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1 Modelling decision-making under uncertainty: a direct comparison
2 study between human and mouse gambling data

3

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21 **Key-words:**

22 Decision-making, Iowa Gambling Task, mouse Gambling Task

23

24 **Abstract:**

25 Decision-making is a conserved evolutionary process enabling us to choose one option among
26 several alternatives, and relies on reward and cognitive control systems. The Iowa Gambling
27 Task allows the assessment of human decision-making under uncertainty by presenting four
28 card decks with various cost-benefit probabilities. Participants seek to maximise their monetary
29 gain by developing long-term optimal-choice strategies. Animal versions have been adapted
30 with nutritional rewards, but interspecies data comparisons are scarce. Our study directly
31 compares the non-pathological decision-making performance between humans and wild-type
32 C57BL/6 mice. Human participants completed an electronic Iowa Gambling Task version, while
33 mice a maze-based adaptation with four arms baited in a probabilistic way. Our data shows
34 closely matching performance between both species with similar patterns of choice behaviours.
35 However, mice showed a faster learning rate than humans. Moreover, both populations were
36 clustered into good, intermediate and poor decision-making categories with similar
37 proportions. Remarkably, mice characterised as good decision-makers behaved the same as
38 humans of the same category, but slight differences among species are evident for the other
39 two subpopulations. Overall, our direct comparative study confirms the good face validity of
40 the rodent gambling task. Extended behavioural characterisation and pathological animal
41 models should help strengthen its construct validity and disentangle the determinants in
42 animals and humans decision-making.

43

44 **Introduction**

45 Do animals gamble for food just like humans gamble for money? Most species, including human
46 beings, have to make accurate assessments of the cost-benefit trade-off in reward-driven
47 contexts. For example, the longer an animal is searching for food, the more likely it is to
48 accumulate more and better rewards, however, the more likely it is to encounter a predator.
49 Thus, decision-making (DM) is an essential mechanism for survival in partly predictable
50 situations (de Froment et al., 2014). The underlying principles of how living beings achieve
51 efficient DM are still not fully understood, and assessing human DM using animal models
52 requires further validation. Laboratory tests simulating real-life DM, such as gambling tasks,
53 have been developed. Particularly, the Iowa Gambling Task (IGT) is widely used to assess
54 human DM under uncertainty. Participants are required to maximise the monetary gains by
55 selecting cards from four decks with various cost-benefit probabilities (Bechara et al., 1994).
56 Players face a choice-conflict between playing from long-term disadvantageous decks yielding
57 higher gains but frequent losses, or from advantageous ones associated with smaller immediate
58 rewards and less frequent penalties. Thus, optimal decisions involve the animal refraining from
59 the preferred large immediate rewards whilst opting for lower but more frequent gains, leading
60 to long-term benefits.

61 The IGT was originally created to study DM impairments in patients with ventromedial
62 prefrontal cortex damage. Compared to healthy participants who progressively learn to select
63 the advantageous decks, the impaired patients decisively underperform by being unable to set
64 the optimal strategy from repeated negative outcomes. Besides this, many IGT studies with
65 healthy populations have shown a high interindividual performance variability (Bechara and
66 Damasio, 2002; Bechara et al., 2002; Steingroever et al., 2013). Indeed, several clinical reports
67 indicated that, while a majority of healthy participants develop the optimal strategy (good DM
68 individuals), others do not acquire a preference for one deck over the others, which is indicative
69 of a lack of learning (poor DM individuals) (Bechara et al., 2001, 2002; Glicksohn et al., 2007a).
70 The literature has shown that many factors may account for this variability in gambling
71 performance. For example, Bechara et al. explain the poor IGT performance in terms of atypical
72 sensitivity to the reward or punishment. Mechanisms underlying this atypical sensitivity are
73 numerous and still not fully elucidated. Among the potential contributors to IGT failure, the
74 presence of personality characteristics associated with risky behaviour (Buelow and Suhr,
75 2009), of weaknesses in executive functioning (Brand et al., 2007), a low motivation (Giustiniani
76 et al., 2015), a negative affect at the time of task (Suhr and Tsanadis, 2007) as well as low
77 educational (Davis et al., 2008) and low intellectual levels (Barry and Petry, 2008) have been
78 reported. These data illustrate a behavioural continuum with an overlap in choice strategies
79 between human non-pathological and pathological conditions.

80

81 Interestingly, animal versions of the IGT with species-appropriate adjustments to assess DM in a
82 design comparable to humans (van den Bos et al., 2006; van Enkhuizen et al., 2013;
83 Heilbronner, 2017; Pittaras et al., 2016; Rivalan et al., 2009, 2013; Visser et al., 2011; Young et
84 al., 2011; Zeeb et al., 2009) have been developed. For example, in rodent gambling tasks the
85 decks of cards have been replaced by mazes or operant chambers equipped with different

86 options of varying outcomes; monetary gains are replaced with nutritional rewards since
87 money and food are thought to drive similar behaviours (Lehner et al., 2017).
88 Similar to human studies, rodents with lesions perform sub-optimally in adapted IGT versions
89 and show a delay in adopting a consistent strategy compared to healthy individuals (Rivalan et
90 al., 2011; Winstanley and Clark, 2015). For the majority of healthy rodents, as the task
91 progresses a raise in advantageous choices is observed, which is commonly accompanied by
92 individuals clustering in three subpopulations who reflect the variable choice strategies (van
93 Enkhuizen et al., 2014; Pittaras et al., 2016; Rivalan et al., 2009). Good DM individuals quickly
94 develop a strong preference for the advantageous options, while poor DM individuals display
95 the worst performances, either not showing any preference for neither advantageous nor
96 disadvantageous options or displaying a long-term preference for the disadvantageous ones.
97 Intermediate DM individuals perform between the other two subgroups. Whether these
98 interindividual variabilities observed in both healthy human and animal populations are similar
99 has never been directly assessed to substantiate the face validity of the models.

100

101 Animal and human versions of gambling tasks usually evaluate performance with different
102 analytical methods (Bechara et al., 2001; Zeeb and Winstanley, 2013) and are hence not
103 compared in a direct manner even if animal gambling tasks have been specially created to
104 simulate human DM processes. However, direct comparative research will be a valuable
105 approach allowing clinicians and researchers to bridge their findings, rendering translational
106 studies as a direct tool genuinely meaningful (van Enkhuizen et al., 2014).

107 Here, we bridge the clinical and preclinical findings on DM processes featuring uncertainty by
108 directly comparing the performance of healthy humans and mice for the first time in the same
109 study using IGT-adapted tasks and identical analytical methods.

110 Based on the recent literature addressing the validity of mouse gambling tasks (mGT) (van den
111 Bos et al., 2013; van Enkhuizen et al., 2014; Heilbronner, 2017; Pittaras et al., 2016; Winstanley
112 and Clark, 2015), we forecasted a good face validity of our animal model with a similar overall
113 performance regarding the human population (Giustiniani et al., 2015). To check for the
114 existence of a similar variability in the choice strategies among the species, we then compared
115 the stratification of both populations according to the endpoint performances. To evaluate the
116 construct validity, we further studied the behavioural indexes of the cognitive processes sub-
117 serving the optimal choices. Finally, we sought to find the correlations with an endpoint
118 performance, focusing on the parameters of rigidity (Pittaras, 2013), flexibility (van Enkhuizen
119 et al., 2014) and win-stay and lose-shift choices (de Visser et al., 2011). We also analysed the
120 psychometric scores from human participants and reward sensitivity data in mice, to relate the
121 performance or choice strategies to additional behavioural traits.

122

123

124 **Experimental procedures**

125

126 **Participants.** To reduce conceptual and methodological differences between the tasks, we
127 controlled factors known to interfere with the results such as sex differences and the presence
128 of instructions, especially in humans. In that respect, we recruited only male subjects because
129 they have been described as less risky than females, choosing the advantageous options more

130 frequently in the IGT (Singh, 2016) and its rodent adaptations (van den Bos et al., 2006). Further
131 characterisations will include both genders, allowing us to take into account the variability we
132 accepted to overlook in the present study (Prendergast et al., 2014).

133
134 **Humans.** Forty healthy right-handed participants (mean age \pm SEM = 24.7 \pm 5.1; range 19-38)
135 were involved in the study. None reported a previous medical history of psychiatric disorders,
136 substance or alcohol abuse, neurological diseases, traumatic brain injury or stroke, and none
137 reported taking any medication.

138 Participants received information regarding the aim of the task and gave their written informed
139 consent to take part in the study. Given the influence of real money playing a significant role on
140 motivation, subjects were informed that the monetary payment would be proportional to the
141 global gain obtained in the task (Meyer, 2004; Meyer et al., 2000; Miedl et al., 2010). Due to the
142 ethical considerations and independent of individual performance, all participants received the
143 maximum amount of €85 at the end of the experiment. The protocol was approved by the
144 Committee of Protection of Persons (CPP-Est-11; authorisation given by the General Health
145 Administration (ANSM 2016-A00870-51 and NCT 02862821)).

146
147 **Mice.** Forty C57BL/6JRj mice (Ets Janvier Labs, Saint-Berthevin, France) were used for this study.
148 Inbred animals such as C57BL/6J are known to behave uniformly and display low interindividual
149 variability (Festing, 2014) (but see recent work by Tuttle et al. (Tuttle et al., 2018)). All animals
150 were 3-5 months old at the time of testing, group-housed and maintained under a 12 hour-
151 circadian cycle with a constant temperature (22 \pm 2°C). Water was available *ad libitum* and all
152 mice were food-restricted at 80-90% of their free-feeding weight (mean weight (g) \pm SEM = 22.2
153 \pm 0.2) in order to motivate exploration and completion of the nutritionally rewarding task
154 (Rivalan et al., 2009). Experiments were performed in behavioural rooms with tight luminous
155 intensity. All procedures met the NIH guidelines for the care and use of laboratory animals and
156 were approved by the University of Franche-Comte Animal Care and Use Committee (CEBEA-
157 58). All efforts were taken to minimise animal suffering during the testing according to the
158 Directive from the European Council on the 22nd of September 2010 (2010/63/EU).

159
160 **Human gambling task.** The task was an adapted electronic version of the IGT (Giustiniani et al.,
161 2015), whose aim was to maximise monetary gain through successive selections between four
162 decks. The decks' composition, values and scheduled reward-penalty were predetermined
163 identically to match the original IGT (Bechara, 1997; Bechara and Damasio, 2005; Bechara et al.,
164 1994). The decks looked identical, but differed in composition. Decks A and B were
165 disadvantageous, yielding immediate rewards but involved major economic losses on the long
166 run. Decks C and D were advantageous, yielding frequent small wins and smaller long-term
167 penalties, resulting in long-term gain. The decks also varied in their schedule of losses, with
168 decks B and D featuring infrequent, decks A and C frequent losses, respectively. All decks
169 contained an infinite number of cards in this computerised version of the IGT.. The monetary
170 reward was converted from US Dollars to Euros in order to match the currency of the test
171 subjects. At the beginning of the task, participants had a loan of €2,000.
172 Contrary to most IGT experiments, participants were not provided with information regarding
173 the presence of advantageous or disadvantageous decks and the number of trials. This ensured

174 that a somewhat partial advantage compared to the animals was avoided (Macphail, 1996) (but
175 see Rivalan's work (Rivalan et al., 2011)). In the absence of such information the final
176 performance usually worsen; therefore, the exploration phase typically lengthens and the
177 optimal strategy is hardly found in 100 trials (Balodis et al., 2006; Fernie and Tunney, 2006;
178 Glicksohn et al., 2007b). However, when more trials are allowed, many individuals performing
179 poorly in the first 100 trials are able to achieve good final performance (Balodis et al., 2006;
180 Buelow et al., 2013; Bull et al., 2015). To that purpose, the number of trials was increased from
181 100 to 200. A full description of the electronic version of the IGT is given in Giustiniani et al.
182 (2015).

183
184 **Mouse gambling task.** DM was evaluated using an mGT adapted from published protocols
185 (Pittaras et al., 2016; Visser et al., 2011). The experiment took place in a completely opaque
186 four-arm radial maze (identical and equidistant arms, 37 cm long and 5.7 cm wide), with the
187 common central zone used as a start-point. Mice were rewarded with grain-based pellets (20
188 mg Dustless Precision Pellets® Grain-Based Diet, PHYMEP s.a.r.l., Paris, France) or punished
189 with grain-based pellets previously treated with quinine (180 mM quinine hydrochloride,
190 Sigma-Aldrich, Schnellendorf, Germany). Quinine pellets were poorly palatable but edible.

191 Prior to every experimental session, the animals were acclimatised to the behavioural room for
192 30 minutes. The experimental design was composed of 5 blocks of 20 trials over five days (a
193 total of 100 trials per animal). The first ten trials of each block took place during the morning,
194 the second ten trials during the afternoon. Before the first trial of the first block, mice had 3
195 minutes to explore and eat inside the maze (*first habituation period*). From the second block,
196 mice had 2 minutes to explore the maze before the first trial, but no food was available
197 (*general habituation period*). These habituation periods aimed to reduce the stressing effect of
198 the animals' first exposure to the dispositive. After this habituation, mice were placed at the
199 start-point inside an opaque cylindrical structure to avoid early orientation. The cylinder was
200 removed after 5 seconds and animals were allowed to choose an arm. Mice had one minute to
201 choose an arm, explore it and eat the reward. An extra-minute was given if the choice was not
202 made in time..

203 Our mGT was adapted in order to minimise the effect of satiety during the task. For that, two
204 arms gave access to a small reward (1 pellet) in the first trial of each half block (trials 1, 11, 21,
205 31, 41, 51, 61, 71, 81 and 91) and bigger rewards (3-4 pellets) in the other 18 choices of each
206 block with a small probability of presenting a punishment (3-4 quinine pellets, twice in 18
207 possible choices) (*advantageous arms C' and D'*). Arm C' and D' provided a maximal amount of
208 50 and 66 rewards per block, respectively.

209 The other two arms (*disadvantageous arms A' and B'*) gave access to a bigger reward (2 pellets)
210 during the first trials of each half block, but bigger punishments (4-5 quinine pellets) and a
211 smaller reward-possibility (4-5 pellets, once in 18 possible choices) in the block's remaining 18
212 choices. Arm A' gave access to a maximal amount of 10 rewards per block, arm B' until 14.
213 Between consecutive trials, the animals were placed in their home cages for 90 seconds. The
214 localisation of advantageous and disadvantageous arms was randomised with different award
215 and punishment sequences for each animal.

216

217 **Determination of interindividual differences.** A k-mean clustering method, already used in
218 mouse gambling tasks (Pittaras, 2016; Pittaras et al., 2016), was applied to identify
219 interindividual differences in both, human and mice populations. This enabled the automatic
220 identification of the objects' optimum partition into a specific number of clusters, minimising
221 and maximising the intra and inter-cluster variance, respectively (Timmerman et al., 2013). In
222 accordance with the literature (Pittaras et al., 2016), the mean percentage of advantageous
223 choices was calculated for the tasks' final 30% when performance was highly stable (W: $p < 0.01$
224 in mice and humans). The individual performances were then divided into three groups: *good*,
225 *intermediate* and *poor decision-makers (DMs)*.

226
227 **Choice behaviours: rigidity, flexibility, lose-shift and win-stay scores.** Maximisation of benefits
228 and the reduction of costs, which characterise optimal performances, require flexibly adapting
229 contingencies in order to favourably orient future choices. To compare different DM strategies,
230 behavioural measures of cognitive processes at the beginning and the end of the task have
231 been calculated. We measured our populations' rigidity score by calculating the highest
232 percentage of choice of a deck or arm. The flexibility score is then the proportion of switches
233 from one deck or arm to another. The lose-shift score, as a measure of negative outcome
234 aversion, was assessed by calculating the proportion of switches after a penalty outcome. Win-
235 stay scores likewise reflect the choice of the same option after receiving a reward. Each
236 behavioural measure was calculated at the beginning (first 40% of the task) and at the end of
237 the experiment (last 40% of the task), according to previous studies (Pittaras et al., 2016).

238
239 **Reward sensitivity.** In humans, the Behavioural Inhibition and Activation System scales
240 (BIS/BAS) allowed us to approach behavioural motivation (Rizvi et al., 2016). In mice, reward
241 sensitivity was evaluated at the end of the mGT using the sucrose preference test (adapted
242 from (Lutz et al., 2013)). For details, see Supplementary data.

243 244 **Data analysis**

245
246 **Whole group analyses.** A population's overall performance in terms of the advantageous
247 choices for the gambling tasks was analysed with Bayesian and frequentist approaches. To
248 consider learning rates, the relative risk (the ratio of the 'risk' of success in both populations
249 (humans/mice) -RR) was measured. The resulting proportions were compared by Beta laws,
250 whose parameters are interpreted in terms of the number of successes and failures,
251 establishing the probability law of success rates' ratio. A credibility interval, inside which a
252 parameter has a given probability (CI), was then calculated.

253 Hereafter, in order to address the behavioural kinetics the performance was divided into five
254 blocks, each representing 20% of the task. The performance of each block was compared to the
255 chance level using Student's tests (t-tests). The evolution of the performance was assessed by
256 the analysis of variance (ANOVA), with the factor being 20%-blocks. Differences between
257 populations were analysed using a partially repeated ANOVA with species as the between-
258 subject variable and 20%-blocks as the within-subject variable.

259 The evolution of choice behaviours scores was first compared for each group using a t-test,
260 followed by a comparison of the overall population's scores by two-way repeated-measures
261 ANOVA with factors species and time course (first and last 40% of the task).
262 BIS/BAS data in humans and sucrose preference in mice were analysed using the Kruskal-Wallis
263 (KW) test (see Supplementary data). Correlations between the endpoint performance
264 (percentage of advantageous choices in the last 30% of the task) and choice behaviours were
265 also carried out. Comparisons were Bonferroni corrected when necessary to account for the
266 multiple comparisons.

267
268 **Interindividual data analysis.** For each group, the evolution of the gambling performance was
269 assessed by repeated-measures ANOVAs, with the factors being 20%-Blocks and clusters (*good*,
270 *intermediate* and *poor DMs*), followed by Mann Whitney U (MW) tests to show subgroup
271 differences two by two. Each interindividual distribution was also compared between mice and
272 humans using an MW test.

273 We used Wilcoxon (W) tests to compare, for each subgroup, the evolution of the gambling
274 performance relative to the chance level. The subgroup's proportions of each population were
275 compared using the Chi-square test. Differences in the choice behaviour scores between the
276 subgroups in mice and humans were assessed by KW tests for the beginning and the end of the
277 task. These measures were also compared between the species using MW tests. All MW and W
278 tests were Bonferroni corrected.

279 The statistical significance threshold of all the tests was set at $p < 0.05$.

280

281 **Results**

282

283 **Overall gambling performance: mice learn faster than humans (Figure 1 and Supplementary 284 Analysis 1)**

285 The Bayesian analysis revealed a difference in the learning rate between the species (Fig. 1A),
286 showing that mice learned faster than humans did: after 100 trials, mice had better overall
287 gambling performance (CI 95% = 1.191 to 1.277). However, comparing the last 100 mice and
288 human trials shows similar performances (CI 95% = 0.956 to 1.016).

289

290 In order to circumvent variations in the gambling tasks' designs and to allow for the direct
291 comparison of data, we analysed performance as a function of task progression, expressed as
292 percentages. Splitting all trials into five 20% trial-blocks (Fig. 1B) clearly shows that humans
293 acquired the task contingencies after completion of 40% of the task, performing above the
294 chance level from the third 20%-block onwards (t-test, $p < 0.01$). A learning effect has been
295 evidenced as the performance gradually improved over time ($F(4,156) = 15.4$; $p < 0.0001$) after
296 20% of the task was completed and till the end ($p < 0.0001$, above the behavioural output of
297 the 1st 20%-block).

298 Mice, however, performed above the chance level already after the first 20% of the task, thus,
299 orientating towards the favourable choices earlier than humans (t-test, $p < 0.0001$). The
300 performance progressively improved over time ($F(4,195) = 11.9$; $p < 0.0001$) from the second
301 20%-block (2nd block: $p < 0.05$, 3rd block: $p < 0.001$, 4th and 5th blocks: $p < 0.0001$) and compared
302 to the beginning of the task.

303 The comparison of the IGT and mGT performances shows no significant effect of the species in
304 the percentage of advantageous choices ($F(1,78) = 3.1$; $p = 0.80$). Both populations performed
305 similarly along the task progression, as shown by the absence of a statistical difference in the
306 interaction between factors (species and 20%-Blocks) ($F(4,312) = 0.06$; $p = 0.99$).

307
308 These results show that both species learn the task contingencies, however demonstrating that
309 mice are faster learners than humans are. When compared as function of task progression,
310 both populations display a similar improvement in performance and reach equivalent final
311 performance despite the design differences.

312 313 **Comparable categories of good, intermediate and poor DMs with similar proportions among** 314 **the species (Figure 2 and Supplementary Figure 1 and Analyses 2 & 3)**

315 In Fig. 2, A1 and B1 we plot individual data showing larger dispersion in humans than in mice.
316 Intraspecies variability was investigated using k-mean clustering stratification according to the
317 endpoint performance, discriminating three subpopulations: good, intermediate and poor DMs.
318 Individuals majoratively displaying the optimal strategy were referred to as good DMs and
319 represent 42.5% of the human population (mean percentage of advantageous choices \pm SEM:
320 97.4 ± 0.8) and 40% of the mice population (91.3 ± 1.5). Poor DMs remained at around 50% of
321 advantageous choices, hence showing no significant preference for advantageous nor for
322 disadvantageous options, represent 25% of humans (34.3 ± 5.2) and 22.5% of mice (54.1 ± 2.5).
323 The third subpopulation corresponds to individuals that developed a preference towards some
324 options -although they did not find the optimal strategy. These intermediate DMs represent
325 32.5% of humans (64.5 ± 2.4) and 37.5% of mice (73.8 ± 1.0). The proportions of each
326 subpopulation in humans and mice were compared, and no significant differences were found
327 (Chi-square test = 0.011, $p = 0.99$; confirmed by Bayesian analysis, see Supplementary Analysis
328 2) (Fig. 2, A2 and B2).

329
330 In humans, good DMs performed above the chance level after 40% of the task was completed
331 (W , $p < 0.01$), while intermediate and poor DMs differed from the chance level only in the last
332 20%-block ($p < 0.05$). Furthermore, the ANOVA revealed a significant interaction between the
333 clusters and 20%-blocks ($F(8,148) = 16.2$; $p < 0.0001$). Good DMs performed differently than
334 poor DMs from the second 20%-block onwards (MW, 2nd block: $p < 0.05$, 3rd to 5th blocks: $p <$
335 0.0001), and differently than intermediate DMs in the last 60% of the task (3rd block: $p < 0.001$,
336 4th and 5th blocks: $p < 0.0001$). Intermediate and poor DMs performed differently from the third
337 block onwards (3rd block: $p < 0.01$, 4th block: $p < 0.05$, 5th block: $p < 0.0001$) (Fig. 2, A3).

338 Regarding mouse data, intermediate and good DMs performed above the chance level soon
339 after 20% of the task was completed (W , good 2nd to 5th blocks: $p < 0.01$; intermediate 2nd and
340 3rd blocks: $p < 0.05$, 4th and 5th blocks: $p < 0.01$), while poor DMs did not differ from the chance
341 level ($p > 0.05$). The ANOVA also revealed a significant interaction between the factors (F
342 $(8,185) = 5.3$; $p < 0.0001$). Mice from the good DM category performed differently than poor
343 DMs after 40% of the task was completed (MW, 3rd block: $p < 0.05$, 4th and 5th blocks: $p <$
344 0.0001), and differently from the intermediate DMs later on (4th block: $p < 0.001$; 5th block; $p <$
345 0.0001). Mice from the intermediate and poor DM categories performed differently only during
346 the last 20% of the task ($p < 0.0001$).

347
348 When comparing the gambling performance in mice and humans for each subpopulation,
349 differences were found for intermediate DMs (MW, $p < 0.05$), with mice making more
350 advantageous choices than humans. On the contrary, humans from the good DM category
351 achieved more advantageous choices than mice of the same subgroup ($p < 0.01$). Furthermore,
352 humans from the poor DM category made worse decisions than mice ($p < 0.01$). In addition,
353 mice from the intermediate subgroup developed a weaker preference for the most
354 advantageous option (D') than good DMs did, whilst humans from the same category chose the
355 best deck (D) as good DMs did (see Supplementary Fig.1 and Analysis 3).

356
357 Collectively these data reveal that both mice and human populations clustered into three
358 comparable DM categories with closely matching proportions. However, the performance
359 dispersion was more pronounced in the human population.

360
361 **Relationship between the DM performance and choice behaviours in humans and mice**
362 **(Figure 3 and Supplementary Figures 2 and 3)**

363 Correlations between the endpoint performance and behavioural determinants of DM
364 (Supplementary Fig. 2)

365 In humans, rigidity scores significantly correlated with the final performance at the beginning (r
366 = 0.428, $p < 0.05$) and at the end of the task ($r = 0.489$, $p < 0.01$). Flexibility scores showed a
367 negative correlation with the endpoint performance at the beginning of the task ($r = -0.509$, $p <$
368 0.01), which disappeared at the end ($p > 0.05$). No significant correlation was found for the lose-
369 shift choices and the endpoint performance, independently of the moment of the experiment.
370 However, the win-stay choices at the beginning of the task significantly correlated with the
371 endpoint performance ($r = 0.518$, $p < 0.01$).

372 In mice, like in humans, rigidity scores significantly correlated with the endpoint performance at
373 the end of the task ($r = 0.669$, $p < 0.001$) but not at the beginning ($p > 0.05$). On the contrary, no
374 correlation was found for flexibility and the endpoint performance at the beginning of the task
375 ($p > 0.05$), but a negative correlation was found at the end ($r = -0.595$, $p < 0.001$). In the same
376 way as humans, no correlation was found regarding the lose-shift choices ($p > 0.05$), but a
377 significant correlation between the win-stay choices and endpoint performance at the end of
378 the task ($r = 0.582$, $p < 0.001$).

379
380 In brief, DM strategies in humans and mice seem to rely on comparable adaptive choice
381 behaviours that correlate with the endpoint performance.

382
383 Evolution of choice behaviours during task progression (Fig. 3 and Supplementary Fig. 3)

384 In both populations, a significant effect of the time course was found for flexibility ($F(1,78) =$
385 48.4, $p < 0.0001$), lose-shift ($F(1,78) = 15.8$; $p < 0.001$) and the win-stay scores ($F(1,78) = 51.9$,
386 $p < 0.0001$) (Fig. 3).

387 Whereas no global difference among the species was found for any parameters, a significant
388 interaction between the factors (species and time course) was found for rigidity ($F(1,78) = 4.6$,
389 $p < 0.05$). Both populations became more rigid along the task (t-test, $p < 0.0001$), humans were

390 significantly less rigid than mice at the beginning ($p < 0.05$) but not at the end of the experiment
391 ($p = 1$) (Fig. 3).

392

393 The interspecies comparisons in all subpopulations revealed that, at the beginning of the task,
394 humans from the intermediate and poor DM categories were significantly less rigid than the
395 corresponding mice (MW, intermediate: $p < 0.0001$; poor: $p < 0.01$) but not good DMs ($p >$
396 0.05). At the end of the task, this property only remained preserved for humans from the
397 intermediate DM subgroup ($p < 0.01$).

398 Flexibility scores were similar in both species for the intermediate and poor DMs at the
399 beginning and the end of the experiment ($p > 0.05$). However, humans from the good DM
400 category remained less flexible than mice of the same subgroup throughout the experiment
401 (beginning: $p < 0.05$; end: $p < 0.001$). No subgroup differences in the lose-shift and win-stay
402 choices were observed between the populations at the beginning of the task ($p > 0.05$). In the
403 end, only mice from the good DM category were more prone to switch from an option after a
404 penalty than humans ($p < 0.05$). However, humans from the good DM category continued
405 choosing the same option after a positive outcome more frequently than mice ($p < 0.01$). No
406 differences were found for the other subgroups ($p > 0.05$) (see Supplementary Fig. 3).

407

408 Overall, these data show that humans and mice do not differ in their choice strategies at the
409 population level, but suggest there are slight differences in the intermediate and poor DMs
410 subpopulations among the species. Remarkably, mice and humans from the good DM category
411 behaved alike.

412

413

414 **Discussion**

415 The goal of this study was to directly compare DM under uncertainty between humans and
416 mice using IGT adaptations according to the literature (van den Bos et al., 2006; Giustiniani et
417 al., 2015; Pittaras et al., 2016). Our study shows closely related performance curves when
418 comparing data as a function of task progression, suggesting that our animal model is a suitable
419 candidate to bridge the findings between preclinical and clinical data. Therefore, our study
420 offers a chance to get a better insight into the common conserved cognitive processes among
421 mammals.

422 Humans rewarded with money and mice rewarded with food started the task with an
423 explorative search, displaying an equal preference for either the advantageous or
424 disadvantageous options. A preference for advantageous choices progressively emerged in
425 both populations during what has been referred to as the exploitation phase (Daniel et al.,
426 2017; Rivalan et al., 2013; Visser et al., 2011). The overall performance was very similar,
427 however, mice more promptly selected advantageous options than humans. The learning
428 curves observed in our mice confirm previous animal results obtained in similar conditions
429 (Pittaras, 2013; Pittaras et al., 2016) and in other variants of rodent gambling tasks (van
430 Enkhuizen et al., 2014; de Visser et al., 2011).

431 Mice being faster than humans in developing a favourable strategy could be explained in terms
432 of the rewards' nature, which is considered a major limitation for animal versions of gambling
433 tasks. Modelling loss of reward in animals in a similar manner as in humans is a challenge. Food

434 aids in the survival of species: it is a primary reinforcer since it strengthens behaviour and
435 satiates the basic biological drives. Money, however, is a secondary reinforcer: its value is
436 relative to the primary reinforcer. Hunger and satiety are factors difficult to control, which
437 patently influence animals motivational state (Bos et al., 2014; Brevers et al., 2013). However,
438 due to its subjective nature, the interest in money is also difficult to control, which raises similar
439 concerns and can lead to similar consequences. This is the reason why the performance
440 alignment in our mice and human participants is relevant.

441 In addition to the challenge associated with the reward nature and processing, the internal
442 state (see *the somatic marker theory* (Verdejo-García and Bechara, 2009)) and context also
443 generate differences in behaviour. Animal automated operant testing would also help deepen
444 the analysis of motivational aspects for instance (Nithianantharajah et al., 2015).

445

446 A good validity of the model should also be substantiated by similar choice strategies, which
447 can be investigated from additional cognitive proxies sub-serving behaviour (Winstanley and
448 Clark, 2015). A closer look at the endpoint performance revealed that they correlated with the
449 choice behaviours similarly but not identically in both populations. In fact, as advantageous
450 choices increased along the task progression, preference for one option progressively emerged
451 (increased rigidity), while fewer options were explored (decreased flexibility) with individuals
452 becoming more sensitive to the reward (increased win-stay choices) and tending to more easily
453 cope with penalties (decreased lose-shift choices).

454 Our results also highlighted close common interindividual variability in mice and humans when
455 clustered into three subgroups of individuals, ranging from good over intermediate to poor
456 DMs. Whether this clustering reflects the speed of acquiring a favourable strategy, or actually
457 to different behavioural strategies could be further investigated (by a computational modelling
458 analysis, for instance). However, the similar matched proportions of these subgroups for both
459 species strengthen the face validity of our animal model.

460 Good DMs composed the largest subgroup in both species. Several human studies correlate a
461 good performance predominantly with the development of an optimal strategy, accepting risky
462 options (Barbalat et al., 2010; Charpentier et al., 2017). In mice studies a good performance is
463 related to a secure strategy (Pittaras et al., 2016). Interestingly, mice from this category needed
464 less time than humans to perform above chance level. Regarding the other subgroups, humans
465 from the good DM category developed a stronger preference for one option over the
466 intermediate and poor DMs, whereas mice of the same category differed only from the poor
467 DMs. The evolution of the penalty aversion was also similar for both species, suggesting that
468 the cognitive strategies underlying the DM performance might be similar in both species, at
469 least for the good DM subgroup.

470 Individuals conforming to the intermediate DM category, while selecting advantageous choices
471 more often, maintained a high level of exploration of all the options but did not achieve the
472 best strategy to maximise their rewards. However, IGT studies have shown that the
473 performance can be significantly enhanced with additional trials (Overman and Pierce, 2013).
474 Furthermore, mice from this category became more sensitive to a reward along the task
475 progression, whereas humans did not. This suggests that intermediate categories might not
476 completely overlap between the species.

477 The subgroup with the worst performance, poor DMs, maintained the exploration of all the
478 available options, exhibiting high behavioural flexibility. Nevertheless, they did not manage to
479 find a favourable strategy along the task, suggesting an ineffective exploration of options.
480 However, humans from this category ended the task performing significantly below the chance
481 level in terms of the advantageous choices, which did not happen in the animal population. This
482 kind of deleterious preference has also been described in mice following singled-session mGT
483 protocols (van Enkhuizen et al., 2014) and other rodent IGT versions (Rivalan et al., 2009, 2013).
484 Mice performing poorly in the gambling tasks have been proposed as models for the
485 vulnerability of pathological gambling or addiction (van den Bos et al., 2013; Pittaras et al.,
486 2016), in the same line of clinical studies seeking behavioural markers of pathological
487 predisposition or endophenotypes (Cavedini et al., 2010; Zhang et al., 2015). Indeed, these
488 animals seem less risk-averse, a trait that has been already interpreted as an indicator of
489 weaker cognitive control over immediate loss (de Visser et al., 2011).

490 Concerning the endpoint performance, interindividual variabilities show a larger spread in the
491 human population, accounting for better and worse decisions. The extreme upper scores in
492 humans might be a consequence of a longer gambling design (Balodis et al., 2006; Buelow et
493 al., 2013; Bull et al., 2015). Food restriction in our animals could also explain why they never
494 preferred the disadvantageous options. Noticeably, very low performance more reminiscent of
495 human data than ours (Rivalan et al., 2009, 2013), illustrates that performance output highly
496 depends on task design.

497
498 A general common pattern between humans and mice subpopulations has not been fully
499 revealed when the endpoint performance is correlated with choice behaviours. By themselves,
500 rigidity, flexibility and sensitivity to positive and negative outcomes cannot explain the
501 evolution of the performance, neither their emergence, in the three subgroups equally. The IGT
502 alone, unfortunately, does not allow to distinguish reward maximisation from ambiguity
503 aversion for instance; its output is insufficient to determine why a participant selected an
504 option. In this perspective, further behavioural characterisation has been attempted. In
505 humans, we evaluated the motivation to avoid aversive and to approach goal-oriented
506 outcomes, respectively by the behavioural inhibition and activation system's scales (BIS/BAS).
507 The endpoint performance did not correlate with the BIS/BAS scores in humans (data not
508 shown). In parallel, the reward sensitivity assessed by the sucrose preference task in mice did
509 not significantly differ between the subgroups (see Supplementary Fig. 4). These results
510 contrast with those from Pittaras et al. (2016), who described a stronger sucrose preference for
511 good decision-makers ("safe") compared to mice which perform poorly ("risky"). Moreover,
512 reward sensitivity did not correlate with the endpoint performance either (data not shown),
513 whereas poor performance was likely mediated by sensitivity to a high reward in a single
514 session mGT (van Enkhuizen et al., 2014). These apparent discrepancies could be accounted for
515 by protocol variations and suggest complex relationships between reward sensitivity and DM
516 strategies (van Enkhuizen et al., 2014).

517
518 A similar overall performance and comparable gambling strategies observed between both
519 species suggest that they share conserved cognitive processes essential for successful DM. A
520 wide range of comparative approaches, in rodents and in humans, have been proposed to

521 discern between these processes during cognitive tasks, both at the attentional and the
522 mnemonic level (Steckler and Muir, 1996). The literature has also shown that there is a
523 strikingly similar range of cognitive abilities between rodents and humans, as well as a
524 remarkably high degree of anatomical overlap in their brain functions (Woolley et al., 2013).
525 Rodents are even able to outperform humans in some learning tasks (Vermaercke et al., 2014),
526 but we do believe that our slightly differing kinetics are mainly accounted for by the task design
527 variability (including the rewards' nature, the number of trials and the tasks 'probabilistic
528 schedule).

529
530 To conclude, our data thus far suggest that in DM, mice behave in a way similar to humans:
531 they tend to choose the option with the best long-term payoff more often as the task
532 progresses. Our results point to close patterns of choice behaviours present across species, but
533 the parameters we evaluated are insufficient to draw a firm conclusion for the relationship
534 between reward maximisation and risk aversion. Extensive behavioural characterisations and
535 validated animal models will be crucial to study brain regions and circuits involved in DM, and
536 the relationships between reward and cognitive control systems. Nonetheless, our results
537 directly support good face validity of the mouse version of IGT. Future studies including
538 pathological animal models, manipulations with pharmacological tools or brain stimulation
539 techniques and computational modelling should help disentangle processes sub-serving choice
540 strategies, clarifying DM in animals and humans.

541
542

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545

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555

556

557 **Author contributions**

558 Conceived and designed the experiments: LC, JG, DG and YP

559 Performed the experiments: LC, JG, CV, TC, BR, CJ and DG

560 Wrote the paper: LC, JG, MN, LP, EH, DF, DG and YP

561

562

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732 **Supplementary information**

Figure Legends

Figure 1. Gambling performance in human and mice populations

(A) Performances expressed as percentage of advantageous choices (mean \pm SEM) during task progression (blocks of 20 trials). After 100 trials, mice performed better than humans did (CI 95% = 1.191 to 1.277), but final performances were similar (CI 95% = 0.956 to 1.016). (B) No significant (ns) differences between species when comparing performance in 20% trial-blocks (repeated measures ANOVA). Human performance differed from chance level from the 3rd 20%-block onwards, while mice performance was already different from the 2nd block (t-test: mice: #####, $p < 0.0001$; human: **, $p < 0.01$: ****, $p < 0.0001$).

Figure 2. Comparable categories of good, intermediate and poor DMs with similar proportions among species

Distribution in humans (A1) and mice (B1) of individual performance at the end of the task used for k-mean clustering.

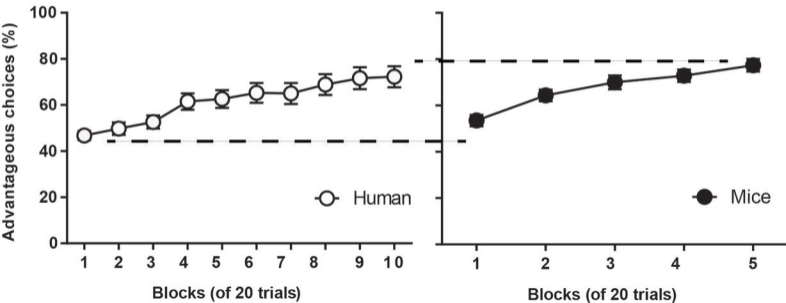
Proportions in humans (A2) and mice (B2) of individuals in good (red), intermediate (pink) and poor (grey) DM subpopulations (χ^2 , $p = 0.99$).

Gambling performance in human (A3) and mice (B3) during task progression (20% trial-blocks). W tests to show group performance different from chance level (50%) (*, $p < 0.05$; **, $p < 0.01$). MW tests to show group differences (good vs intermediate: &, $p < 0.05$; &&, $p < 0.01$; &&&, $p < 0.001$; &&&&, $p < 0.0001$; good vs poor: ¶; intermediate vs poor: §).

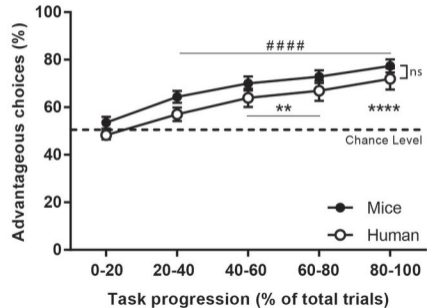
Figure 3. Evolution of choice behaviors during task progression

Significant progression of the rigidity, flexibility, lose-shift and win-stay choices for human and mice populations, between the beginning and the end of the task. Comparison of choice strategies at the population level by repeated measures ANOVA and post hoc t-tests (beginning vs end of the task: #, $p < 0.05$; ##, $p < 0.01$; ####, $p < 0.0001$; humans vs mice: *, $p < 0.05$).

A

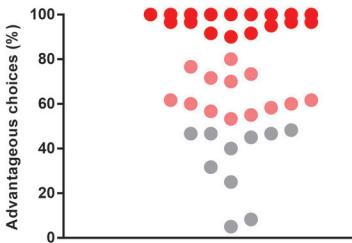


B



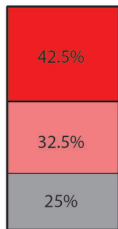
Distribution of individual data for population stratification

A1.



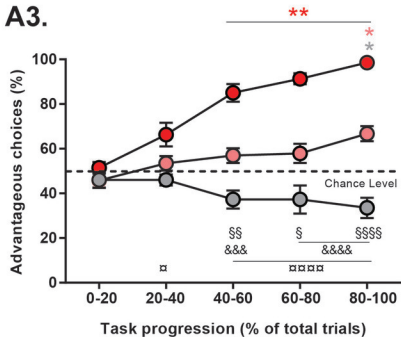
Individuals proportions in each subpopulation

A2.

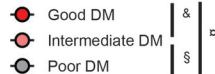


Gambling performances for each subpopulation

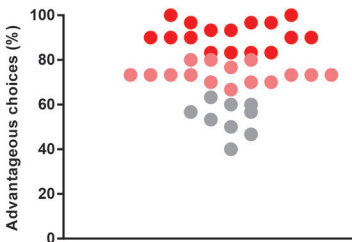
A3.



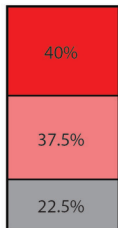
HUMANS



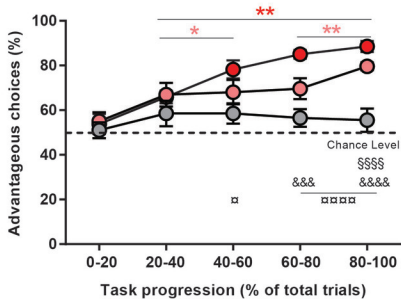
B1.



B2.

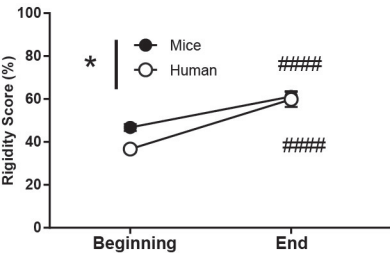


B3.

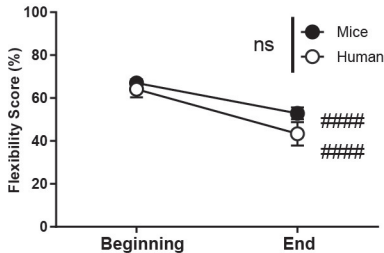


MICE

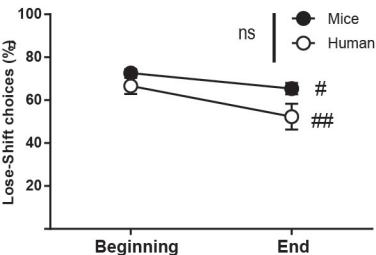
Rigidity



Flexibility



Lose-shift choices



Win-stay choices

