Poor decision-makers motivation, working memory performance, and repartition across two rat inbred strains

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Summary

A minority of healthy individuals exhibit a combination of behavioral traits reminiscent, at least in part, of addiction and predicting poor decision-making (DM), namely motor impulsivity, inflexibility, risk-taking, and higher motivation in Wistar Han rats. Two behavioral features, motivation and working memory, play a role in DM capacities although the precise relationship is not entirely known. Additionally, we previously reported that neurotransmitters e.g., dopamine - modulation was tightly linked to poor DM. The goal of the study was to investigate the detailed motivational functions involved in poor DM including saccharin intake and reward-seeking/incentive behaviors under different internal states i.e., *ad libitum* or food-deprived. Maze-based spatial working memory was also evaluated. Moreover, two rat inbred strains, Lewis and Fisher 344 (F344) rats, known for modeling vulnerability to drug addiction and affected by substantial variations in the mesolimbic dopaminergic route, were run in the decision-making task (Rat Gambling Task, RGT). We found that Wistar Han poor decision-makers (NPERF) display higher saccharin intake levels and a drastic increased reward-seeking behavior on a fixed schedule. NPERF were not more sensitive to the internal state in responding to saccharin delivery in fixed and progressive schedules. A few relationships were found within motivation functions, and with DM, that is a positive correlation between saccharin intake and reward-seeking behavior, and two negative correlations between saccharin intake; reward-seeking, and DM. NPERF were significantly not impaired in working memory. Lewis and F344 rats performed fewer nose-pokes visits during the RGT compared to Wistar Han rats, and improved performance early in the task. A higher proportion of NPERF was observed in Lewis as compared to F344 rats. Altogether, these findings complete the preclinical panel of behavioral functions that relate to poor decision-making and extend a presumed role of dopamine in such processes.

Keywords: decision-making, motivation, working memory, dopamine, RGT, correlations

Introduction

Real-life decision-making is impaired in several psychiatric conditions but also in a subset of healthy individuals for whom high immediate gratifications prevail over long-term gain in humans and rodents (Rivalan et al., 2009; Bechara et al., 1994). Psychological features and cognitive processes related to decision-making capacities have been studied in pathological states (Kovacs et al., 2017; Brevers et al., 2014) while healthy individuals with poor decision-making performance are largely neglected (Suhr and Tsanadis, 2010; Suhr and Hammers, 2006). Decision-making results from the integration of executive functions that allow solving complex tasks. Thus, higher-order cognitive processes including planification, inhibition, and deduction abilities are essential components to achieve good decisions in complex and conflictual situations (Chudasama et al., 2006; Royall et al., 2002). It is noteworthy that there is no consensus yet as to what extent working memory performance relates to the decision-making process (Brand et al., 2006). Obvious evidence however are in favor of a non-direct relationship between these cognitive domains, and clinical studies indicated a possible functional link between working memory and decision-making, especially in addict patients (Bechara and Martin, 2004).

A Rat Gambling Task that tracks decision-making capacities like in the above situation, closely mimics the same principle of the Iowa Gambling Task, a human model of real-life decision-making (Rivalan et al., 2011; Rivalan et al., 2009; Bechara et al., 1997). Like in humans, a minority of healthy Wistar Han rats persist to choose the disadvantageous options. Theoretically, it has been hypothesized that a continuum between the normal and the pathological state emerges along with possible behavioral dimensions such as the impulsivity and compulsion dimension (Dellu-Hagedorn et al., 2018), common aspects relevant to addiction (Koob and Volkow, 2010). In this framework, categorized maladapted - poor performers as “healthy” individuals could share certain behavioral and neurobiological features as pathological states, raising eventual endophenotype identification and/or vulnerability markers to decision-making related disorders (Gottesman and Gould, 2003). It has been shown that these poor aforementioned decision-maker individuals exhibit a combination of behavioral traits reminiscent of addiction, namely motor impulsivity, inflexibility, risk-taking, and higher motivation in some circumstances that are good predictors of decision-making performance (Rivalan et al. 2013). These poor decision-makers also displayed impaired goal-directed behavior (Fitoussi et al., 2018), a characteristic tightly coupled with the development of drug abuse (Vandaele et al., 2018), but preliminary data favored no enhanced drug responsiveness

in self-administration models. At the neurobiological level, poor decision-makers recruit a limited prefronto-subcortical network while performing the RGT (Fitoussi et al., 2015); with some common identified neurobiological substrates relevant to executive functioning, such as the orbitofrontal cortex and medial prefrontal cortex (Costa et al., 2021; Keiflin et al., 2013; de Visser et al., 2011; Balleine and O'Doherty, 2010). It is important that key subcortical brain regions including the nucleus accumbens (core) and the amygdala (basolateral nucleus) play a critical role in such behavioral phenotypes pointed out a major involvement of motivational functions (Zeeb et al., 2013; Balleine et al., 2005; Berridge, 2004). It was previously observed that poor decision-makers exhibit higher motivation after the manipulation of the reward magnitude during a progressive ratio schedule (Rivalan et al., 2009). Thus, additional features underlying this phenomenon may be responsible such as metabolic and cost variables (Baldo et al., 2013).

Aside from a limited network sustaining poor decision-making capacities during the RGT, neurotransmitter levels have been shown to relate to poor decisions, especially dopamine action in cortical and subcortical brain regions including the infralimbic cortex (a subpart of the medial prefrontal cortex) and nucleus accumbens (Fitoussi et al., 2015; Cardinal et al., 2001). However, a causal relationship has not been investigated. In this respect, two rat inbred strains are of particular interest, namely the Lewis and Fisher 344 (F344) rats. Indeed, the Lewis rats are a good candidate for their ability to sustain self-administration of drugs of abuse (Cadoni, 2016), a behavioral feature that has been linked to dopamine level modulation. Additional dopaminergic system characteristics have been reported including those related to dopamine metabolism and neural activity (Haile et al., 2001; Harris and Nestler, 1996; Minabe et al., 1995;). Anxiety level and stress differences could also be described in these rat models (Ramos et al., 1997; Chaouloff et al., 1995).

The goal of the present study was twofold: 1) to investigate the motivational functions of poor decision-makers measured in the RGT including saccharin intake in a free-choice procedure, reward-seeking/incentive behaviors in fixed ratio 5 (FR5), and progressive ratio (PR) under *ad libitum* or food-deprived conditions, as well as the possible functional relationship between working memory measured in an 8-radial maze and decision-making capacities; 2) the repartition of poor decision-makers among two rat inbred strains, that is Lewis, and F344 rats as compared to Wistar Han rats.

Material and Methods

Animals. Male Wistar Han, Lewis and Fisher (F344) rats (Charles River, Lyon, France) aged from 13 to 15 weeks were used. They were housed in groups of four in a temperature-controlled room (22 °C) on an inverted 12-h light/dark cycle (light on at 08:00 p.m.). Tests were conducted during the dark phase of the cycle. They had free access to water and were moderately food-deprived (95 % of free-feeding weight) throughout the experiments. All procedures were conducted in strict accordance with the 2010-63-EU and with the approval of the Bordeaux University Animal Care and Use Committee (Permit Number: 5012087-A).

The RGT. Behavioral apparatus and procedures. Twelve identical operant chambers (Imetronic, Pessac, France; adapted from 5-choice serial reaction time chambers) were used for the Rat Gambling Task (RGT). Four circular holes were available on a curved wall and could be dimly illuminated with a white light-emitting diode (LED) located at their rear. A food magazine on the opposite wall was connected to an external dispenser delivering food pellets (45 mg, formula P, TestDiet, USA). A clear vertical Plexiglas partition (Imetronic, Pessac, France) (28 cm × 9.5 cm × 9.30 cm) with a central opening (7 cm × 9.7 cm) was placed across the middle of the chamber, parallel to the food wall. Data collection was automated using control software (Imetronic, Pessac, France) running on a computer outside the testing room.

Training. Procedures were run as previously described (Fitoussi et al., 2015). During training (5–7 days), rats (n = 48) learned to associate a nose-poke visit with the obtention of a food pellet until 100 pellets were reached. If not, the session ended within 30 minutes. The next step was to associate two nose-poke visits with the obtention of a food pellet, the same criterion as above. The latter was defined to ensure that the visit of the animal was voluntary. Finally, animals were submitted to two additional sessions: (1) two nose-poke visits led to two food pellets delivered as the next RGT test session. A criterion of 100 food pellets or 15 minutes was defined; and (2) two nose-poke visits led to one food pellet as the next RGT test session. A criterion of 50 pellets or 15 minutes was defined.

RGT test. After training, rats were tested in a 60-min RGT test session during which they could freely choose between four options (A–D) (exploration) before establishing their preference (exploitation). Choices C and D vs. A and B led to the immediate delivery of one vs. two pellets respectively, but choices A and B were disadvantageous in the long-term since they could be followed by much longer, unpredictable penalties. Good (PERF) and poor decision-makers (NPERF) were differentiated based on the percentage of advantageous choices (70 and 30 %, respectively) during the last 20 min of the test. Individual differences among good decision-

makers were also analyzed. Good decision-makers with a fast time course to make good choices (PERF FAST), on average superior to 50% within the first 10-20 minutes, were counted as well as good decision-makers with a slower time course to make good choices (PERF SLOW), on average inferior to 50% within the first 10-20 minutes. Undecided rats with intermediate scores were discarded because of the small number of rats in this category.

Working memory, 8-radial maze. Habituation and training. On the first day, rats could freely explore each arm separately as well as the central platform for 1 minute. On the following day, rats were placed on the central platform with closed arms for 10 seconds. At the end of the delay, rats could freely explore the maze and each baited arm. Each time the rat returned to the central platform, the arm was closed. The session ended when all baited arms were visited. This was performed for 2 consecutive sessions.

Acquisition. This step lasts 8 days, a session a day. Like the previous phase, each arm was baited, and the rat was placed on the central platform for 10 seconds before the arms were opened. The difference with the training was the fact that if the rat returned on a previously visited arm, all the doors of the maze were closed for 6s, and then re-opened. The session ended when all arms were visited or 16 visited counted (20 minutes, if not).

Test, delay effect. During this step, sessions were similar as previously, but the delay between choices varied: 1s, 6s (like the acquisition), and 12s, a session per condition and per day. The criterion for ending the session was similar to the above.

Saccharin intake, dose-curve effect. We ran a novel procedure. The procedure consists of two hours-session. Two water bottles were placed on the right versus left side during the first session i.e., habituation. Then, the amount of liquid (water) consumed was monitored for two subsequent days as well as a spatial preference (a session a day). After validating equal amount of consumed water, rats were then allowed to freely drink the water or saccharin solution (replacing one previous water bottle) at the following doses: 0.009% (0.5 mM), 0.018% (1 mM), 0.055% (3 mM), 0.09% (5 mM), 0.18% (10 mM), 0.36% (20 mM), 0.54% (30 mM), and 0.9% (50 mM). Two consecutive sessions with stable consummatory behavior were required before switching to another dose together with bottle location (i.e., left or right side). The procedure ended with two sessions of water consumption only.

Fixed-ratio 5, progressive ratio 2. The comparison of operant behavior and motivated-related behaviors was assessed using a fixed-ratio 5 and a progressive ratio 2 procedures. During fixed-ratio 5, five lever presses were required to earn a dose of saccharin. The session ended within 30 minutes. During the progressive ratio 2, lever presses escalated throughout the session two by two lever presses (ex: 2, 4, 8, 16, 32, etc.) to earn a dose of saccharin. The session ended

within 30 minutes. In these procedures, the state need of the animal was assessed by either food-deprived them (same as before) or letting them *ad libitum*. The minimal dose of 0.055% of saccharin or the maximal dose of 0.18% were tested in each condition. Five sessions per condition were required.

General data analysis. Comparisons of behavioral scores (mean ± SEM) with random choice (50 %) in the RGT were made using a two-tailed t-test for groups and subgroups of good and poor decision-makers. Statistical analyses were then made using ANOVAs, e.g., comparison of scores time-course between groups (repeated measures, group and time factors), number of choices, number of visits, saccharin scores, and working memory parameters, followed by the post-hoc PLSD Fisher test when required (Statistica, Statsoft 7.0). Linear regression analyses were made using Pearson correlation (r).

Results

Inter-individual differences in decision-making. Inter-individual differences in decision-making as previously shown (see meta-analysis, Rivalan et al., 2013, we report distinct patterns of choice preference within a single RGT session (Fig. 1). All rats (n = 19) initially selected the various options randomly before developing a preference (Fig. 3): they clustered into two distinct categories depending on their final preference: (1) a majority of good decision-makers (PERF, n = 13) with a strong preference for advantageous options (70 % preference); and (2) a minority of poor decision-makers (NPERF, n = 6) that persevered in choosing disadvantageous options (70 % preference). Importantly, all rats sampled the four options during the first 10 min and experienced the long penalties at least once. Among PERF, rats could be distinguished according to the time course of decision-making. Some rats (SLOW, n = 6) still chose the options randomly during the first 20 min (comparison with chance level (50 %), t Student = 1.52, ns), whereas others (FAST, n = 7) promptly orientated their choices toward advantageous choices (Fig. 1A). The total number of visits (Fig. 3B) of PERF and NPERF was similar ($F_{2,19}$ = 2.77, ns). Consequently, the number of choices in either A, B, C, and D holes varied greatly between PERF and NPERF. NPERF performed more A and B options than C and D options, and related to PERF, both PERF FAST and PERF SLOW ($F_{2,19} = 23.75$, $p < 0.01$) (Fig. 3C). Additionally, the pellet consumption of PERF was largely superior to NPERF ($F_{2, 19} = 17.89$, $p < 0.01$) (data not shown).

Inter-individual differences in working memory. Inter-individual differences in working memory were assessed during the acquisition and delay test of the procedure. During acquisition (Fig. 4A, C, E), we revealed no difference in working memory performances as shown by the total number of choices ($F_{2,19} = 3.42$, ns), and the percentage of errors/8 choices parameters ($F_{2,19} = 4.90$, ns). However, we did reveal striking differences in the number of perseverations (returns to a previously visited arm) during this phase on day 4, day 6, and day 9 ($F_{2, 19} = 31.41$, $p < 0.05$; PLSD Fisher, $p < 0.01$). NPERF perseverated more than PERF. During the delay test (Fig. 4B, D, F), we did not report a difference in working memory performance as shown by the total number of choices ($F_{2,19} = 6.75$, ns) and the percentage of error/8 choices parameters ($F_{2, 19} = 5.65$, ns), even if a not statistically significant trend was noted for the 12s delay duration. Finally, we did not report any difference in perseverations during the delay test ($F_{2, 19} = 7.78$, ns).

Inter-individual differences in saccharin intake, dose-curve analysis. During this phase, the basal consumption of water and different doses of saccharin were tested. Saccharin doses were as followed: 0.009%, 0.018%, 0.055%, 0.09%, 0.18%, 0.36%, 0.54%, and 0.9% and this was compared to the consumption of water. During this procedure (Fig. 5), all rats developed a stronger consumption of saccharin as doses increase (see. 0.055% vs. 0.18%) ($F_{2,19} = 18.98$, $p < 0.001$) (Fig. 5A) and decreased as saccharin became aversive (see. 0.18% vs. 0.9%) ($F_{2, 19} = 24.89$, $p < 0.01$) showing the specificity of saccharin consumption due to its palatability. NPERF demonstrated a higher consumption through the levels of saccharin. Indeed, they showed a higher consumption than PERF FAST for the doses of 0.055%, 0.09%, and 0.54% ($F_{2,19} = 23.64$, $p < 0.05$) and from rats at the doses of 0.18% and 0.36% ($F_{2, 19} = 19.73$, $p < 0.01$). This saccharin consumption was much higher than the consumption of water, for all rats, stable throughout the daily sessions ($F_{2, 19} = 28.62$, $p < 0.001$). The basal water consumption was stable before ($F_{2, 19} = 5.87$, ns) and after ($F_{2, 19} = 3.22$, ns) the dose-curve effect of saccharin (Fig. 3B). As a result, all rats developed a strong preference for saccharin as doses increased (see. 0.055% vs. 0.18%) ($F_{2, 19} = 27.98$, $p < 0.01$) (Fig. 5C).

Inter-individual differences in FR5 and PR2, food-deprived or ad libitum. During this procedure of FR5 (Fig. 6A), rats were not different at the dose min or the dose max, either food-deprived (dose min: $F_{2,19} = 5.98$, ns; dose max: $F_{2, 19} = 4.76$, ns) or *ad libitum* (dose min: $F_{2, 19} = 6.21$, ns; dose max: $F_{2, 19} = 8.45$, ns). However, when *ad libitum*, a strong difference appeared, NPERF showed a higher number of lever presses than PERF, at the minimal ($F_{2, 19} = 28.78$, $p < 0.05$) and maximal ($F_{2, 19} = 24.90$, $p < 0.01$) doses. Surprisingly, we detected no difference between PERF and NPERF during the PR2 (Fig. 6B) whether animals were food-deprived or *ad libitum*,

at the minimal (food-deprived: $F_{2, 19} = 6.56$, ns; ad libitum: $F_{2, 19} = 4.98$, ns) and maximal (food-deprived: $F_{2, 19} = 5.67$, ns; ad libitum: $F_{2, 19} = 9.97$, ns) doses. However, the saccharin consumption at the maximal dose was higher when animals were *ad libitum* ($F_{2, 19} = 26.76$, $p < 0.05$).

Analyzing qualitatively and separately variables of interest (Fig. 7), certain considered parameters were correlated. In fact, consummatory behavior at the optimal dose (Fig. 7A) was not correlated with the 10 first choices (DM) ($r = 0.40$, $p = 0.067$). But the number of animals was limited in this study demonstrating that the functional relationship between DM and palatability for a non-caloric reward is fragile. It suggests a non-neglect link between DM and reward sensitivity aborting metabolism influence. Interestingly, the reward-seeking measure (Fig. 7B) did correlate with DM ($r = 0.48$, $p = 0.05$) indicating that the functional link between reward-seeking behavior as measured in FR5 and DM is more robust as compared to the aforementioned analyzed correlated measurements. But expectedly, and to continue our assumption, consummatory behavior at the optimal dose (Fig. 7C) was correlated with reward-seeking measure (FR5 at the optimal dose, *ad libitum*) ($r = 0.5$, $p < 0.05$).

The main interest of this study was to decipher the relationship between DM and working memory, aside from the behavioral traits predicting NPERF. We found no correlated measures between WM parameters and DM (Fig. 8A and B) (r = 0, 06, p = 0,8, ns; r = 0, 26, p = 0, 23, ns) suggesting a non-functional relationship between these. Because of the previous statistical conclusion regarding working memory and decision-making abilities, it suggests a possible indirect relationship ("functional") between those. It supports a non-direct relationship between working memory performances and decision-making abilities at least at the time to explore concurrent options in dedicated conflictual and uncertain situations.

Inter strain differences, Wistar Han, Lewis and F344. Inter-individual differences in decision-making as previously shown (Fig. 9). All Wistar Han rats (n = 10) initially selected the various options randomly (Fig. 9A) before developing a preference: they clustered into two distinct categories depending on their final preference: (1) a majority of good decision-makers (PERF, n = 6) with a strong preference for advantageous options (70 % preference); and (2) a minority of poor decision-makers (NPERF, n = 6) that persevered in choosing disadvantageous options (70 % preference). Importantly, all rats sampled the four options during the first 10 min and experienced the long penalties at least once. Among PERF, rats could be distinguished according to the time course of decision-making. Some rats (SLOW, n = 3) still chose the options randomly during the first 20 min (comparison with chance level (50 %), t Student = 1.87, ns), whereas others (FAST, n = 3) promptly orientated their choices toward advantageous

choices. The total number of visits of PERF and NPERF was similar ($F_{2,10}$ = 2.23, ns). Consequently, the number of choices in either A, B, C, and D holes varied greatly between PERF and NPERF. NPERF performed more A and B options than C and D options, and related to PERF, both PERF FAST and PERF SLOW ($F_{2,10}$ = 32.45, $p < 0.01$). Additionally, the pellet consumption of PERF was largely superior to NPERF ($F_{2, 10}$ = 27.67, $p < 0.01$).

All Lewis rats (n = 12) (Fig. 9B) initially selected the various options randomly before developing a preference: they clustered into two distinct categories depending on their final preference: (1) a majority of good decision-makers (PERF, n = 6) with a strong preference for advantageous options (70 % preference); and (2) a minority of poor decision-makers (NPERF, n = 4) that persevered in choosing disadvantageous options (70 % preference). Among PERF, rats could be distinguished according to the time course of decision-making. Some rats (SLOW, n = 3, see above) (comparison with chance level (50 %), t Student = 2.34, ns), whereas others (FAST, n = 3, see above). The total number of visits of PERF and NPERF was similar ($F_{2,12}$ = 3.56, ns). Consequently, the number of choices in either A, B, C, and D holes varied greatly between PERF and NPERF. NPERF performed more A and B options than C and D options, and related to PERF, both PERF FAST and PERF SLOW ($F_{2,12}$ = 17.89, $p < 0.01$). Additionally, the pellet consumption of PERF was largely superior to NPERF ($F_{2, 12}$ = 25.43, $p < 0.01$).

All Fisher (F344) rats (n = 7) (Fig. 9C) initially selected the various options randomly before developing a preference: they clustered into two distinct categories depending on their final preference: (1) a majority of good decision-makers (PERF, n = 5) with a strong preference for advantageous options (70 % preference); and (2) a minority of poor decision-makers (NPERF, n = 2) that persevered in choosing disadvantageous options (70 % preference). Among PERF, rats could be distinguished according to the time course of decision-making. Some rats (SLOW, n = 1) whereas others (FAST, n = 4). Unlike the other strains, Fisher rats tend to be faster in elaborating their choices whether PERF FAST, PERF SLOW, or NPERF. The total number of visits to PERF and NPERF was similar ($F_{2,7}$ = 1.21, ns). Consequently, the number of choices in either A, B, C, and D holes varied greatly between PERF and NPERF. NPERF performed more A and B options than C and D options, and related to PERF, both PERF FAST and PERF SLOW ($F_{2,7}$ = 13.45, $p < 0.01$). Additionally, the pellet consumption of PERF was largely superior to NPERF ($F_{2, 7}$ = 17.78, $p < 0.01$).

Importantly, we found strain differences in the total number of visits (Fig. 9D). Indeed, Lewis and Fisher (F344) rats displayed fewer visits than the Wistar rats ($F_{3,31}$ = 27.89, $p < 0.05$).

The main result of this subpart of our work was that Fisher (F344) rats showed more PERF than Lewis rats. Accordingly, they showed less NPERF than Lewis rats ($F_{2, 21}$ = 28.43, $p < 0.05$). In

terms of percentage (Fig. 9E), it appeared that Fisher rats demonstrated 71% of PERF against 29% of NPERF, whereas Lewis rats demonstrated 58% of PERF against 42% of NPERF. This is supported by the percentage of choices (10 first choices), and the decision-making (DM) variable(s) (Fig. 9F). Indeed, Wistar Han rats poorly performed as compared to Lewis and Fisher (F344) rats ($F_{2, 21} = 17.45$, $p < 0.05$) by choosing more A/B options. Surprisingly, RGT (total number of) visits did not correlate with the latter variable (percentage of choices, 10 first choices) ($r = 0.04$, ns).

Discussion (inter and intra strains)

In this study, we aimed at investigating the motivational functions involved in poor decision-makers phenotype as measured in an RGT task (de Visser et al., 2011), as well as the functional relationship between working memory and decision-making. Second, we were investigating the repartition of poor decision-makers in inbred rat strains showing substantial modifications in the dopaminergic system.

Because poor decision-makers in the RGT (healthy population) displayed higher motivation in PR only when two pellets were delivered each trial (Rivalan et al., 2009), we sought to investigate the motivational functions in these rats. We reported a double dissociation between saccharin intake/hedonia, reward-seeking behavior in FR5, and incentive motivation in PR when the reward was saccharin, a non-caloric reward. It is noteworthy that this dissociation was reported in the literature but not for saccharin which represents a good index for the vulnerability to drug abuse (Caroll et al., 2008; Holtz et al., 2015). In addicts, it is well-known that *wanting* or *desire* for drugs increases with time, but not hedonia (Barbano and Cador, 2006; Berridge et al., 2004). However, one study reported a linear relationship between sucrose intake, a caloric reward, and incentive motivation in PR (Brennan et al., 2001). Poor decision-makers as measured in the RGT are sensitive to the deprivation state as reward-seeking behavior increases when food-deprived. However, this internal state was not enough to drive incentive motivation in PR. Overall, the hedonic set-point (Berridge and Kringelbach, 2010) of poor decision-makers is higher for a non-caloric reward that does not drive incentive motivation in such conditions. Integrating these notions to the RGT, it favors a reward magnitude variable that drives the motivation of NPERF, and no metabolic bias that accounts for such motivation. This is also supported by previous work demonstrating the lack of modified performance in the RGT when the food deprivation rate was manipulated (Rivalan et al., 2009). A subtle

cost/benefit balance partially drives poor decisions in the RGT, in healthy individuals (Swithers et al., 2010).

We found no functional relationship between working memory and decision-making capacities in this experiment. Although surprising in animals, it supports human findings. The implication of working memory (WM) to real-life decision-making as measured in the Iowa Gambling Task (IGT) has been debated in the literature (Brand et al., 2006). Indeed, some studies revealed that a low WM load could be associated with IGT performance, while others reported no obvious relationship (Bagneux et al., 2013; Brand et al., 2006). Most researchers assumed the existence of an asymmetric relationship between WM and decision-making, that is, impaired IGT performance does not obligatory rely on WM, but impaired WM leads to poor IGT performance (Bagneux et al., 2013). This was also supported by the effects of dorsolateral prefrontal cortex lesions, a human brain region critically involved in WM (Li et al., 2021; Petrides, 2000, Funahashi, 2006; Goldman-Rakic, 1996; Fuster and Alexander, 1971), and imaging studies (Ernst et al., 2002; Li et al., 2010). It suggests the existence of distinct decision mechanisms within the prefrontal cortex as well as executive functioning (Bechara and Martin, 2004). In animals, it has been shown that intelligence and learning abilities covary with working memory (Dudchenko, 2004; Matzel and Kolata, 2010; Kolata et al., 2005), as the IGT and RGT involved a temporary phase of learning (Fellows 2004; Bagneux et al., 2013). Our work favors an asymmetric relationship, but no working memory impairment associated with poor RGT performance in healthy individuals. It is noteworthy that additional investigations may shed the light on this question in other WM paradigms (Dudchenko, 2004). In the operant chamber configuration, a dissociation may arise as a trend was however observed, and perseverative behavior was quantified that confirmed previous data collected in Wistar Han rats. Especially, they displayed perseverative-like responding and motor impulsivity (Rivalan et al., 2013).

The second goal of this study was to determine the proportion of poor decision-makers in inbred rat strains that have been proposed as a genetic model for the vulnerability to drug addiction. As we demonstrated that Wistar Han rats displayed a combination of behavioral traits reminiscent of addiction (Fitoussi et al., 2018; Rivalan et al., 2013), it was relevant to examine this population in these rat strains. Moreover, it was shown that a critical set of genes could be involved in addiction (not only one gene), and 40-60% were involved in the variation to the responsiveness of drug of abuse (Cadoni, 2016). As such, inbred rat strains are critical candidates for the vulnerability to addiction, and in our experimental context, to decision-making evaluation. No study had investigated this relationship. Since we found that there were fewer poor decision-makers in F344 rats as compared to Lewis rats, it implies that

neurobiological markers could be involved in decision-making capacities in the RGT, especially dopamine (Cadoni, 2016). It has been shown that Lewis rats are more sensitive to the reinforcing effects of drugs of abuse, using conditioned place preference (Kosten et al., 1994; Guitart et., 1992), operant self-administration (Martin et al., 1999; Ambrosio et al., 1995), and intracranial self-stimulation paradigms (Lepore et al., 1996, Chen et al., 1991). Additionally, these rat inbred strains displayed substantial variation in the dopaminergic transmission (mesolimbic), essentially via *in vitro* studies (Haile et al., 2001; Harris and Nestler, 1996; Beitner-Johnson et al., 1991). The nucleus accumbens seems to be a pivotal region where TH and DAT levels play a critical role (Gulley et al., 2007; Flores et al., 1998; Harris and Nestler, 1996). Further, dopaminergic neurons in the ventral tegmental area demonstrated more burst events in Lewis rats as compared to F344 rats. It supports our previous work that reported higher dopaminergic levels at rest of the healthy poor decision-makers (Fitoussi et al., 2015) although the functionality of the nucleus accumbens of Lewis and F344 rats is not entirely known.

One major result of this study is the improved performance of Lewis and F344 rats early in the task as compared to Wistar Han rats. It has been shown that this critical phase corresponds to the exploration, a dedicated step for sampling the available options (Berntson et al., 2011; Craig et al., 2009). It also involved a part of learning. The fact that the inbred rat strains are better performers than Wistar Han rats is presently unknown. Usually, Lewis rats displayed higher striatal dopamine levels as compared to F344 where Wistar Han rats would exhibit an intermediate level. It is noteworthy that dopaminergic levels in prefrontal regions, especially the infralimbic cortex could explain, at least in part, this phenomenon (Fitoussi et al., 2015). Additionally, this improved performance parallels the lower number of visits (as compared to Wistar Han rats) pointed out a dopaminergic component (Carker et al., 2013), striatal or prefrontal.

Overall, these results supported the current literature and expected data regarding decision-making capacities in these rat inbred strains.

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Figure legends

Figure 1: Photographs from the two main tasks, decision-making (Rat Gambling Task, RGT) and working memory (8-radial maze).

(1) RGT photography from the back of the operant chamber that shows the central Plexiglas wall and the four holes i.e., available options; (2) 8 -radial maze photography from the extremity of an arm that shows the distance traveled by the animals after collecting a reward, and (3) 8-radial maze photography from the central platform that shows the distance to travel to collect a reward.

Figure 2: Decision-making and working memory tasks.
(A) During the decision-making task (Rat Gambling Task measured in the operant chamber), the animal could choose between four holes (options) that lead to an immediate reward. The good options C and D lead to one food pellet (immediately) but low unpredictable penalties, i.e. time-out (12s or 6s) versus A and B options that lead to two food pellets (immediately) but high unpredictable penalties i.e. time-out (444sor 222s); (B) During the working memory task (measured in 8 -radial maze), all baited arms must be visited with three "retention" delay during the test session, i.e. 1s, 6s or 12s between choices.

Figure 3: RGT performance.
(A) Pattern of choices of good decision-makers, PERF FAST versus PERF SLOW, and poor decision-makers. SLOW good decision-makers displayed a longer time course to choose the advantageous options (especially during the first 20 minutes) than FAST good decision-makers. Poor decision-makers persisted to choose the disadvantageous options. (B) Total number of visits and (C) Number of choices in the holes A, B, C, and D for the FAST and SLOW good decision-makers, and poor decision-makers. Good decision-makers preferred C and D choices. ** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, t-test Student.*

Figure 4: 8-radial maze performance.
(A) Total number of choices during acquisition in the working memory task, (B) Total number of choices during the test of working memory during 1s, 6s, and 12s retention delay. (C) Number of errors for the 8 first choices during acquisition and (D) performance parameter i.e., number of errors for the 8 first choices during retention delays for FAST and SLOW good decision-makers, and poor decision-makers. There was no difference between all the groups. Additional parameters i.e., (E) number of perseverations during acquisition and (F) during the test phase during retention delays for FAST and SLOW good decision-makers, and poor decision-makers. ** $p < 0.05$, # $p < 0.05$ (comparison between FAST good decision-makers and poor decision-makers), ANOVA.*

Figure 5: Saccharin intake level (hedonia).
(A) Saccharin dose-curve effect for FAST and SLOW good decision-makers, and poor decision-makers. Poor decision-makers consumed more saccharin from the 0.055% dose to 0.54% dose. (B) Water consumption was similar between all groups, and (C) Saccharin preference during the dose-curve experiment. All rats developed a saccharin preference from the 0.054% dose. ** $p < 0.05$ (comparison all rats), # $p < 0.05$ (comparison FAST good and poor decision-makers). ANOVA.*

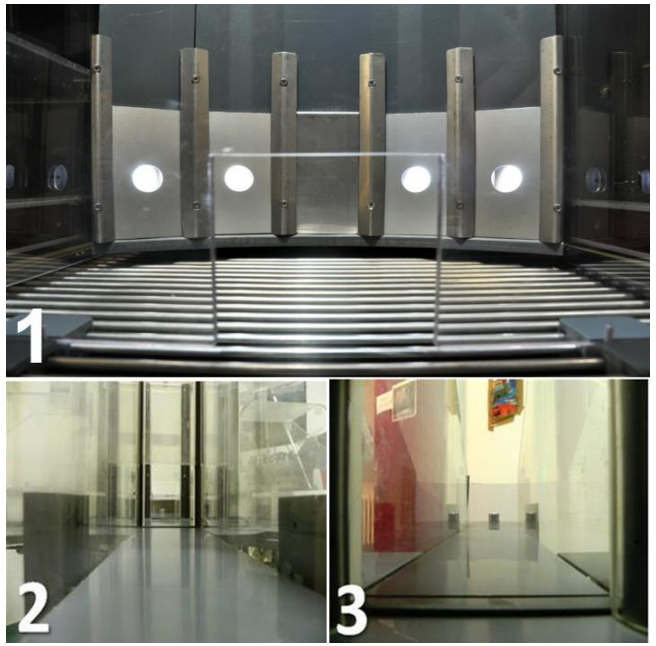
Figure 6: Reward-seeking and incentive motivation evaluation.
(A) Poor decision-makers displayed a higher reward-seeking behavior in FR5 at the minimum and maximum doses *ad libitum* while (B) incentive motivation was not affected during PR whether food-deprived or *ad libitum*. ** $p < 0.05$, ANOVA.*

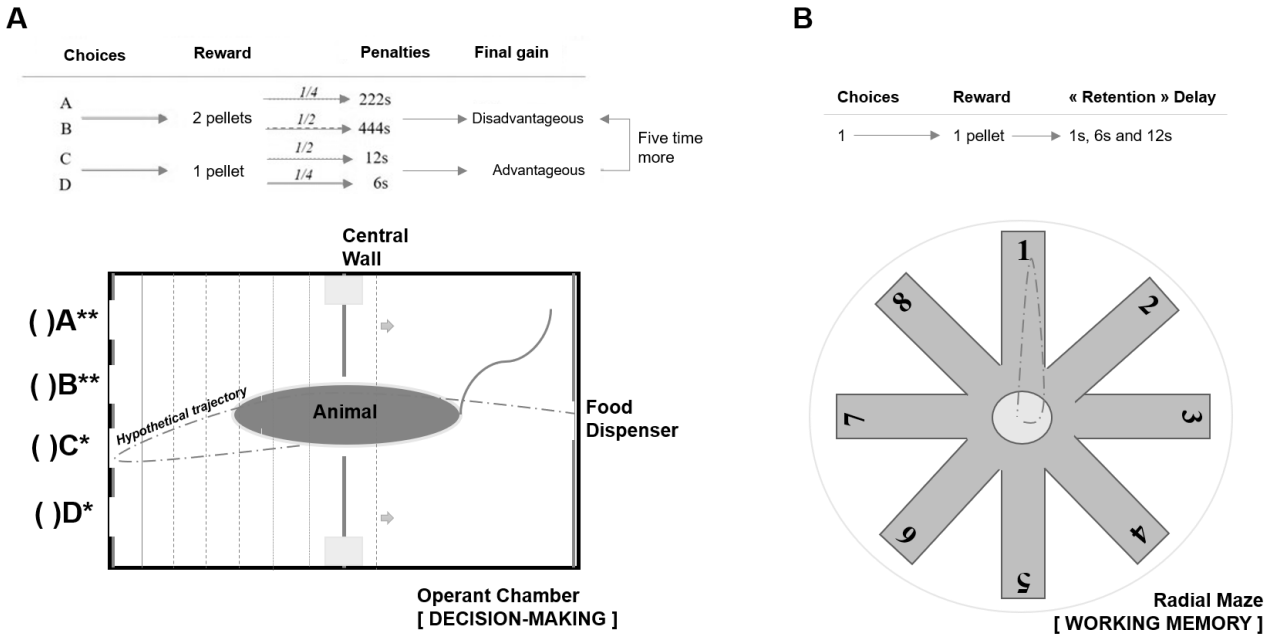
Figure 7: Reward-based and decision-making correlations.
(A) Positive paired correlation between consummatory behavior and decision-making process (DM, 10 first choices), (B) Positive paired correlation between reward-seeking behavior (FR5) and decision-making process, and (C) Positive paired correlation between consummatory behavior and reward-seeking behavior (FR5). White circles refer to NPERF, and black circles to PERF.

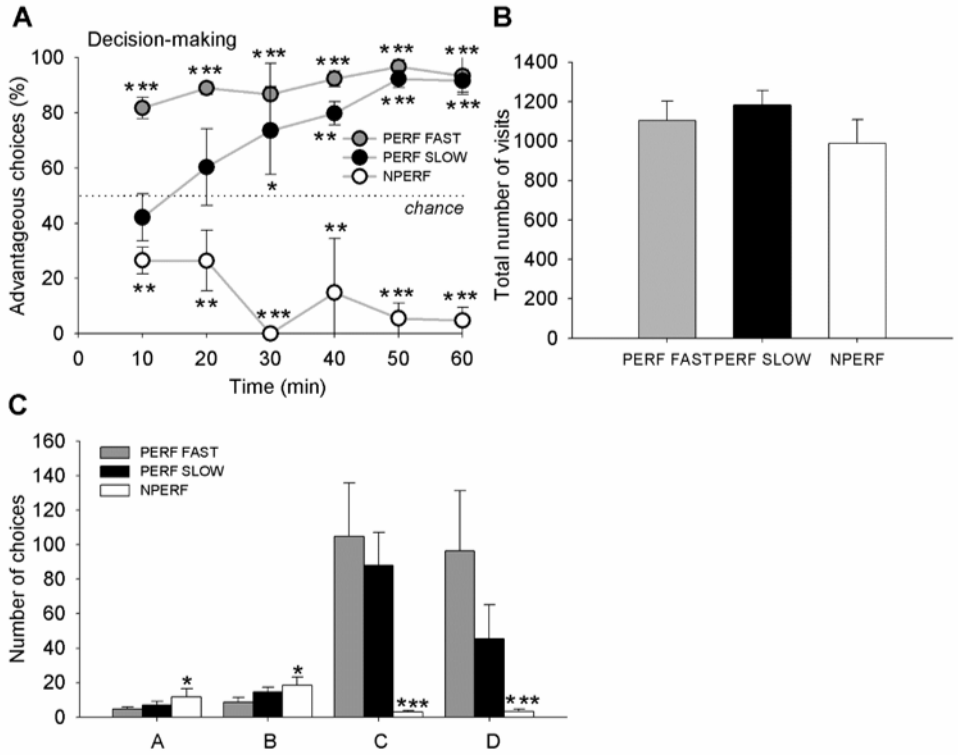
Figure 8: Working-memory-based and decision-making correlations.
(A) Absence of correlation between working memory (retention delay 6s) and decision-making process, and (B) Absence of correlation between working memory (retention delay 12s) and decision-making process. White circles refer to NPERF, and black circles to PERF.

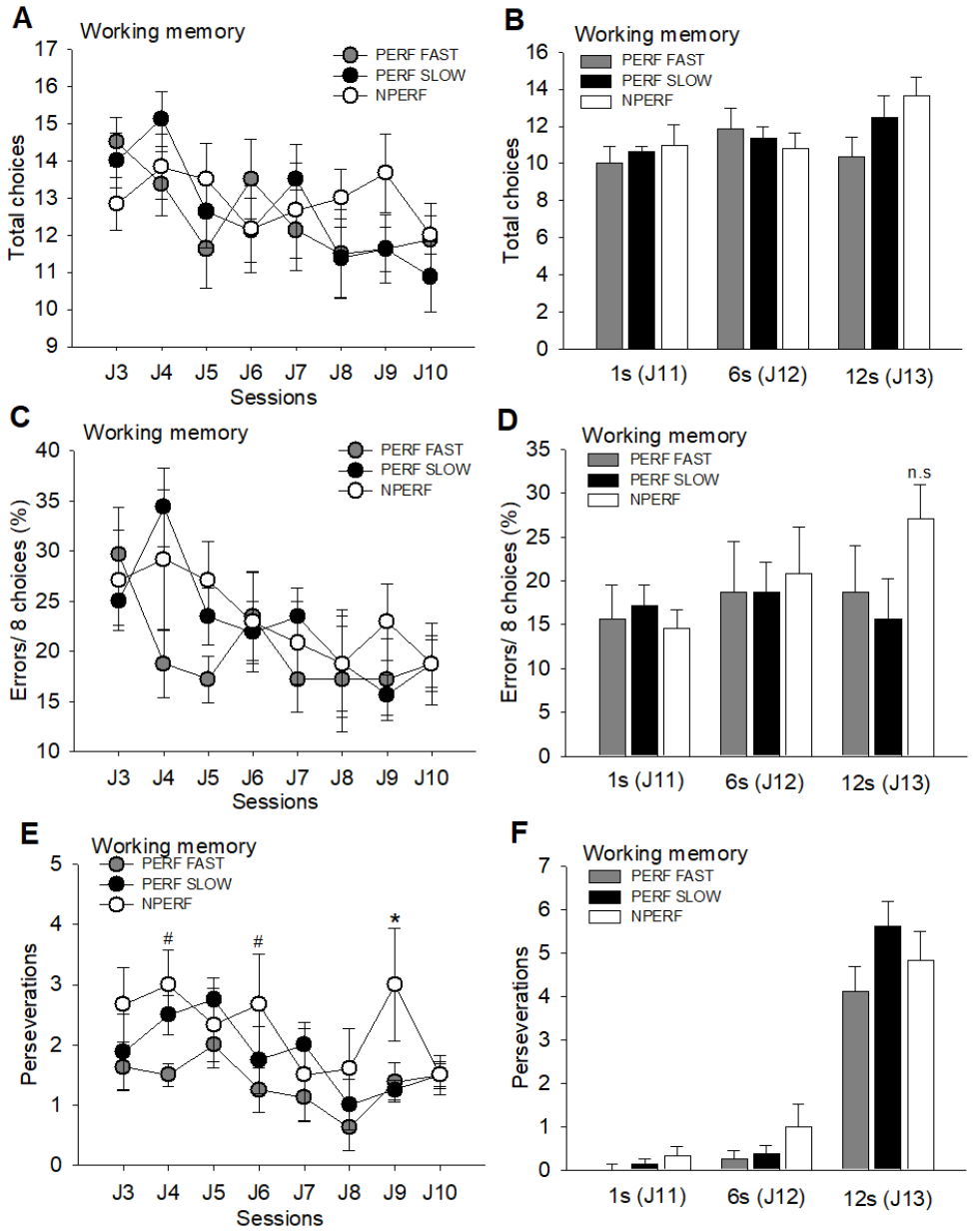
Figure 9: Inbred strain differences in the RGT, Wistar Han, Lewis, and Fischer 344 rats.
(A) Pattern of choices of Wistar Han rats,(B) Pattern of choices of Lewis rats, (C) Pattern of choices of Fischer 344 rats including FAST and SLOW good decision-makers, and poor decision-makers, (D) Total number of visits for the three rat strains: Wistar Han rats did a higher number of visits in the RGT, (E) Proportion of good and poor decision-makers among the strains: Fischer 344 rats displayed a lower number of poor decision-makers as compared to Lewis rats, and (F) 10 first choice performance for the three strains: Wistar Han rats did a poorer

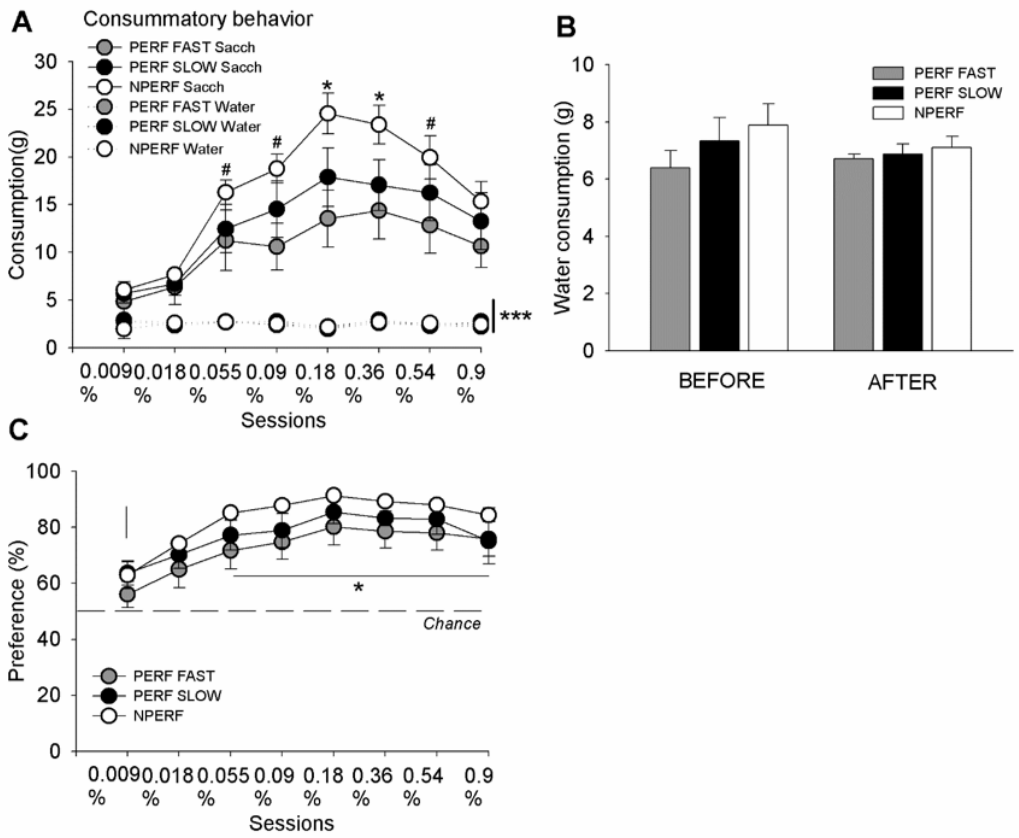
performance in the RGT during this early phase. (G) Lack of correlation between the total number of visits and the 10 first choices. * $p < 0.05$, ** $p < 0.01$, *** $p < O.001$, *t-test Student or ANOVA.*

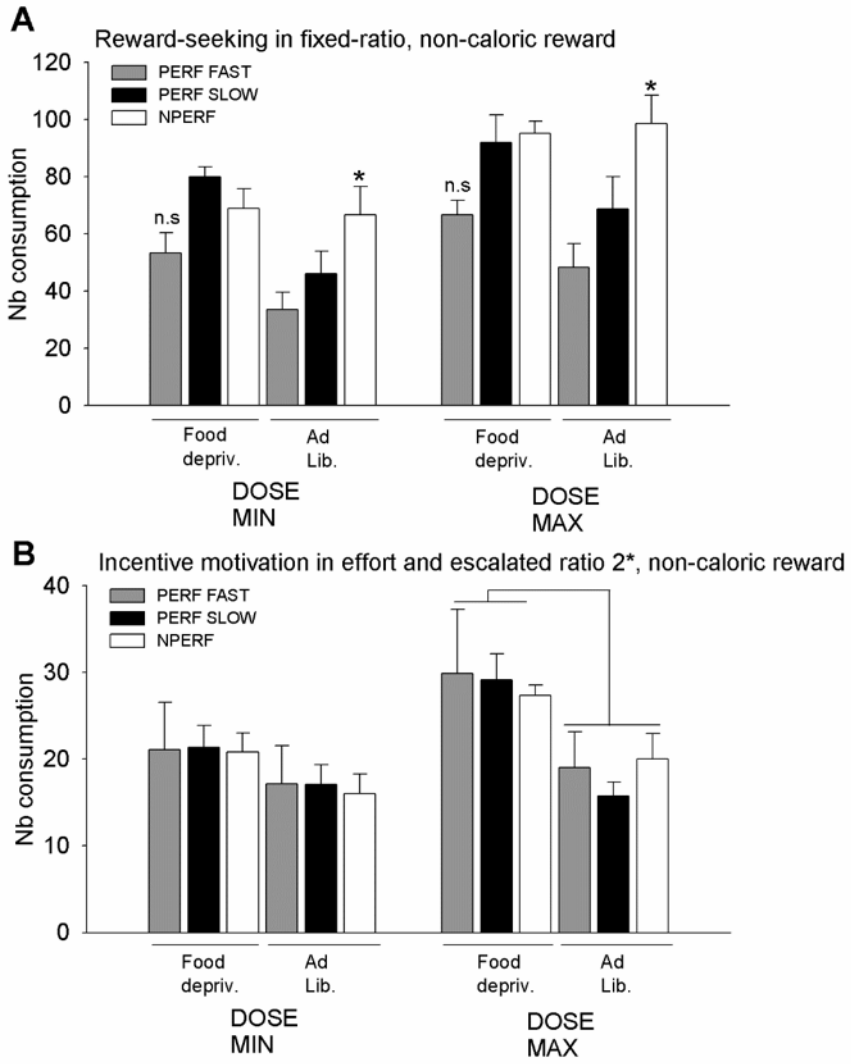

1
2
3

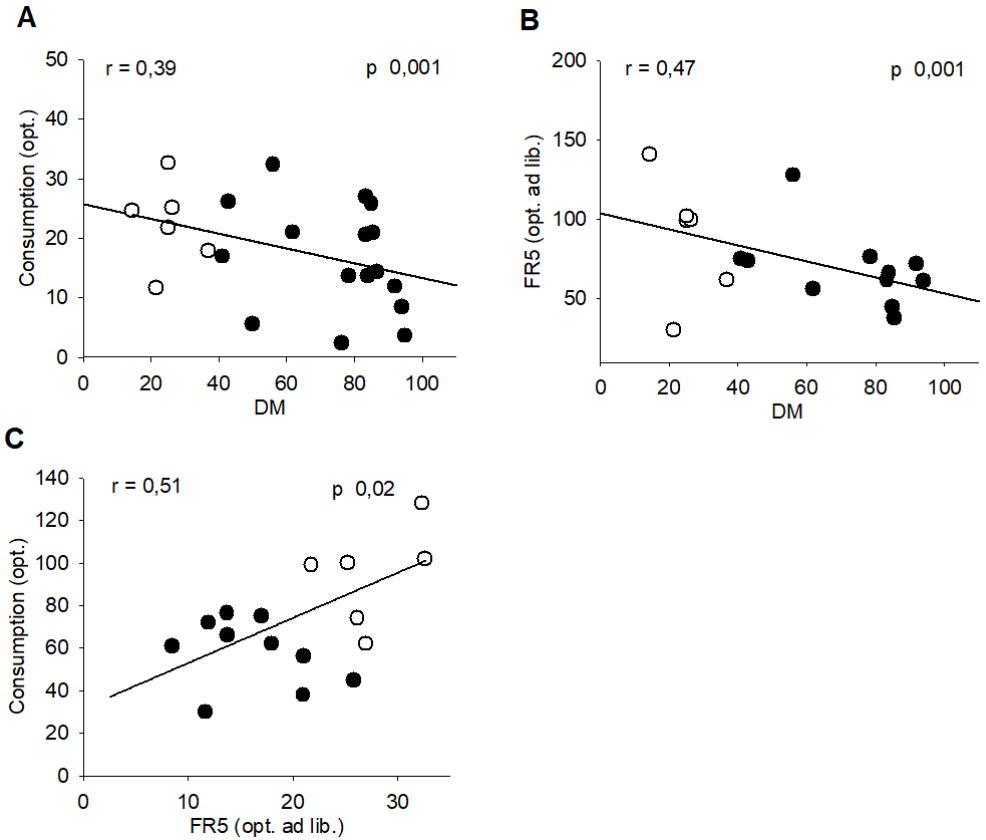

A
Choices
Reward
Penalties
Final gain
A
B
2 pellets
1/4
222s
1/2
444s
Disadvantageous
C
D
1 pellet
1/2
12s
1/4
6s
Advantageous
Five time more
Central Wall
( )A**
( )B**
( )C*
( )D*
Hypothetical trajectory
Animal
Food Dispenser
Operant Chamber
[DECISION-MAKING]
B
Choices
Reward
« Retention » Delay
1
1 pellet
1s, 6s and 12s
1
2
3
4
5
6
7
8
Radial Maze
[WORKING MEMORY]


A
Decision-making
Advantageous choices (%)
Time (min)
PERF FAST
PERF SLOW
NPERF
chance
B
Total number of visits
PERF FAST
PERF SLOW
NPERF
C
Number of choices
PERF FAST
PERF SLOW
NPERF
A
B
C
D


A
Working memory
PERF FAST
PERF SLOW
NPERF
Total choices
Sessions
J3 J4 J5 J6 J7 J8 J9 J10
B
Working memory
PERF FAST
PERF SLOW
NPERF
Total choices
1s (J11)
6s (J12)
12s (J13)
C
Working memory
PERF FAST
PERF SLOW
NPERF
Errors/ 8 choices (%)
Sessions
J3 J4 J5 J6 J7 J8 J9 J10
D
Working memory
PERF FAST
PERF SLOW
NPERF
n.s
Errors/ 8 choices (%)
1s (J11)
6s (J12)
12s (J13)
E
Working memory
PERF FAST
PERF SLOW
NPERF
#
#
*
Perseverations
Sessions
J3 J4 J5 J6 J7 J8 J9 J10
F
Working memory
PERF FAST
PERF SLOW
NPERF
Perseverations
1s (J11)
6s (J12)
12s (J13)


A
Consummatory behavior
PERF FAST Sacch
PERF SLOW Sacch
NPERF Sacch
PERF FAST Water
PERF SLOW Water
NPERF Water
Consumption(g)
Sessions
0.009 %
0.018 %
0.055 %
0.09 %
0.18 %
0.36 %
0.54 %
0.9 %
***
B
PERF FAST
PERF SLOW
NPERF
Water consumption (g)
BEFORE
AFTER
C
Preference (%)
Chance
PERF FAST
PERF SLOW
NPERF
Sessions


A
Reward-seeking in fixed-ratio, non-caloric reward
PERF FAST
PERF SLOW
NPERF
Nb consumption
120
100
80
60
40
20
0
n.s
*
n.s
*
Food depriv.
Ad Lib.
Food depriv.
Ad Lib.
DOSE MIN
DOSE MAX
B
Incentive motivation in effort and escalated ratio 2*, non-caloric reward
PERF FAST
PERF SLOW
NPERF
Nb consumption
40
30
20
10
0
Food depriv.
Ad Lib.
Food depriv.
Ad Lib.
DOSE MIN
DOSE MAX


A
r = 0,39
p 0,001
Consumption (opt.)
DM
B
r = 0,47
p 0,001
FR5 (opt. ad lib.)
DM
C
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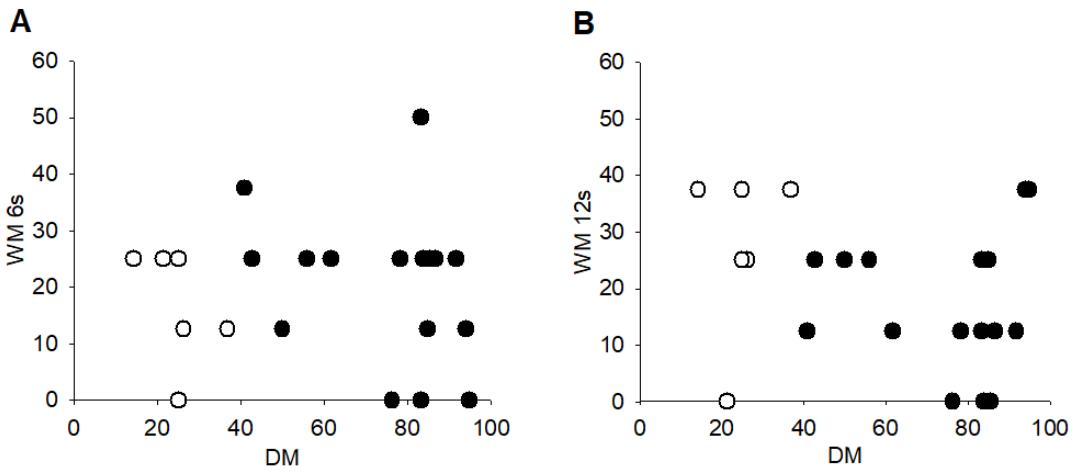
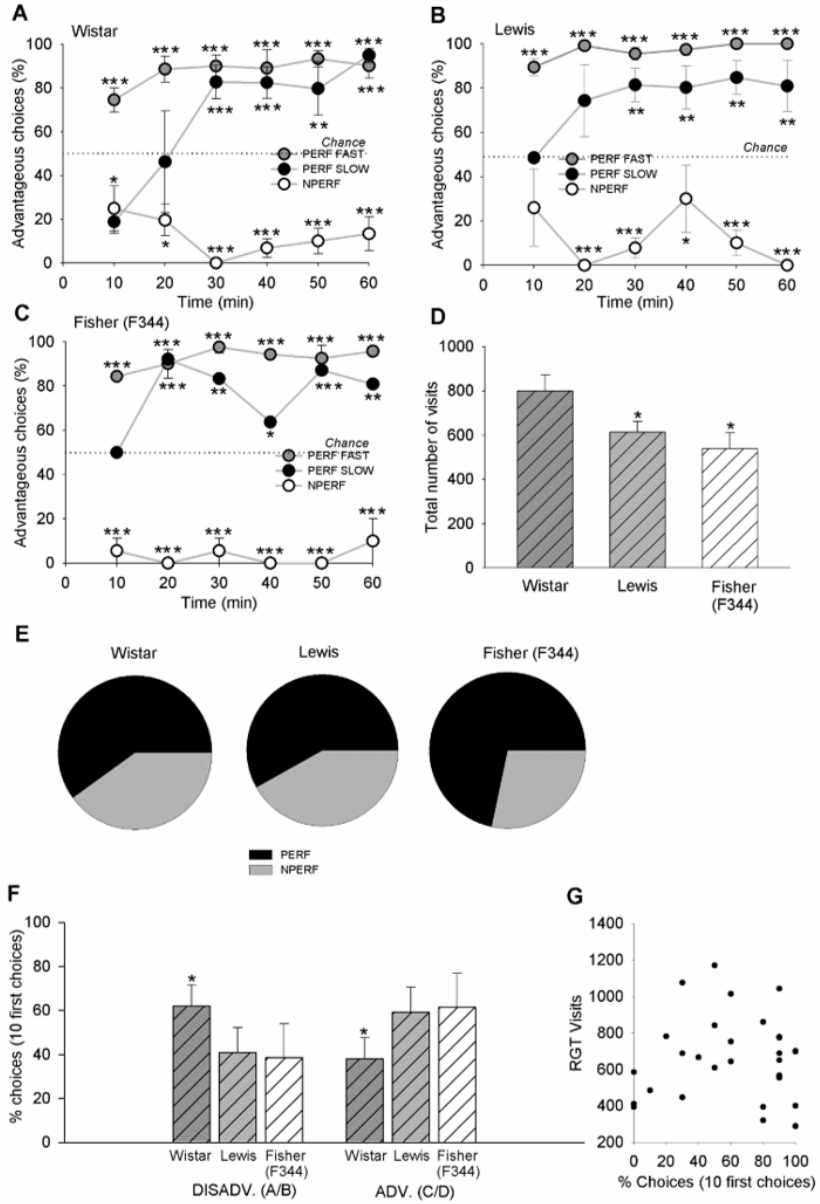
p 0,02
Consumption (opt.)
FR5 (opt. ad lib.)


A
WM 6s
DM
B
WM 12s
DM


A
Wistar
Advantageous choices (%)
Time (min)
Chance
PERF FAST
PERF SLOW
NPERF
B
Lewis
Advantageous choices (%)
Time (min)
Chance
PERF FAST
PERF SLOW
NPERF
C
Fisher (F344)
Advantageous choices (%)
Time (min)
Chance
PERF FAST
PERF SLOW
NPERF
D
Total number of visits
Wistar
Lewis
Fisher (F344)
E
Wistar
Lewis
Fisher (F344)
PERF
NPERF
F
% choices (10 first choices)
Wistar
Lewis
Fisher (F344)
DISADV. (A/B)
ADV. (C/D)
G
RGT Visits
% Choices (10 first choices)