 switched their spatial preference from the nose-poke holes previously associated with the  
435 advantageous options (in the RGT) to the nose-poke holes currently associated with the  
436 advantageous options (Supplementary Fig. 2). 22% of DA GDMs and 20% of WH GDMs had  
437 no clear preference for either advantageous or disadvantageous options during the reversed-  
438 RGT. Finally, 39% of DA GDMs and 47% of WH GDMs showed an inflexible pattern of  
439 choices similar to the PDM rats (Fig. 1E) and kept choosing the hole(s) previously preferred  
440 in the RGT (Supplementary Fig. 2).

441



442

443

444

445

446

447

448

449

450

451

452

453

454

455

456

**Figure 1. Order and duration of testing and cognitive abilities of Dark Agouti (DA) and Wistar Han (WH) rats in the RGT, reversed-RGT, DDT, PDT and FIEXT.** **A** Order and duration of testing. RGT: Rat gambling task. VBS: Visible burrow system, with faeces collection (asterisks) before and after VBS housing. EPM: Elevated plus maze. DDT: Delay discounting task. SRt: Social recognition test. PDT: Probability discounting task. Cognitive tasks are in white and social tasks are in grey. d: day. **B** Advantageous choices in the RGT. Data are mean + SD, one sample t-test vs. 50%. **C** Individual (mean) scores during the last 20 min of the RGT. The dashed line at 70% and 30% of advantageous choices visually separates good decision makers (GDMs), intermediates (INTs) and poor decision makers (PDMs). **D** Motivation for the reward in the RGT, with filled circles representing GDMs, triangles representing INTs and empty circles representing PDMs; Wilcoxon rank sum test, GDM vs. PDM. **E** Flexibility scores in the reversed-RGT. **F** Choice of the large reward option as a function of the delay of reward delivery. Lines indicate the medians, and areas shaded in grey (DA) or blue (WH) indicate the 5<sup>th</sup> to 95<sup>th</sup> percentiles. The dashed line indicates the 50%

457 chance level. The asterisk denotes significant difference (Wilcoxon sign test) from 50%  
458 choice for DA (\*above curve) and WH (\*below curve). **G** Area under the curve for the DDT;  
459 Wilcoxon rank sum test, DA vs. WH. **H** Choice of the large reward option as a function of the  
460 probability of reward applied. Lines indicate the median, and areas shaded in grey (DA) or  
461 blue (WH) indicate the 5<sup>th</sup> to 95<sup>th</sup> percentiles. The vertical dashed line shows the indifference  
462 point (20% chance of receiving 5 pellets). The asterisk shows significant difference  
463 (Wilcoxon sign test) from 50% choice for DA (\*above curve) and WH (\*below curve). **I** Area  
464 under the curve for the PDT. Wilcoxon rank sum test, DA vs. WH. **J** Mean number of nose  
465 pokes during the 1 min FI expressed for the 10 s segments + SD. **K** Mean number of nose  
466 pokes during all 1 min FI (last 4 days). **L** Mean number of nose pokes during the 5 min EXT  
467 expressed for the 1 min segments + SD. Wilcoxon rank sum test, DA vs. WH. **M** Mean  
468 number of nose pokes during all EXT (last 4 days). \*  $p < 0.05$ . DA in black and WH in blue.  
469

#### 470 **3.1.4. Cognitive impulsivity in the DDT**

471 In both strains, increasing the delay of delivering a highly palatable large reward decreased  
472 the preference for this option (Fig. 1F; Wilcoxon sign test, delay 0 s: DA 0.95 CI [85.1, 93.0],  
473  $p < 0.001$ , WH 0.95 CI [81.4, 88.7],  $p < 0.001$ ; delay 10 s: DA 0.95 CI [73.1, 93.0],  $p <$   
474  $0.001$ ). The sooner an individual rejects the large reward that is increasingly delayed, the  
475 more impulsive it is. On average, the DA rats preferred an immediate one-pellet reward over a  
476 delayed five-pellet reward when the delay reached 30 s (Wilcoxon sign test, 0.95 CI [19.4,  
477 26.5],  $p < 0.001$ ). Similarly, on average, WH rats preferred an immediate one-pellet reward  
478 over a delayed five-pellet reward when the delay reached 20 s (Wilcoxon sign test, 0.95 CI  
479 [10.8, 31.3],  $p = 0.001$ ). Interestingly, although the preference for the high-reward option at a  
480 delay of 0 s was very strong in both strains (91% in DA and 84% in WH), the performance  
481 was significantly different between strains (Fig. 1F; Wilcoxon rank sum test with continuity  
482 correction,  $W = 891$ ,  $p = 0.002$ ). After normalizing performances to the preference at a delay  
483 of 0 s, the comparison of the AUC indicated that WH rats lost the preference for the high-  
484 reward option earlier than DA rats when the delay was added (Fig. 1G; Wilcoxon rank sum  
485 test,  $W = 923$ ,  $p < 0.001$ ). Within strains (and as expected for WH) [8], GDMs and PDMs had  
486 the same switching point and AUCs (Supplementary Fig. 3A and B).

487

#### 488 **3.1.5. Cognitive risk taking in the PDT**

489 In both strains, decreasing the probability of delivery of the most rewarding option (five  
490 pellets) also decreased the preference for this option (Fig. 1H; Wilcoxon sign test, probability  
491 100%: DA 0.95 CI [73, 91.2],  $p < 0.001$ ; WH 0.95 CI [80, 90],  $p < 0.001$ ). A delivery  
492 probability of 20% for the five-pellet option is the point of indifference at which both options  
493 (certain – one pellet vs. uncertain – five pellets) are, on average, equivalent. If an animal  
494 prefers the certain option (one pellet) over the uncertain option ( $P = 80\%$  to  $20\%$  – five  
495 pellets), it indicates an aversion to uncertainty. If an animal prefers the uncertain option ( $P =$   
496  $20\%$  to  $9\%$  – five pellets) over the certain option (one pellet), it indicates risk taking. DA rats  
497 lost their preference for the (uncertain) high-reward option when probability dropped to 17%  
498 (Wilcoxon sign test, 0.95 CI [50.8, 72.8],  $p = 0.063$ ). WH rats lost their preference when  
499 probability dropped to 20% (Wilcoxon sign test, 0.95 CI [40.8, 66.7],  $p = 0.361$ ). Comparison  
500 of the AUCs indicated that DA maintained a higher preference for the high reward with the  
501 decrease of reward probability than WH (Fig. 1I; Wilcoxon rank sum test,  $W = 516$ ,  $p =$   
502  $0.006$ ). In both strains, the AUCs were comparable between GDMs and PDMs  
503 (Supplementary Fig. 3C and D).

504

### 505 **3.1.6. Anticipatory and perseverative behaviour in the FI-EXT schedule of** 506 **reinforcement**

507 DA anticipatory activity was higher, particularly during the first 20 s of the FI (Fig. 1J; non-  
508 parametric ANOVA with permutation, 1<sup>st</sup> segment  $p < 0.001$ , 2<sup>nd</sup> segment  $p = 0.004$ ). The  
509 mean number of nose pokes was higher in DA rats than in WH rats for the 1 min FI (Fig. 1K;  
510 Wilcoxon rank sum test with continuity correction,  $W = 589.5$ ,  $p = 0.039$ ). DA rats nose  
511 poked more than WH rats during the 5 min EXT (Fig. 1M; Wilcoxon rank sum test with  
512 continuity correction,  $W = 690$ ,  $p < 0.001$ ), and this was the case during all the 1 min  
513 segments of EXT (Fig. 1L; non-parametric ANOVA with permutation, 1<sup>st</sup> segment  $p = 0.002$ ,  
514 2<sup>nd</sup> segment  $p = 0.045$ , 3<sup>rd</sup> segment  $p < 0.001$ , 4<sup>th</sup> segment  $p = 0.001$ , 5<sup>th</sup> segment  $p = 0.015$ ).

515 Within strains, DA PDMs (n=7) nose poked significantly more than DA GDMs during EXT  
516 (Supplementary Fig. 4B; Wilcoxon rank sum test with continuity correction,  $W = 35$ ,  $p =$   
517  $0.043$ ); however, this was not observed in WH.

518

### 519 **3.1.7. Natural behaviours expressed in the VBS**

520 In both strains, the behaviours most frequently observed in the VBS were huddle, eating and  
521 struggle at feeder (with median number of occurrences  $> 5$  in 100 30 s videos on the last two  
522 days of VBS housing; Fig. 2A). The 19 other scored behaviours (allogrooming, attending,  
523 drinking, grooming, aggressive grooming, attack, embracing, fight, following, mounting,  
524 mutual upright posture, pinning, struggle at water, struggle in tunnel, flight, freezing, lateral  
525 defence, supine posture and upright defence) were seen more rarely (median number of  
526 occurrences  $< 5$  in 100 30 s videos on the last two days of VBS housing) and are grouped in  
527 the composite category “19 others” in Figure 5 (for further details, see Supplementary Fig.  
528 5A). Considering the three most frequent behaviours, DA rats huddled more and struggled at  
529 the feeder less than WH rats (Fig. 2B; Wilcoxon rank sum tests with continuity correction,  
530 huddle:  $W = 984$ ,  $p < 0.001$ ; struggle at feeder:  $W = 313.5$ ,  $p = 0.005$ ). Strains did not differ  
531 in their number of bouts of eating. The occurrences of huddle, eating and struggle at feeder  
532 were similar between PDMs and GDMs in both strains (Supplementary Fig. 5B).

533

### 534 **3.1.8. Total distance travelled in the VBS**

535 Both DA and WH rats changed their activity (i.e., the distance travelled) with the light/dark  
536 phase (Fig. 2C). Both strains were more active during dark phases (Fig. 2C). Over all days,  
537 locomotion in WH rats was higher than in DA rats during both dark and light phases (Fig. 2D;  
538 dark phase: Wilcoxon rank sum test,  $W = 45$ ,  $p < 0.001$ ; light phase: Wilcoxon rank sum test,  
539  $W = 313$ ,  $p < 0.001$ ). During the dark phase, the WH PDMs were more active than the WH  
540 GDMs (Supplementary Fig. 5C; Wilcoxon rank sum test,  $W = 60$ ,  $p = 0.005$ ).

541

### 542 **3.1.9. Place preference in the VBS**

543 DA rats preferred to stay in the burrow area significantly more than WH rats, both during the  
544 dark phase (Fig. 2E, top panel; Wilcoxon rank sum test,  $W = 105$ ,  $p < 0.001$ ) and during the  
545 light phase (Fig. 2E, bottom panel; Wilcoxon rank sum test,  $W = 371$ ,  $p = 0.001$ ).  
546 Furthermore, during the light phase, WH rats were mostly present in the entry zones of the  
547 burrow area (Fig. 5E). The WH GDMs preferred staying in the burrow more than the WH  
548 PDMs during the dark phase (Supplementary Fig. 5D; Wilcoxon rank sum test,  $W = 195$ ,  $p =$   
549  $0.038$ ) and the same tendency was observed in DA rats (Supplementary Fig. 5D).

550

### 551 **3.1.10. Total time spent in the open area of the VBS across days**

552 The DA rats spent less time in the open area starting from day 2 (non-parametric ANOVA  
553 with permutation, day 2  $p = 0.030$ ) than WH rats (Fig. 2F). There was no difference in the  
554 time spent in the open area across day between DA GDMs and DA PDMs, whereas in WH  
555 the PDMs tended to spend more time in the open than GDMs starting on day 3  
556 (Supplementary Fig. 5E).

557

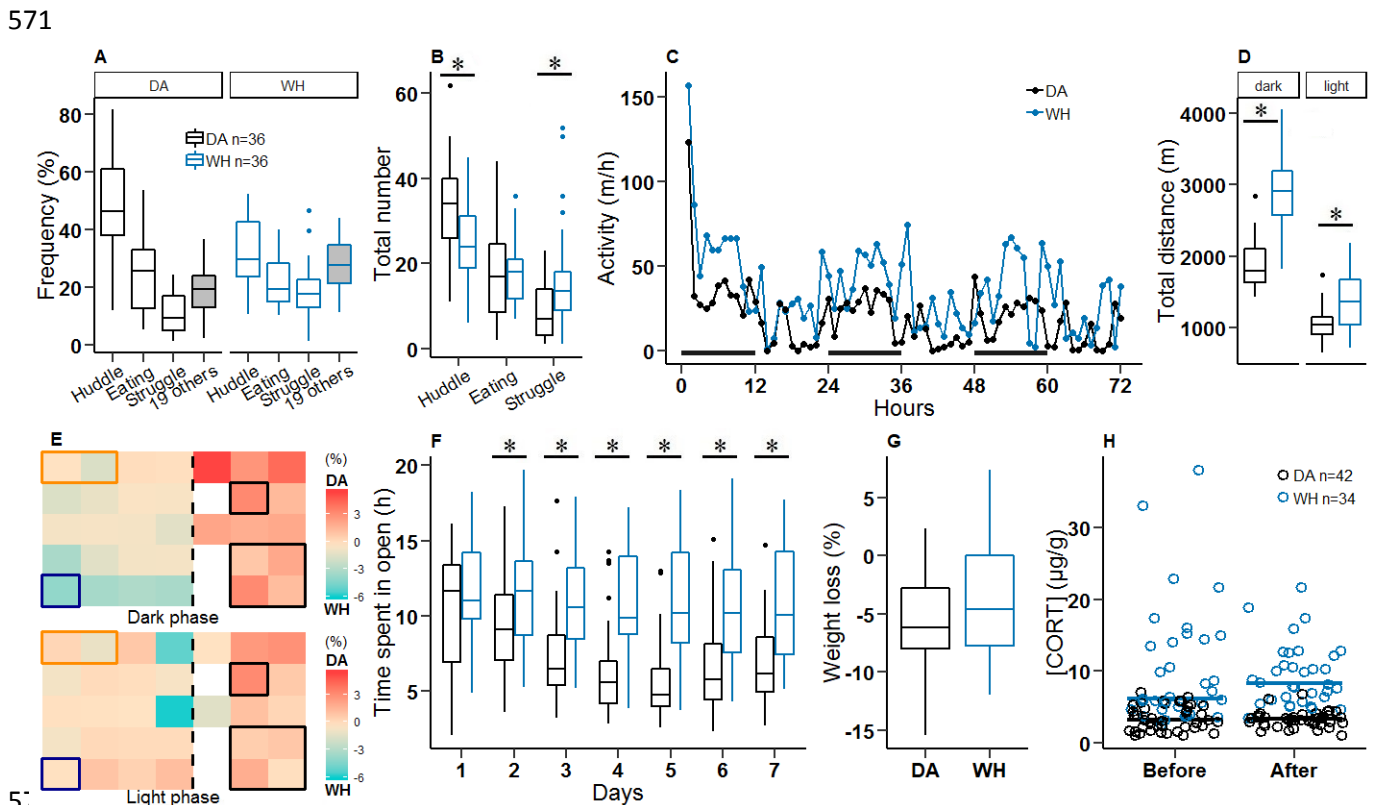
### 558 **3.1.11. Weight loss during VBS housing**

559 Before being housed in the VBS (and in general), DA rats were smaller and lighter than WH  
560 rats (Supplementary Fig. 5F; Wilcoxon rank sum test with continuity correction  $W = 0$ ,  $p <$   
561  $0.001$ ). During their stay in the VBS, DA and WH rats lost the same relative weight (Fig. 2G).  
562 However, DA GDMs lost more weight than DA PDMs (Supplementary Fig. 5G; Wilcoxon  
563 rank sum test with continuity correction,  $W = 35$ ,  $p = 0.039$ ).

564

### 565 **3.1.12. Corticosterone (metabolite) levels after VBS housing**

566 At baseline (before the VBS housing), the concentration of corticosterone in DA rats was  
 567 lower than in WH rats (Fig. 2H; Wilcoxon rank sum test  $W = 206$ ,  $p < 0.001$ ). After VBS  
 568 housing, the corticosterone levels in DA and WH rats were unchanged (Fig. 2H). In both  
 569 strains, corticosterone levels were not different between GDMs and PDMs, either before or  
 570 after VBS housing (Supplementary Fig. 5H).



573 **Figure 2 - Daily activity, behavioural and biological measures of Dark Agouti (DA) and**  
 574 **Wistar Han (WH) rats during the Visible Burrow System (VBS) housing. A** Relative  
 575 frequency of occurrence of behaviours in the VBS. White boxes represent a unique type and  
 576 grey boxes represent a composite behaviour category. “Struggle” = “struggle at feeder”. “19  
 577 Others” comprised the 19 behaviours (all behaviours minus the three main behaviours) scored  
 578 during the VBS video analysis but which had a median  $< 5$  in each strain due to their rare  
 579 occurrence. **B** Occurrence of the three main types of behaviours observed in the VBS (50 min  
 580 observation). **C** Typical locomotor activity of one DA and one WH individual during the first  
 581 three days in the VBS. Bars indicate dark phase. **D** Total distance travelled during the dark  
 582 and light phases over seven days in the VBS. **E** Difference in place preference (%) between  
 583 DA and WH during the dark and light phases over seven days of VBS housing. Red indicates  
 584 a preference of the DA relative to WH for each of the 32 zones of the VBS (corresponding to  
 585 the 32 RFID detectors located beneath the VBS cage). Rectangles indicate the locations of  
 586 feeder (orange), water bottle (blue), and small and large chambers in the burrow area (black).  
 587 The vertical dashed line indicates the separation between the open area (left side) and the  
 588 burrow area (right side). **F** Total time spent in the open area. **G** Weight loss after VBS  
 589 housing. **H** Concentration of corticosterone in faeces before and after VBS housing.

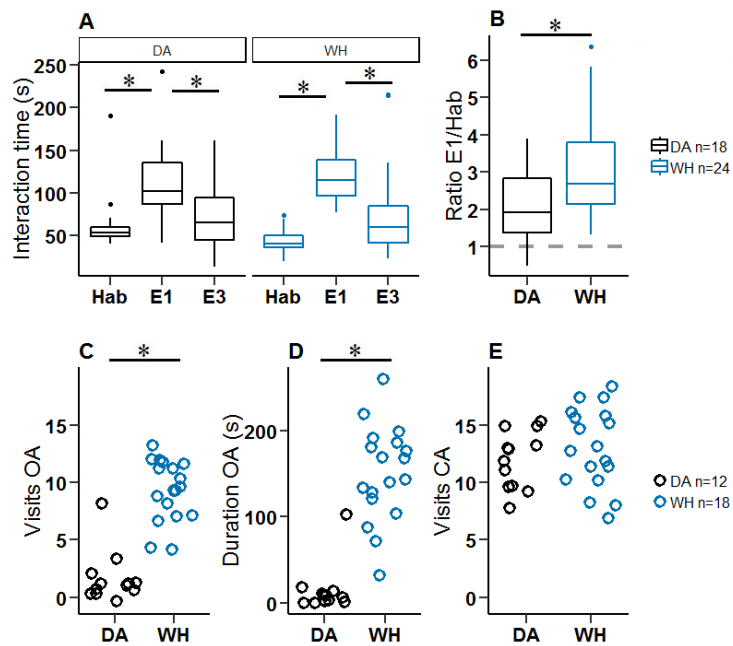


590 Horizontal bar: median of each group. DA in black and WH in blue; Panels A-G: WH, n = 36;  
591 DA, n = 36 and panel H: WH, n = 34; DA, n = 42. \*  $p < 0.05$ , DA vs. WH, Wilcoxon rank  
592 sum test except panel F ANOVA with permutations for repeated measures. The VBS test was  
593 conducted with n = 6 individuals in the cage at a time.  
594

### 595 **3.1.13. Social preference and social recognition memory in the SRt**

596 In the SRt, both strains exhibited a clear preference for social vs. non-social cues and an  
597 accurate short-term social recognition memory. Rats spent more time exploring the unfamiliar  
598 social partner during the encounter 1 (E1) than an unfamiliar non-social cue (empty box)  
599 during the habituation phase (Hab, Fig. 3A; Wilcoxon rank sum test with continuity  
600 correction, WH:  $W = 576$ ,  $p < 0.001$ ; DA:  $W = 258.5$ ,  $p < 0.001$ ). Exploration time was twice  
601 as long in E1 as in Hab (Fig. 3B; social preference ratio E1/Hab  $> 1$ , Wilcoxon sign test DA:  
602 0.95 CI [1.3, 2.8],  $p = 0.030$  and WH: 0.95 CI [2.2, 3.4],  $p < 0.001$ ). WH rats had a higher  
603 social preference ratio than DA rats (Wilcoxon rank sum test,  $W = 121$ ,  $p = 0.016$ ). The third  
604 time WH and DA rats encountered the same animal (E3), the time spent exploring this animal  
605 was significantly reduced compared to their first encounter (E1), indicating effective short-  
606 term social recognition memory (Fig. 3A; Wilcoxon rank sum test with continuity correction,  
607 WH:  $W = 484.5$ ,  $p < 0.001$ ; DA:  $W = 225$ ,  $p = 0.018$ ). Due to experimental limitations, long-  
608 term social recognition memory could not be evaluated, although it is likely that both strains  
609 did have such memory (Supplementary Fig. 6A). In both strains, the social preference ratio  
610 and short-term memory ratio did not differ between GDMs and PDMs (Supplementary Fig.  
611 6C and D).

612



613  
 614 **Figure 3 - Social preference, social short-term recognition and exploration of the EPM**  
 615 **in Dark Agouti (DA) and Wistar Han (WH) rats.** A Interaction times during the social  
 616 recognition test. Hab: non-social cue (empty box) present during the habituation phase; E1:  
 617 first encounter with intruder (unfamiliar); E3: third encounter with same intruder (familiar);  
 618 Wilcoxon rank sum test Hab vs. E1 and E1 vs. E3. B Social preference represented as the ratio  
 619 of exploration times in E1 and in Hab, DA vs. WH (Wilcoxon rank sum test). C Total number  
 620 of visits to the open arms (OA), DA in black and WH in blue. D Time spent in the OA, DA  
 621 vs. WH (Wilcoxon rank sum test). E Total number of visits to the closed arms (CA).  
 622 Maximum exploration time was 10 min. DA in black and WH in blue, \*  $p < 0.05$ .

623

### 624 3.1.14. Exploration in the EPM

625 DA rats expressed very different behaviour in the EPM compared to WH rats. DA rats very  
 626 rarely (or never) visited the open arms of the maze (Fig. 3C; Wilcoxon rank sum test with  
 627 continuity correction,  $W = 5.5$ ,  $p < 0.001$ ) and for a very short time (Fig. 3D; Wilcoxon rank  
 628 sum test with continuity correction,  $W = 3$ ,  $p < 0.001$ ) compared to WH rats. Only one DA  
 629 individual visited the part of the maze that was furthest from enclosing walls (the last third of  
 630 the open arms), as opposed to all the individuals in WH (data not shown). DA and WH rats  
 631 had the same number of visits to closed arms (Fig. 3E). Within strains, no differences were  
 632 observed between PDMs and GDMs for the parameters of total number of visits to open arms,  
 633 total time spent in open arms or total number of visits to the last third of the open arms  
 634 (Supplementary Fig. 7).

635

636 **3.1.15. Inter-individual differences within DA and WH**

637 In both strains, GDMs and PDMs showed similar tendencies in all tests (see Table 2 for  
 638 details). In both strains, PDMs were faster to collect the reward than GDMs in the RGT, and  
 639 all showed higher cognitive inflexibility in the reversed-RGT. In the VBS, the WH PDMs  
 640 were more active during the dark phase, did not prefer the burrow area during the dark phase  
 641 and spent more time in the open area on day 4 than the WH GDMs. In the VBS, the DA  
 642 PDMs lost less weight than the DA GDMs (Table 2).

643

644 **Table 2: Behaviours of the GDMs and PDMs in DA and WH strains.**

645

<b>Trait</b>	<b>Test</b>	<b>Parameter</b>	<b>GDM vs. PDM within strain</b>
Sensitivity to reward	RGT	Latency to collect reward	Both strains: PDMs faster than GDMs
Cognitive flexibility	Rev-RGT	Flexibility index	Both strains: All PDMs and 1/3 GDMs inflexible
Cognitive impulsivity	DDT	AUC-DDT	No difference
Cognitive impulsivity	DDT	Switch point	No difference
Cognitive risk taking	PDT	AUC-PDT	No difference
Cognitive risk taking	PDT	Switch point	17% for DA GDMs, 25% for DA PDMs (n = 6).  25% for WH GDMs, 33% for WH PDMs.
Anticipatory activity	FI	Mean number of nose pokes	No difference
Perseverative activity	EXT	Mean number of nose pokes	DA PDMs (n = 7) poked more than DA GDMs
Affiliative behaviour	VBS	Occurrences	No difference in huddle
Aggressive behaviour	VBS	Occurrences	No difference (in struggle at feeder, struggle in tunnel, mutual upright posture and pinning)
Defensive behaviour	VBS	Occurrences	No difference in supine posture
Maintenance behaviour	VBS	Occurrences	No difference in grooming, eating and drinking
Distance travelled	VBS	Total distance (dark phase)	WH PDMs were more active during the dark phase than WH GDMs
Place preference	VBS	Place preference	WH PDMs had less burrow occupation during the dark phase than WH GDMs. DA PDMs tended to have less burrow

---

Time in open	VBS	Time spent in open per day	occupation than DA GDMs. WH PDMs spent more time in open on day 4 than WH GDMs (non-parametric ANOVA with permutations, day 4 $p = 0.023$ )
Stress response	VBS	CORT variation	No difference
Weight loss	VBS	Weight loss	DA PDMs lost less weight than DA GDMs
Social preference	SRT	Ratio interaction times E1/Hab	No difference
Short-term recognition	SRT	Ratio interaction times E1/E3	No difference
Exploration EPM	EPM	Visits to open arm	No difference

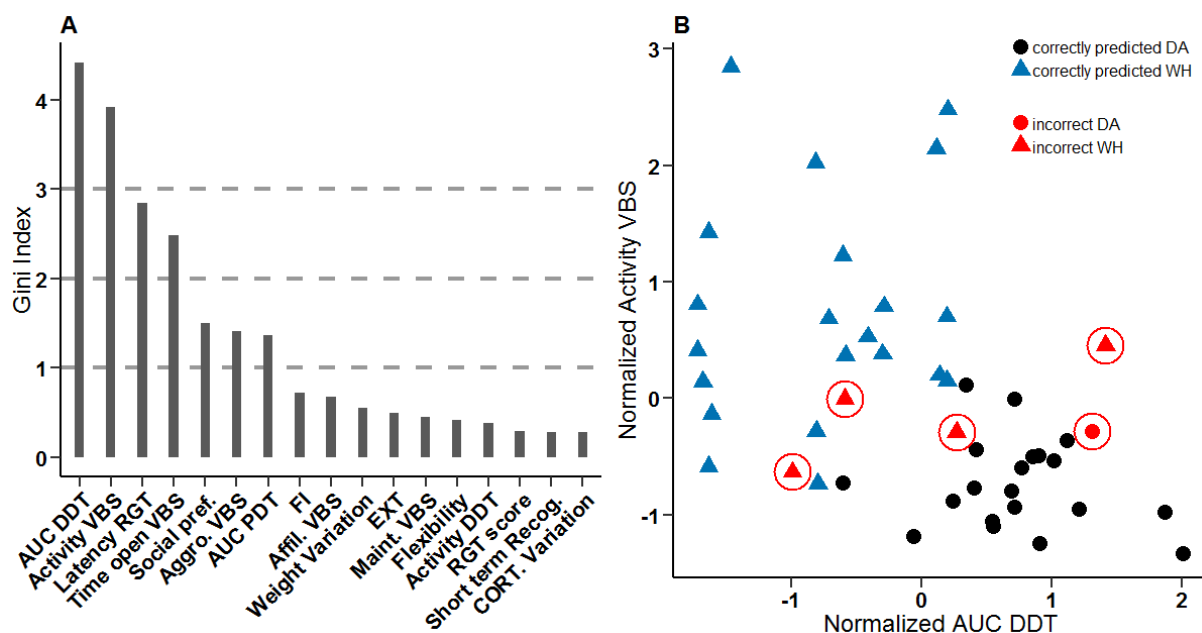
---

646

### 647 **3.2. Identification of the key variables discriminating WH from DA strain**

648 We performed an RF classification with a leave-one-out cross-validation (LOOCV) to  
649 quantify the efficiency of each of the previously described cognitive and social functions to  
650 distinguish WH and DA strains from each other. The RF was run using the behavioural and  
651 biological variables described above (Refer to the Methods section for a description of  
652 adjustment of measures and variables due to missing values). In brief, the decision trees of the  
653 RF with LOOCV led to the prediction of the strain of each of a given individual by comparing  
654 its performance (for each variable) to the performance of the other individuals for which the  
655 strain was known. For WH and DA variables, the prediction of the strain was high, with an  
656 accuracy of 84% ( $\pm 0.72$  SD over 10 runs). The importance of each variable to accurately  
657 differentiate the strains was given by the Gini index of the RF (Fig. 4A). The most  
658 discriminating variables were the AUC of the DDT and the distance travelled in the VBS  
659 (Gini index  $> 3$ ), followed by the latency to collect a reward in the RGT and the total time  
660 spent in the open area in the VBS ( $3 > \text{Gini index} > 2$ ; Fig. 4A). Of lesser significance were  
661 the social preference index in the social preference test, the AUC of the PDT, and the number  
662 of aggressive behaviours in the VBS ( $2 > \text{Gini index} > 1$ ). The least discriminating variables  
663 were the total number of affiliative behaviours, the weight variation and the total number of  
664 maintenance behaviours in the VBS; the mean number of responses during FI and EXT; the

665 decision-making score in the RGT; the variation of CORT levels; the short-term recognition  
666 memory in the social recognition test; the total activity in the DDT; and the flexibility score in  
667 the reversed-RGT (Gini index < 1; Fig. 4A). As an example, an RF classification including  
668 the two most discriminating variables (the distance travelled in the VBS and the AUC of the  
669 DDT) attributed the correct strain to 41 rats out of a total of 46 rats (Fig. 4B). On the contrary,  
670 an RF including only the variables with a Gini index < 1 resulted in a drop in accuracy to 50%  
671 (chance level, not shown).



672  
673 **Figure 4 - Discriminating classification of the DA and WH.** A Gini index for each trait  
674 used for the random forest (RF) classification. Dashed lines are included to sort the variables  
675 in groups of importance. pref. = preference, Aggro. = aggressive, affil. = affiliative, maint. =  
676 maintenance, CORT = corticosterone. B RF classification for the two most discriminating  
677 variables. DA, n = 24, in black; WH, n = 22, in blue. Symbols show predicted strain by the  
678 RF. DA: dot, WH: triangle. Red circles indicate an incorrect prediction.

679

## 680 4. Discussion

### 681 4.1. Behavioural performance of PDMs and GDMs from DA and WH strains

682 One of the advantages of the RGT is the possibility it offers to uncover which decision-  
683 making strategy each individual of a healthy population of rats will spontaneously use to cope  
684 with complex and uncertain choice options. Here we found that, similar to WH, each

685 individual DA could be classified in one of the three typical categories. We identified GDM  
686 strategists, which secured more food over the long term, although they earned smaller amount  
687 of food in each trial; PDM strategists, which secured less food over the long term, although  
688 they earned larger amounts of food in each trial but were penalized by long waiting periods;  
689 and INT individuals, which seemed indifferent to reward options. Although not significant,  
690 the higher number of GDMs found in the DA rats compared to the WH rats could explain  
691 their more advantageous performance as a group (averaged performance) during the RGT  
692 compared to the WH, which on average stayed at chance level for the entire duration of the  
693 test. In a follow-up study, we will evaluate the effect of a lack of central 5-HT on the animals'  
694 decision-making abilities in the RGT. Thus, the large number of GDMs in healthy individuals  
695 will help us to quantify the effect of this genetic manipulation, which is expected to shift the  
696 behavioural profile from GDM to PDM.

697 Interestingly and independent of strain, we found that all GDM and PDM rats behaved as  
698 expected with regard to their decision-making type in the reversed-RGT and in anticipation of  
699 rewards (test of reward sensitivity in the RGT) [6]. All PDMs of either strain rapidly and  
700 steadily chose the least advantageous options in the long term in the RGT; they were more  
701 sensitive to the reward than GDMs and were unable to flexibly adjust their behaviour during  
702 the reversed-RGT. For humans, a new computational modelling of the analogous Iowa  
703 Gambling Task called Outcome-Representation Learning predicts that poor decision making  
704 of drug users could be due to higher reward sensitivity and more exploratory behaviour (in  
705 cannabis users), lower punishment sensitivity (in abstinent heroin users) and higher  
706 inflexibility perseverance (in abstinent amphetamine users) [48]. The expression of the same  
707 key features between PDMs of genetically distinct strains of rats and, to a certain extent, to  
708 results found in humans [49,50] suggests a strong conservation of this potential  
709 endophenotype within and between species.

710 As seen in previous studies in WH rats but now also in DA rats, the GDMs were not a single  
711 homogeneous group of rats [5,8]. While some (50% to 75%) were faster than others in  
712 choosing the advantageous options during the RGT (at only 20 min of test), in the reversed-  
713 RGT only one-third of GDMs were able to flexibly adjust their behaviour.

714 In addition, differences were not observed between PDMs and GDMs in either strain in  
715 cognitive impulsivity (DDT) or risk-based decision-making tests (PDT). Although the result  
716 of the DDT was expected [8], the lack of difference in the PDT between PDMs and GDMs  
717 was more surprising. Indeed, in another version of the RGT (i.e., the rGT, with a testing phase  
718 lasting three days and two options only (a reward, given as sweet pellets, or a punishment,  
719 given as quinine pellets)), poorer decision-making abilities were correlated with higher  
720 preferences in the PDT for the risky (large reward, uncertain outcome) options [24]. The  
721 differences between the experimental procedures of each study (the protocols of the RGT/rGT  
722 and the PDT were equivalent, but not identical) and in the definition of what constituted poor  
723 decision making (in RGT, spontaneous healthy PDMs were different from GDMs; in rGT, all  
724 rats were “GDMs”, but some individuals made poorer decisions than others) may be the  
725 reasons for the discrepancies between these results. However, it is noteworthy that in the  
726 human literature a loss of control over risk (probability)-based choices is not characteristic of  
727 all PDM-associated psychiatric disorders. Patients with pathological gambling [51], alcohol  
728 dependence [52], schizophrenia [53] and autism [54] are more risky decision makers than  
729 patients with obsessive-compulsive disorder [55], pathological buying disorder, Huntington’s  
730 disease [56] or suicidal attempts [57]. These and our results indicate that preference for high-  
731 risk (probabilistic) options may be a marker of pathology rather than a marker of vulnerability  
732 to diseases and thus may be preferentially observed in “ill-induced” PDMs than in healthy  
733 PDM rats.

734 In the FI-EXT test, we only witnessed increased motor impulsivity in DA PDMs during EXT,  
735 and did not witness this in either FI or EXT in WH. This inconsistent result in WH rats

736 compared to our previous study may be due to the use of a different manipulandum (nose-  
737 poke holes instead of levers) for the operant response [8]. It is also possible that for WH rats,  
738 repetitive nose poking in a hole was too physically demanding to exhibit anticipatory or  
739 perseverative behaviours compared to pressing a lever. Very few studies have investigated the  
740 consequences of this difference in operant responding. Although Mekarski [58] defended nose  
741 poking to be a more innate behaviour than lever pressing, it has also been shown that  
742 escalation behaviour is better achieved with lever pressing and not nose poking in mice [59].  
743 We also explored if PDM and GDM rats differed in their social skills. In the VBS, compared  
744 to GDM rats, PDM rats expressed a higher level of activity, less occupation of the burrow  
745 during dark phases, longer time spent in the open area of the cage (WH PDMs), and limited  
746 weight loss (DA PDMs). In the VBS, these features characterize dominance in rats (along  
747 with the number and location of wounds, which were not witnessed in this study) [60],  
748 suggesting a more dominant status for PDM rats than for GDM rats. In the same line, Davis et  
749 al., [61] found that individual dominance correlated with higher motivation for rewards and  
750 higher exploration of risky zones in the EPM. These are also two known characteristics of  
751 PDM rats [6]. Interestingly, PDMs were not more aggressive or less affiliative in the VBS  
752 than GDMs and presented a similar interest for the social cue in the SRt. While the  
753 experimental measurement of dominance in rats is often reduced to a one-time measure of  
754 aggression level (i.e., the resident intruder paradigm), Buwalda et al. [62] showed that the  
755 level of aggression in the resident-intruder paradigm and in the VBS were not correlated with  
756 dominance. However, a more realistic view of dominance should consider its  
757 multidimensional features including privileged access to resources [63,64], lower sensitivity  
758 to stressors [65] and non-agonistic behaviours [66]. Indeed, social hierarchy is a dynamic  
759 feature that depends on the outcome of each type of interaction [66,67]. In humans, excessive  
760 aggression is a disruptive symptom widely distributed among psychiatric disorders. Studies  
761 have shown that decision making and aggression-related behaviours could share biological



762 markers, such as MAO A, SERT, TPH1 and TPH2 proteins [68,69]. In further studies, we  
763 will use the rich semi-natural and around-the-clock experimental conditions of our VBS  
764 housing to explore more specifically which social domains and how social hierarchy develop  
765 along with decision-making abilities and serotonin manipulations.

766 The reproducibility and conservation of the socio-cognitive and behavioural phenotypes of  
767 GDM and PDM individuals in the two genetically different strains of WH and DA rats  
768 support a good translational validity of these complex phenotypes, not only between strains  
769 but likely also between species (e.g., rats and humans). Following the Research Domain  
770 Criteria framework (RDoC), which promotes the exploration of cross-species endophenotypes  
771 for better translational value of preclinical studies [70,71], this study presents the PDM rats as  
772 a promising animal model for the identification of the specific biological circuits underlying  
773 equivalent patterns of deficits which could be observed in patients (or healthy relatives) and  
774 independently of their disorders' categories. Both DA and WH rat strains offer interesting  
775 individual variations in behaviour, allowing the use of both strains for the study of the  
776 underlying mechanisms of poor decision making and associated disorders. It will be possible  
777 to examine the risk factors responsible for the transition from vulnerability to pathology by  
778 comparing the expression of each of the PDM-associated traits and how the neural substrates  
779 of this phenotype overlap or differ in ill-induced *vs.* healthy PDMs.

780

#### 781 **4.2. Strain differences between DA and WH**

782 Beside the inter-individual differences within strains, we found at the group level that WH  
783 rats were, on average, more sensitive to reinforcement and more impulsive in the DDT, but  
784 less prone to take risks in the PDT compared to DA rats. In the DDT and PDT, WH rats  
785 dismissed both the delayed and uncertain option more rapidly than the DA rats in favour of  
786 the immediate or certain option, although this meant that the option associated with the largest  
787 reward (absolute value) was abandoned for a one-pellet option. The discounting factor (delay

788 or probability) appeared to have a stronger impact on the subjective evaluation of rewards by  
789 WH rats, and WH rats had a lower tolerance to uncertain situations when rewards were  
790 involved compared to DA rats. In the VBS, WH rats were more aggressive, more active  
791 (higher distance travelled) and spent more time in the open area of the VBS than DA rats.  
792 In biomedical research, the WH line is one of the two most commonly used strains of rats (the  
793 other being Sprague Dawley) [72]. This research included studies investigating reward-related  
794 disorders such as drug addiction [73,74] and poor impulse control-related disorders such as  
795 substance abuse, eating disorders, ADHD or manic disorders [75,76]. WH rats are also used  
796 in studies on reward processing and valuation [77], and have been found to have a high  
797 tendency for compulsive and impulsive behaviours [78,79].  
798 In contrast, DA rats made more perseverative responses in the FI-EXT test in anticipation of a  
799 reward and during extinction phases, indicating either a lower tolerance to frustrating inactive  
800 phases of the test or higher motor impulsivity compared to WH. Knowing that the conditions  
801 for this test may not have been optimal (as the low level of activity may be due to the  
802 requirement for nose-poke holes instead of lever presses) and that such higher motoric  
803 response was not similarly observed in the training phase of the DDT (as both variables are  
804 correlated) [8], we prefer not to place too much emphasis on this result. Finally, DA rats were  
805 more affiliative in the VBS, preferred hiding in the burrows and were more fearful of the open  
806 arms of an EPM. They also had a weaker social preference in the SRt, which could be due to  
807 the avoidance of the centre of the open field during the first 5 min of habituation in this test.  
808 These results could confirm a specific fear of the elevated and widely open spaces, as  
809 discussed elsewhere [80,81].  
810 With DA rats presenting a more compulsive, anxious and prosocial phenotype, this strain  
811 seems promising for studies on anxiety-related disorders. For example, patients diagnosed  
812 with anxiety disorder are extremely fearful/anxious of real-life threats (as opposed to unreal  
813 life-threatening concerns of OCD patients); they can express un-ritualized compulsive

814 behaviours and, in the case of social anxiety disorder (social phobia), a subcategory of anxiety  
815 disorder, they show strong social contact avoidance and/or seek to reduce their social fear  
816 (DSM-5) [82]. Anxiety indeed appear to be a trait often witnessed in inbred lines of mice  
817 [33]. Finally, and despite their remarkable differences, DA and WH rats also shared similar  
818 traits. For example, they presented higher levels of huddling, eating and struggling at the  
819 feeder than other behaviours during VBS housing, and equivalent corticosterone level and  
820 weight loss after VBS housing.

821

### 822 **4.3. Prediction of the strain differences with RF analysis**

823 Although we identified specific traits on which DA and WH strains spontaneously differed in  
824 performance, using a RF classification method helped to determine which of these traits were  
825 more characteristic of one strain than the other. These were the ability to wait for a reward in  
826 the DDT, the motivation to collect a reward in the RGT, and the level of activity and time  
827 spent in the open area of the VBS. The RF classifier was less able to accurately differentiate  
828 strains based on the expression of their affiliative and maintenance behaviours, weight  
829 variation, decision making or flexibility. The RF classification results were similar to those  
830 obtained after a principal component analysis (Supplementary Fig. 8A and D).

831 In other words, the most critical difference between WH and DA rats related to behavioural  
832 control when facing a (delayed or non-delayed) reward as seen in the DDT (cognitive  
833 impulsivity) and the RGT (reward seeking), respectively. Based on this observation, it could  
834 also be argued that the increased time the WH rats spent in the open area of the VBS was  
835 driven by the presence of the only food source of the cage being in this area, although this  
836 zone was also potentially the most aversive zone of the cage.

### 837 **5. Conclusion**

838 In this study, we compared several abilities of DA and WH rats at the group and the  
839 individual levels using multiple cognitive tests, a social naturalistic set-up and assays of  
840 physiological responses.

841 Both the dimensional and group approaches provided new insights for the preferential use of  
842 each strain in future neuropsychopharmacological studies and further advanced our  
843 knowledge of the complex phenotype of the healthy PDM and GDM. At the group level, we  
844 identified specific traits on which these genetically distinct strains spontaneously differed the  
845 most (AUC of the DDT, distance travelled in the VBS, latency to collect a reward in the RGT  
846 and total time spent in the open area in the VBS). The WH and DA strains could  
847 preferentially be used to model reward sensitivity and impulsivity on one side and  
848 compulsivity and anxiety-related behaviours on the other side.

849 At the individual level, we could reproduce previous findings in WH rats and generalize them  
850 to the DA strain. Each PDM individual of either strain displayed a similar naturally occurring  
851 combination of behavioural traits, including a higher sensitivity to reward, higher cognitive  
852 inflexibility and higher social rank, but no cognitive impulsivity in delay- or probability-based  
853 decision-making tasks, no deficits in social recognition and no differences in corticosterone  
854 response to stressors. The multidomain profile of the PDM individuals should be suitable to  
855 reveal bio-behavioural specificities highly relevant for the study of human mental illnesses. In  
856 a follow-up study, we will directly interfere with rats' central serotonergic system and  
857 evaluate the impact of this intervention in the concomitant modulation of the PDM-associated  
858 traits.

859

#### 860 Acknowledgements:

861 We want to thank Patrik Bey, Melissa Long, Alexej Schatz, Dr. Martin Dehnhard and his  
862 team and the FEM team for their technical assistance and our colleagues of the Winter lab  
863 who made insightful comments on a previous version of the manuscript.

864 Declaration of interest:

865 The authors declare no conflict of interest.

866 Funding:

867 This work was funded by a DFG grant (RI 2474/2-1) attributed to Marion Rivalan (PI) and  
868 Natalia Alenina. This work was supported by the Russian Science Foundation to Natalia  
869 Alenina.

870

871 References:

- 872 [1] F. Dellu-Hagedorn, M. Rivalan, A. Fitoussi, P. De Deurwaerdère, Inter-individual differences in  
873 the impulsive/compulsive dimension: deciphering related dopaminergic and serotonergic  
874 metabolisms at rest, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 373 (2018).  
875 doi:10.1098/rstb.2017.0154.
- 876 [2] E.J. Nestler, S.E. Hyman, Animal models of neuropsychiatric disorders, *Nat. Neurosci.* 13 (2010)  
877 1161–1169. doi:10.1038/nn.2647.
- 878 [3] M. Rivalan, C. Blondeau, F. Dellu-Hagedorn, Chapter2. Modeling symptoms of mental disorders  
879 using a dimensional approach in the rat., *Loop.* (2009).  
880 <http://loop.frontiersin.org/publications/41109606>.
- 881 [4] B. Cao, J. Wang, M. Shahed, B. Jelfs, R.H.M. Chan, Y. Li, Vagus Nerve Stimulation Alters Phase  
882 Synchrony of the Anterior Cingulate Cortex and Facilitates Decision Making in Rats, *Sci. Rep.* 6  
883 (2016) 35135. doi:10.1038/srep35135.
- 884 [5] A. Fitoussi, C. Le Moine, P. De Deurwaerdère, M. Laqui, M. Rivalan, M. Cador, F. Dellu-  
885 Hagedorn, Prefronto-subcortical imbalance characterizes poor decision-making: neurochemical  
886 and neural functional evidences in rats, *Brain Struct. Funct.* 220 (2015) 3485–3496.  
887 doi:10.1007/s00429-014-0868-8.
- 888 [6] M. Rivalan, S.H. Ahmed, F. Dellu-Hagedorn, Risk-prone individuals prefer the wrong options on  
889 a rat version of the Iowa Gambling Task, *Biol. Psychiatry.* 66 (2009) 743–749.  
890 doi:10.1016/j.biopsych.2009.04.008.
- 891 [7] M. Rivalan, E. Coutureau, A. Fitoussi, F. Dellu-Hagedorn, Inter-Individual Decision-Making  
892 Differences in the Effects of Cingulate, Orbitofrontal, and Prelimbic Cortex Lesions in a Rat  
893 Gambling Task, *Front. Behav. Neurosci.* 5 (2011). doi:10.3389/fnbeh.2011.00022.
- 894 [8] M. Rivalan, V. Valton, P. Seriès, A.R. Marchand, F. Dellu-Hagedorn, Elucidating Poor Decision-  
895 Making in a Rat Gambling Task, *PLoS ONE.* 8 (2013) e82052. doi:10.1371/journal.pone.0082052.
- 896 [9] R. van den Bos, W. Davies, F. Dellu-Hagedorn, A.E. Goudriaan, S. Granon, J. Homberg, M.  
897 Rivalan, J. Swendsen, W. Adriani, Cross-species approaches to pathological gambling: a review  
898 targeting sex differences, adolescent vulnerability and ecological validity of research tools,  
899 *Neurosci. Biobehav. Rev.* 37 (2013) 2454–2471. doi:10.1016/j.neubiorev.2013.07.005.
- 900 [10] B.N. Cuthbert, Research Domain Criteria: toward future psychiatric nosologies, *Dialogues Clin.*  
901 *Neurosci.* 17 (2015) 89–97.
- 902 [11] A.V. Kalueff, A.M. Stewart, C. Song, I.I. Gottesman, Targeting dynamic interplay among  
903 disordered domains or endophenotypes to understand complex neuropsychiatric disorders:  
904 Translational lessons from preclinical models, *Neurosci. Biobehav. Rev.* 53 (2015) 25–36.  
905 doi:10.1016/j.neubiorev.2015.03.007.
- 906 [12] H.G. Baumgarten, Z. Grozdanovic, Psychopharmacology of central serotonergic systems,  
907 *Pharmacopsychiatry.* 28 Suppl 2 (1995) 73–79. doi:10.1055/s-2007-979623.

- 908 [13] S. Enge, M. Fleischhauer, K.-P. Lesch, A. Reif, A. Strobel, Serotonergic modulation in executive  
909 functioning: linking genetic variations to working memory performance, *Neuropsychologia*. 49  
910 (2011) 3776–3785. doi:10.1016/j.neuropsychologia.2011.09.038.
- 911 [14] D. Kiser, B. Steemers, I. Branchi, J.R. Homberg, The reciprocal interaction between serotonin  
912 and social behaviour, *Neurosci. Biobehav. Rev.* 36 (2012) 786–798.  
913 doi:10.1016/j.neubiorev.2011.12.009.
- 914 [15] D. Mendelsohn, W.J. Riedel, A. Sambeth, Effects of acute tryptophan depletion on memory,  
915 attention and executive functions: A systematic review, *Neurosci. Biobehav. Rev.* 33 (2009)  
916 926–952. doi:10.1016/j.neubiorev.2009.03.006.
- 917 [16] T.W. Robbins, A.F.T. Arnsten, The neuropsychopharmacology of fronto-executive function:  
918 monoaminergic modulation, *Annu. Rev. Neurosci.* 32 (2009) 267–287.  
919 doi:10.1146/annurev.neuro.051508.135535.
- 920 [17] J. Waider, N. Araragi, L. Gutknecht, K.-P. Lesch, Tryptophan hydroxylase-2 (TPH2) in disorders of  
921 cognitive control and emotion regulation: a perspective, *Psychoneuroendocrinology*. 36 (2011)  
922 393–405. doi:10.1016/j.psyneuen.2010.12.012.
- 923 [18] C.A. Winstanley, The utility of rat models of impulsivity in developing pharmacotherapies for  
924 impulse control disorders, *Br. J. Pharmacol.* 164 (2011) 1301–1321. doi:10.1111/j.1476-  
925 5381.2011.01323.x.
- 926 [19] S.N. Young, M. Leyton, The role of serotonin in human mood and social interaction. Insight  
927 from altered tryptophan levels, *Pharmacol. Biochem. Behav.* 71 (2002) 857–865.
- 928 [20] A.R. Maher, G. Theodore, Summary of the comparative effectiveness review on off-label use of  
929 atypical antipsychotics, *J. Manag. Care Pharm. JMCP*. 18 (2012) S1-20.
- 930 [21] C.B. Nemeroff, Psychopharmacology of affective disorders in the 21st century, *Biol. Psychiatry*.  
931 44 (1998) 517–525.
- 932 [22] E. Hollander, J. Rosen, Impulsivity, *J. Psychopharmacol. Oxf. Engl.* 14 (2000) S39-44.  
933 doi:10.1177/02698811000142S106.
- 934 [23] J.R. Homberg, R. van den Bos, E. den Heijer, R. Suer, E. Cuppen, Serotonin transporter dosage  
935 modulates long-term decision-making in rat and human, *Neuropharmacology*. 55 (2008) 80–84.  
936 doi:10.1016/j.neuropharm.2008.04.016.
- 937 [24] S. Koot, F. Zoratto, T. Cassano, R. Colangeli, G. Laviola, R. van den Bos, W. Adriani,  
938 Compromised decision-making and increased gambling proneness following dietary serotonin  
939 depletion in rats, *Neuropharmacology*. 62 (2012) 1640–1650.  
940 doi:10.1016/j.neuropharm.2011.11.002.
- 941 [25] C.A. Winstanley, J.W. Dalley, D.E.H. Theobald, T.W. Robbins, Fractionating impulsivity:  
942 contrasting effects of central 5-HT depletion on different measures of impulsive behavior,  
943 *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* 29 (2004) 1331–1343.  
944 doi:10.1038/sj.npp.1300434.
- 945 [26] R.L. Barlow, J. Alsiö, B. Jupp, R. Rabinovich, S. Shrestha, A.C. Roberts, T.W. Robbins, J.W. Dalley,  
946 Markers of serotonergic function in the orbitofrontal cortex and dorsal raphé nucleus predict  
947 individual variation in spatial-discrimination serial reversal learning, *Neuropsychopharmacol.*  
948 *Off. Publ. Am. Coll. Neuropsychopharmacol.* 40 (2015) 1619–1630. doi:10.1038/npp.2014.335.
- 949 [27] F. Loiseau, A. Dekeyne, M.J. Millan, Pro-cognitive effects of 5-HT<sub>6</sub> receptor antagonists in the  
950 social recognition procedure in rats: implication of the frontal cortex, *Psychopharmacology*  
951 (Berl.). 196 (2008) 93–104. doi:10.1007/s00213-007-0934-5.
- 952 [28] S.F. de Boer, D. Caramaschi, D. Natarajan, J.M. Koolhaas, The vicious cycle towards violence:  
953 focus on the negative feedback mechanisms of brain serotonin neurotransmission, *Front.*  
954 *Behav. Neurosci.* 3 (2009) 52. doi:10.3389/neuro.08.052.2009.
- 955 [29] L. Lewejohann, V. Kloke, R.S. Heiming, F. Jansen, S. Kaiser, A. Schmitt, K.P. Lesch, N. Sachser,  
956 Social status and day-to-day behaviour of male serotonin transporter knockout mice, *Behav.*  
957 *Brain Res.* 211 (2010) 220–228. doi:10.1016/j.bbr.2010.03.035.
- 958 [30] C.R. McKittrick, D.C. Blanchard, R.J. Blanchard, B.S. McEwen, R.R. Sakai, Serotonin receptor  
959 binding in a colony model of chronic social stress, *Biol. Psychiatry*. 37 (1995) 383–393.

- 960 [31] K. Kaplan, A.E. Echert, B. Massat, M.M. Puissant, O. Palygin, A.M. Geurts, M.R. Hodges, Chronic  
961 central serotonin depletion attenuates ventilation and body temperature in young but not  
962 adult Tph2 knockout rats, *J. Appl. Physiol. Bethesda Md* 1985. 120 (2016) 1070–1081.  
963 doi:10.1152/jappphysiol.01015.2015.
- 964 [32] J.P. Aggleton, The ability of different strains of rats to acquire a visual nonmatching-to-sample  
965 task, *Psychobiology*. 24 (1996) 44–48. doi:10.3758/BF03331952.
- 966 [33] A.H. Tuttle, V.M. Philip, E.J. Chesler, J.S. Mogil, Comparing phenotypic variation between inbred  
967 and outbred mice, *Nat. Methods*. 15 (2018) 994. doi:10.1038/s41592-018-0224-7.
- 968 [34] J. Myerson, L. Green, M. Warusawitharana, Area under the curve as a measure of discounting,  
969 *J. Exp. Anal. Behav.* 76 (2001) 235–243. doi:10.1901/jeab.2001.76-235.
- 970 [35] F. Zoratto, E. Sinclair, A. Manciocco, A. Vitale, G. Laviola, W. Adriani, Individual differences in  
971 gambling proneness among rats and common marmosets: an automated choice task, *BioMed  
972 Res. Int.* 2014 (2014) 927685. doi:10.1155/2014/927685.
- 973 [36] F. Dellu-Hagedorn, Relationship between impulsivity, hyperactivity and working memory: a  
974 differential analysis in the rat, *Behav. Brain Funct.* 2 (2006) 10. doi:10.1186/1744-9081-2-10.
- 975 [37] H. Arakawa, D.C. Blanchard, R.J. Blanchard, Colony formation of C57BL/6J mice in visible  
976 burrow system: Identification of eusocial behaviors in a background strain for genetic animal  
977 models of autism, *Behav. Brain Res.* 176 (2007) 27–39. doi:10.1016/j.bbr.2006.07.027.
- 978 [38] O. Burman, D. Owen, U. Aboulsmail, M. Mendl, Removing individual rats affects indicators of  
979 welfare in the remaining group members, *Physiol. Behav.* 93 (2008) 89–96.  
980 doi:10.1016/j.physbeh.2007.08.001.
- 981 [39] D.J. Rademacher, A.L. Schuyler, C.K. Kruschel, R.E. Steinpreis, Effects of cocaine and putative  
982 atypical antipsychotics on rat social behavior: An ethopharmacological study, *Pharmacol.  
983 Biochem. Behav.* 73 (2002) 769–778. doi:10.1016/S0091-3057(02)00904-8.
- 984 [40] Whishaw, Ian Q, Kolb Bryan, *Behavior of the Laboratory Rat: A Handbook with Tests - Oxford  
985 Scholarship*, (2004).  
986 [http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195162851.001.0001/acprof-](http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195162851.001.0001/acprof-9780195162851)  
987 [f-9780195162851](http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195162851.001.0001/acprof-9780195162851).
- 988 [41] M. Lepschy, C. Touma, R. Hruby, R. Palme, Non-invasive measurement of adrenocortical activity  
989 in male and female rats, *Lab. Anim.* 41 (2007) 372–387. doi:10.1258/002367707781282730.
- 990 [42] C. Touma, N. Sachser, E. Möstl, R. Palme, Effects of sex and time of day on metabolism and  
991 excretion of corticosterone in urine and feces of mice, *Gen. Comp. Endocrinol.* 130 (2003) 267–  
992 278.
- 993 [43] H. Shahar-Gold, R. Gur, S. Wagner, Rapid and Reversible Impairments of Short- and Long-Term  
994 Social Recognition Memory Are Caused by Acute Isolation of Adult Rats via Distinct  
995 Mechanisms, *PLoS ONE*. 8 (2013) e65085. doi:10.1371/journal.pone.0065085.
- 996 [44] R Core Team, R: The R Project for Statistical Computing, R Foundation for Statistical Computing,  
997 Vienna, Austria. <https://www.R-project.org/>, (2018). <https://www.r-project.org/>.
- 998 [45] Maxime Hervé, RVAideMemoire: Testing and Plotting Procedures for Biostatistics, (2018).  
999 <https://CRAN.R-project.org/package=RVAideMemoire>.
- 1000 [46] B. Wheeler, M. Torchiano, lmPerm: Permutation Tests for Linear Models, (2016).  
1001 <https://CRAN.R-project.org/package=lmPerm>.
- 1002 [47] A. Liaw, M. Wiener, Classification and Regression by randomForest, (2002). [https://CRAN.R-](https://CRAN.R-project.org/doc/Rnews/)  
1003 [project.org/doc/Rnews/](https://CRAN.R-project.org/doc/Rnews/).
- 1004 [48] N. Haines, J. Vassileva, W.-Y. Ahn, The Outcome-Representation Learning Model: A Novel  
1005 Reinforcement Learning Model of the Iowa Gambling Task, *Cogn. Sci.* (2018).  
1006 doi:10.1111/cogs.12688.
- 1007 [49] M. Balconi, R. Finocchiaro, Y. Canavesio, Reward Sensitivity (Behavioral Activation System),  
1008 Cognitive, and Metacognitive Control in Gambling Behavior: Evidences From Behavioral,  
1009 Feedback-Related Negativity, and P300 Effect, *J. Neuropsychiatry Clin. Neurosci.* 27 (2015) 219–  
1010 227. doi:10.1176/appi.neuropsych.14070165.

- 1011 [50] A. Bechara, H. Damasio, Decision-making and addiction (part I): impaired activation of somatic  
1012 states in substance dependent individuals when pondering decisions with negative future  
1013 consequences, *Neuropsychologia*. 40 (2002) 1675–1689. doi:10.1016/S0028-3932(02)00015-5.
- 1014 [51] M. Brand, E. Kalbe, K. Labudda, E. Fujiwara, J. Kessler, H.J. Markowitsch, Decision-making  
1015 impairments in patients with pathological gambling, *Psychiatry Res.* 133 (2005) 91–99.  
1016 doi:10.1016/j.psychres.2004.10.003.
- 1017 [52] Y.-T. Kim, H. Sohn, J. Jeong, Delayed transition from ambiguous to risky decision making in  
1018 alcohol dependence during Iowa Gambling Task, *Psychiatry Res.* 190 (2011) 297–303.  
1019 doi:10.1016/j.psychres.2011.05.003.
- 1020 [53] G. Fond, S. Bayard, D. Capdevielle, J. Del-Monte, N. Mimoun, A. Macgregor, J.-P. Boulenger, M.-  
1021 C. Gely-Nargeot, S. Raffard, A further evaluation of decision-making under risk and under  
1022 ambiguity in schizophrenia, *Eur. Arch. Psychiatry Clin. Neurosci.* 263 (2013) 249–257.  
1023 doi:10.1007/s00406-012-0330-y.
- 1024 [54] L. Zhang, J. Tang, Y. Dong, Y. Ji, R. Tao, Z. Liang, J. Chen, Y. Wu, K. Wang, Similarities and  
1025 Differences in Decision-Making Impairments between Autism Spectrum Disorder and  
1026 Schizophrenia, *Front. Behav. Neurosci.* 9 (2015) 259. doi:10.3389/fnbeh.2015.00259.
- 1027 [55] H.W. Kim, J.I. Kang, K. Namkoong, K. Jhung, R.Y. Ha, S.J. Kim, Further evidence of a dissociation  
1028 between decision-making under ambiguity and decision-making under risk in obsessive-  
1029 compulsive disorder, *J. Affect. Disord.* 176 (2015) 118–124. doi:10.1016/j.jad.2015.01.060.
- 1030 [56] N. Adjeroud, J. Besnard, C. Verny, A. Prundean, C. Scherer, B. Gohier, D. Bonneau, N.E.  
1031 Massiou, P. Allain, Dissociation between decision-making under risk and decision-making  
1032 under ambiguity in premanifest and manifest Huntington’s disease, *Neuropsychologia*. 103  
1033 (2017) 87–95. doi:10.1016/j.neuropsychologia.2017.07.011.
- 1034 [57] E.A. Deisenhammer, S.K. Schmid, G. Kemmler, B. Moser, M. Delazer, Decision making under risk  
1035 and under ambiguity in depressed suicide attempters, depressed non-attempters and healthy  
1036 controls, *J. Affect. Disord.* 226 (2018) 261–266. doi:10.1016/j.jad.2017.10.012.
- 1037 [58] J.E. Mekarski, Main effects of current and pimozide on prepared and learned self-stimulation  
1038 behaviors are on performance not reward, *Pharmacol. Biochem. Behav.* 31 (1988) 845–853.
- 1039 [59] J.E. Goeders, K.S. Murnane, M.L. Banks, W.E. Fantegrossi, Escalation of food-maintained  
1040 responding and sensitivity to the locomotor stimulant effects of cocaine in mice, *Pharmacol.*  
1041 *Biochem. Behav.* 93 (2009) 67–74. doi:10.1016/j.pbb.2009.04.008.
- 1042 [60] R.J. Blanchard, L. Dulloog, C. Markham, O. Nishimura, J. Nikulina Compton, A. Jun, C. Han, D.C.  
1043 Blanchard, Sexual and aggressive interactions in a visible burrow system with provisioned  
1044 burrows, *Physiol. Behav.* 72 (2001) 245–254.
- 1045 [61] J.F. Davis, E.G. Krause, S.J. Melhorn, R.R. Sakai, S.C. Benoit, Dominant rats are natural risk takers  
1046 and display increased motivation for food reward, *Neuroscience*. 162 (2009) 23–30.  
1047 doi:10.1016/j.neuroscience.2009.04.039.
- 1048 [62] B. Buwalda, J.M. Koolhaas, S.F. de Boer, Trait aggressiveness does not predict social dominance  
1049 of rats in the Visible Burrow System, *Physiol. Behav.* 178 (2017) 134–143.  
1050 doi:10.1016/j.physbeh.2017.01.008.
- 1051 [63] M.I. Cordero, C. Sandi, Stress Amplifies Memory for Social Hierarchy, *Front. Neurosci.* 1 (2007)  
1052 175–184. doi:10.3389/neuro.01.1.1.013.2007.
- 1053 [64] B. Jupp, J.E. Murray, E.R. Jordan, J. Xia, M. Fluharty, S. Shrestha, T.W. Robbins, J.W. Dalley,  
1054 Social dominance in rats: effects on cocaine self-administration, novelty reactivity and  
1055 dopamine receptor binding and content in the striatum, *Psychopharmacology (Berl.)*. 233  
1056 (2016) 579–589. doi:10.1007/s00213-015-4122-8.
- 1057 [65] D.C. Blanchard, R.L. Spencer, S.M. Weiss, R.J. Blanchard, B. McEwen, R.R. Sakai, Visible burrow  
1058 system as a model of chronic social stress: behavioral and neuroendocrine correlates,  
1059 *Psychoneuroendocrinology*. 20 (1995) 117–134.
- 1060 [66] M.J. Ramirez, Behavioral parameters of social dominance in rats, *Bull. Psychon. Soc.* 15 (1980)  
1061 96–98. doi:10.3758/BF03334477.



- 1062 [67] N. So, B. Franks, S. Lim, J.P. Curley, A Social Network Approach Reveals Associations between  
1063 Mouse Social Dominance and Brain Gene Expression, *PLoS ONE*. 10 (2015).  
1064 doi:10.1371/journal.pone.0134509.
- 1065 [68] N. Alia-Klein, R.Z. Goldstein, A. Kriplani, J. Logan, D. Tomasi, B. Williams, F. Telang, E. Shumay, A.  
1066 Biegon, I.W. Craig, F. Henn, G.-J. Wang, N.D. Volkow, J.S. Fowler, Brain monoamine oxidase A  
1067 activity predicts trait aggression, *J. Neurosci. Off. J. Soc. Neurosci.* 28 (2008) 5099–5104.  
1068 doi:10.1523/JNEUROSCI.0925-08.2008.
- 1069 [69] F. Jollant, C. Buresi, S. Guillaume, I. Jaussent, F. Bellivier, M. Leboyer, D. Castelnau, A.  
1070 Malafosse, P. Courtet, The influence of four serotonin-related genes on decision-making in  
1071 suicide attempters, *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc.*  
1072 *Psychiatr. Genet.* 144B (2007) 615–624. doi:10.1002/ajmg.b.30467.
- 1073 [70] E. Anderzhanova, T. Kirmeier, C.T. Wotjak, Animal models in psychiatric research: The RDoC  
1074 system as a new framework for endophenotype-oriented translational neuroscience,  
1075 *Neurobiol. Stress.* 7 (2017) 47–56. doi:10.1016/j.ynstr.2017.03.003.
- 1076 [71] T. Insel, B. Cuthbert, M. Garvey, R. Heinssen, D.S. Pine, K. Quinn, C. Sanislow, P. Wang, Research  
1077 domain criteria (RDoC): toward a new classification framework for research on mental  
1078 disorders, *Am. J. Psychiatry.* 167 (2010) 748–751. doi:10.1176/appi.ajp.2010.09091379.
- 1079 [72] M.F.W. Festing, Evidence Should Trump Intuition by Preferring Inbred Strains to Outbred Stocks  
1080 in Preclinical Research, *ILAR J.* 55 (2014) 399–404. doi:10.1093/ilar/ilu036.
- 1081 [73] A.D. Lê, H. Kalant, Intravenous self-administration of alcohol in rats-problems with translation  
1082 to humans, *Addict. Biol.* 22 (2017) 1665–1681. doi:10.1111/adb.12429.
- 1083 [74] M. Shoaib, R. Spanagel, T. Stohr, T.S. Shippenberg, Strain differences in the rewarding and  
1084 dopamine-releasing effects of morphine in rats, *Psychopharmacology (Berl.)*. 117 (1995) 240–  
1085 247.
- 1086 [75] A.M. Cano, E.S. Murphy, G. Lupfer, Delay discounting predicts binge-eating in Wistar rats,  
1087 *Behav. Processes.* 132 (2016) 1–4. doi:10.1016/j.beproc.2016.08.011.
- 1088 [76] U. Datta, M. Martini, M. Fan, W. Sun, Compulsive sucrose- and cocaine-seeking behaviors in  
1089 male and female Wistar rats, *Psychopharmacology (Berl.)*. 235 (2018) 2395–2405.  
1090 doi:10.1007/s00213-018-4937-1.
- 1091 [77] T. Brand, R. Spanagel, M. Schneider, Decreased reward sensitivity in rats from the Fischer344  
1092 strain compared to Wistar rats is paralleled by differences in endocannabinoid signaling, *PloS*  
1093 *One.* 7 (2012) e31169. doi:10.1371/journal.pone.0031169.
- 1094 [78] L. Brimberg, S. Flaisher-Grinberg, E.A. Schilman, D. Joel, Strain differences in “compulsive”  
1095 lever-pressing, *Behav. Brain Res.* 179 (2007) 141–151. doi:10.1016/j.bbr.2007.01.014.
- 1096 [79] I. Dela Peña, I.J. Dela Peña, J.B. de la Peña, H.J. Kim, C.Y. Shin, D.H. Han, B.-N. Kim, J.H. Ryu, J.H.  
1097 Cheong, Methylphenidate and Atomoxetine-Responsive Prefrontal Cortical Genetic Overlaps in  
1098 “Impulsive” SHR/NCrl and Wistar Rats, *Behav. Genet.* 47 (2017) 564–580. doi:10.1007/s10519-  
1099 017-9861-3.
- 1100 [80] M. Casarrubea, V. Roy, F. Sorbera, M.S. Magnusson, A. Santangelo, A. Arabo, G. Crescimanno,  
1101 Significant divergences between the temporal structure of the behavior in Wistar and in the  
1102 spontaneously more anxious DA/Han strain of rats tested in elevated plus maze, *Behav. Brain*  
1103 *Res.* 250 (2013) 166–173. doi:10.1016/j.bbr.2013.05.016.
- 1104 [81] A.O. Mehan, P.M. Moran, M. Elliott, A.J. Young, M.H. Joseph, R. Green, A comparison between  
1105 Dark Agouti and Sprague-Dawley rats in their behaviour on the elevated plus-maze, open-field  
1106 apparatus and activity meters, and their response to diazepam, *Psychopharmacology (Berl.)*.  
1107 159 (2002) 188–195. doi:10.1007/s002130100902.
- 1108 [82] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Fifth  
1109 Edition. Washington DC, (2013). <https://www.psychiatry.org/psychiatrists/practice/dsm>.  
1110