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Research report

Sex differences in rat decision-making: The confounding role of extraneous feeder sampling between trials

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ABSTRACT

Although male and female rats appear to perform differently in some tasks, a clear picture of sex differences in decision-making has yet to develop. This is in part due to significant variability arising from differences in strains and tasks. The aim of this study was to characterize the effects of sex on specific response elements in a reinforcement learning task so as to help identify potential explanations for this variability. We found that the primary difference between sexes was the propensity to approach feeders out of the task context. This extraneous feeder sampling affects choice on subsequent trials in both sexes by promoting a lose-shift response away from the last feeder sampled. Female rats, however, were more likely to engage in this extraneous feeder sampling, and therefore exhibited a greater rate of this effect. Once trials following extraneous sampling were removed, there were no significant sex differences in any of the tested measures. These data suggest that feeder approach outside of the task context, which is often not recorded, could produce a confound in sex-based differences of reinforcement sensitivity in some tasks.

1. Introduction

Men and women sometimes differ in the way they use past rewards to guide future choices. It has been suggested that men are more likely to exhibit risk-taking behaviour than women [1–3], whereas women have been suggested to be more sensitive to loss than men [3,4]. Much of the supporting evidence for these sex differences comes from tasks in which subjects choose among options with different expected values, the most prominent of which is the Iowa Gambling Task (IGT). There is strong evidence that men develop an undeviating preference for the optimal choice in fewer trials than do women (for review see: [4]). This difference in strategy has been interpreted as women exhibiting heightened loss-sensitivity relative to men. This interpretation is supported by a recent meta-analysis of several other decision-making tasks [3].

Rodent studies of decision-making have revealed similar disparities due to sex in some situations [5,6], but the evidence is far less conclusive (for review see: [7]). In a rodent analogue of the IGT, male Wistar rats collected more reward than females [8]. However, the same investigators found no sex differences when testing Long Evans rats on the same task [9]. Using a different adaptation of the IGT for rodents [10], another research group found no sex-based differences in Sprague-Dawley rats [11]. Other tasks have been utilized to investigate additional facets of rat decision-making, such as the risky decision-making task (RDT). In the RDT, rats choose between a safe lever, in which they consistently receive a small food reward, and a risky lever, in which they receive a larger food reward accompanied by an increasingly higher chance of receiving a foot shock. Male Long Evans rats chose the risky lever significantly more than the females [5]. Similar to results from human subjects, this effect may be interpreted as a measure of heightened loss-sensitivity in females or heightened risk-taking behaviour in males. Male Sprague-Dawley rats also displayed more impulsive responding than their female counterparts on a signal discrimination task [6]. However, contrary results have been found using delayed discounting tasks, which, are a direct measure of impulsive choice. In this paradigm, animals choose between a small, immediate reward and a larger, delayed reward. There has been no sex differences suggested from studies utilizing delayed discounting tasks in several strains of adult, drug naïve rats, including Long Evans rats [12], Sprague Dawley rats [13], or Wistar rats [14].

The inconsistency in the rat literature raises questions about the generalization of sex discrepancies in the choice domain across mammalian brains. It is possible that this inconsistency is the product of some unexplained factor that is confounding the results. The control of

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motivated behaviour is the product of interactions among several brain networks that process information in unique ways [15,16]. Choice behaviour by rats and humans is often better explained by taking into account such interactions [17–19]. Examining the effect of biological sex on specific behaviours mediated by these distinct brain systems may help explain the apparent inconsistency of past reports. One specific behaviour is Pavlovian approach, which fosters orientation and approach toward rewarding stimuli, such as feeders in an experimental chamber. This is an intrinsic behaviour that can affect choice. For instance, rats will approach nearby feeders more often than distant ones, even if the nearby feeder delivers suboptimal reward [20]. Moreover, these approaches affect subsequent choices [21,22]. Pavlovian approach is ubiquitous across tasks, and is subject to significant variation among individuals [23–25]. Further, sex differences have also been observed in Pavlovian approach [24,26]. Thus, it is possible that sex differences in performance on decision-making tasks may be confounded with Pavlovian approach. Moreover, factors such as apparatus design or strain may influence such approach [27,28], and thereby indirectly affect choice to a larger degree in one sex.

Here we used a well-validated task with unpredictable rewards in order to decompose reinforcement-driven shifts in decisions into several components [17,21,29]. In our task, we are able to assess sensitivity to wins or losses, motivation, and feeder approach behaviour. Specifically, we examine the relationship between motoric measures and choice strategies. These strategies include: 'lose-shift' responding (the animal's propensity to alter their responding after reward absence/punishment); 'win-stay' responding (the animal's likelihood to repeat an action upon receipt of reward); and a newly reported approach behaviour we call extraneous feeder sampling (EFS), wherein rats sample the alternate feeder prior to initiating the subsequent trial [21,22,30]. In light of past research from other labs summarized above [4–8], we expected females to exhibit increased loss-sensitivity as compared to males. However, loss-sensitivity provides an imprecise denotation. Sensitivity to loss may refer to an emotional frustration, a devaluation of reward in a reinforcement learning context, immediate motor behaviour following reward omission, or other responses. In our task, we are specifically referring to the lose-shift response: the immediate decision of the animal to shift feeder choice following reward omission. This appears to be distinct from forms of reinforcement learning that integrate information over several trials [31]. The data presented here suggest that sex-based differences in lose-shift reinforcement are weak or nonexistent, but that there is a difference in feeder approach between trials that can induce an apparent effect of loss sensitivity if not properly controlled. Between-trial behaviour should thus be taken into account so as to avoid misattributing differences in feeder approach to differences in risk, loss-sensitivity, or other factors influencing choice.

2. Methods

2.1. Animals

We collected behavioural performance data from 106 rats in three separate cohorts. Each cohort contained both male and female animals. All animals were bred in our facility, were housed under the same conditions, and were trained using the same protocol. Rats were pair-housed in plastic cages with corncob bedding and a piece of PVC pipe for enrichment. On behavioural testing days, animals were restricted to one hour of water, but otherwise had ad libitum access to food and water. All testing and procedures were approved by the University of Lethbridge Animal Welfare Committee and comply with the Canadian Council on Animal Care. Animals that did not complete at least 150 trials in the testing session were removed from analysis. This exclusion criteria left us with data from three cohorts consisting of: Cohort 1: 28 Long Evans (15 male, 13 female, 71–117 days old); Cohort 2: 23 Long Evans rats (17 male, 6 female, 80–103 days old); and Cohort 3: 28 Long Evans rats expressing a transgene in some cells (Cre+; 13 male, 15 female; 71–112 days old). The animals from Cohort 3 expressed a transgene (cre-recombinase) under the control of the Tyrosine Hydroxylase promoter (see [32] for more details), but had no other manipulations. These animals were included to ascertain whether these germline genetic manipulations to dopamine neurons had a baseline effect on decision-making. While the Cre-lox system is widely used in controlling transcription and translation of specific cell populations, recent studies have called into question the potential for cre toxicity [33,34], DNA damage [35], and illegitimate chromosome rearrangement [36] with the use of these genetic tools. This transgenic cohort was not statistically different from the others (see Results), so their data were pooled with the other cohorts, giving a total of 79 animals (45 male, 34 female) in the study.

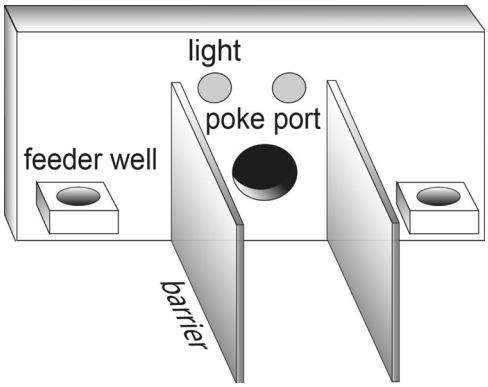

Fig. 1. Illustration of the behavioural apparatus. The two panel lights illuminate, and the overhead house light extinguishes to indicate the rat is able to begin a trial. To initiate a trial, the rat pokes its snout into the center port. The rat then traverses around the barrier (13 cm in length) to a feeder well.

2.2. Behaviour apparatus

Behavioural testing was performed in aluminum operant chambers (Fig. 1) [17]. Briefly, rats were placed in the operant chamber for 45 min sessions. Trials were self-paced, and initiated by the rat performing a nose-poke into the central port. Following nose-poke entry (> 150 ms duration), a tone (6 KHz) was presented to indicate that the animal could then locomote to one of the two adjacent sucrose delivery feeders. If the correct feeder was chosen, a reward (60 μL of 10% sucrose solution) was delivered. If the incorrect feeder was chosen, no sucrose was delivered, the house-light illuminated, and the two panel lights extinguished. The state of the lights then reverted (house-light turned off; panel light turned on). This change in lighting served to indicate that reward was not forthcoming, and was of sufficiently short duration such that it terminated by the time the rats returned to the central poke port; there was therefore no 'time-out' associated with reward omission. Once a feeder was chosen, or if no feeder was chosen in the 15 s following a nose-poke, the trial ended and the rat had to return to the central port to initiate a new trial.

2.3. Experimental design

The behaviour of animals was shaped during the first two training sessions. In the first session, all trials were rewarded to facilitate task acquisition. In the second training session, reward probability was reduced to 0.5. Following these sessions, reinforcement was controlled by an algorithm that attempted to minimize the number of rewards given to the rats by predicting which feeder it would select [17,37]. This was done by examining the choices and reinforcements from the previous four trials. If either feeder was selected at a greater than chance rate in the context of these past trials, it would be unrewarded for the upcoming trial. In doing so, the competitive mode implements the classic 'Matching Pennies' task. Optimal performance (random responding)