The effect of developmental vitamin D deficiency in male and female Sprague-Dawley rats on decision-making using a rodent gambling task

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Abstract

Developmental vitamin D (DVD) deficiency is a plausible risk factor for schizophrenia that has been associated with behavioural alterations including disruptions in latent inhibition and response inhibition. The rodent gambling task (rGT) assesses risk-based decision-making, which is a key cognitive deficit observed in schizophrenia patients. The primary aim of this study was to examine risk-based decision-making in DVD-deficient and control rats on the rGT. We also evaluated the performance of female Sprague-Dawley rats on the rGT for the first time. Adult male and female Sprague-Dawley rats from control and vitamin D deficient dams were trained to perform the rGT in standard operant chambers and their performance and choice-preferences were assessed. Female rats were significantly faster to reach rGT training criteria compared with male rats and DVD-deficient rats were faster to reach training criteria than control animals. After reaching stable performance on the rGT DVD-deficient and control rats showed significant preference for the optimal choice-option in the rGT, but there were no significant effects of sex or diet on these responses. DVD deficiency did not alter the decision-making processes on the rGT because no significant changes in choice-preferences were evident. This is the first study to demonstrate that once established, the performance of females is comparable to male Sprague-Dawley rats on the rGT.

Keywords:

Schizophrenia, Vitamin D, Decision-making, Rat gambling task, Cognition

1.0. Introduction

Schizophrenia is a complex, debilitating, yet poorly understood neuropsychiatric disorder, which affects approximately 1% of the general population. Schizophrenia is associated with an interaction between genetic and environmental factors during critical periods of neurodevelopment and affected individuals develop symptoms including hallucinations and delusions (positive symptoms), restricted affect, deficits in social drive and motivation (negative symptoms), as well as a global decline in cognitive functioning. Decision-making is a complex cognitive function and impairments concern the inability to incorporate future outcomes into beneficial decisions with deficits common among schizophrenia patients (Shurman *et al.*, 2005; de Visser *et al.*, 2011).

Decision-making and impulsivity are clinical features of schizophrenia that affect decision-making (Ouzir, 2013). Decision-making can be examined neuropsychologically via the Iowa gambling task (IGT) and this requires risk-based choice of four decks of cards where preference for low-risk options dictates performance. Impaired IGT performance is evident in, but not limited to, patients with schizophrenia and patients with ventromedial prefrontal cortex damage (Bechara *et al.*, 2000; Shurman *et al.*, 2005). The rat gambling task was adapted from the IGT to assess decision-making and impulsivity in rats and is sensitive to drugs that alter DA and serotonin (5-HT) transmission (Zeeb *et al.*, 2009), as well as neural circuitry comprising the PFC, striatum and amygdala (Paine *et al.*, 2013; Zeeb & Winstanley, 2013). (Zeeb *et al.*, 2009; Baarendse *et al.*, 2013b)

Low prenatal vitamin D has been proposed as a risk factor for schizophrenia based on evidence from epidemiological studies (McGrath, 1999). A population-based control study showed that the risk of schizophrenia was significantly associated with neonatal vitamin D status, with those in the lower quintiles having a two-fold increased risk (McGrath *et al.*, 2010). Additionally, a Finnish birth cohort study investigating vitamin D supplementation during the first year of life found a significantly reduced risk of

schizophrenia among male cohort members (McGrath *et al.*, 2004). A developmental vitamin D (DVD) deficient rat model has been used to explore the phenotype of rats following a transient manipulation of vitamin D during gestation (Eyles *et al.*, 2011b). At birth DVD-deficient rats exhibit a less differentiated brain and greater proliferation across a number of brain regions as compared to control rats (Eyles *et al.*, 2003). DVD-deficient pups also have larger lateral ventricles and altered brain shape as well as a thinner neocortex, reflecting anatomical changes observed in schizophrenia patients.

Behaviourally, adult DVD-deficient rats demonstrate enhanced spontaneous hyperlocomotion and increased activity on the elevated plus maze (Burne *et al.*, 2004) and impaired latent inhibition (Becker *et al.*, 2005), which is a prominent feature of schizophrenia relating to attentional deficits (Weiner, 2003). Dizocilpine (MK-801) induced locomotion is enhanced in DVD-deficient adult rats, which is selectively abolished with the antipsychotic drug haloperidol (Kesby *et al.*, 2006). DVD-deficient rats, under conditions of high attentional load on the 5-choice continuous performance task, have been shown to demonstrate alterations in motivation, impulsivity and response inhibition, which were reversed by the antipsychotic clozapine (Turner *et al.*, 2013). Taken together these findings reveal schizophrenia relevant behavioural alterations in DVD-deficient rats on specific tasks assessing cognitive ability. However, alterations on the 5-choice continuous performance task are not associated with risky decision. Therefore, the primary aim of the current study was to examine the effect of DVD deficiency on behavioural performance in the rGT in male and female Sprague-Dawley rats and it was hypothesized that DVD-deficient rats would demonstrate subtle differences in decision-making in the rGT.

2.0. Materials and methods

2.1. Animals

Forty-nine (7-9 month old) male and female Sprague-Dawley (SD) rats from control and vitamin D deficient dams (The University of Queensland Breeding colony, St Lucia, Brisbane; Male, 450-700g; Female, 214-350g) were used for this experiment (n=10-14/sex/diet). Rats were pair-housed in Macrolon cages with sanichip bedding and wire lids, on a 12h-light-dark cycle (lights on at 0600h). Maternal vitamin D depletion was via manipulation of dietary and lighting sources consistent with a previously described method (Eyles *et al.*, 2011b). Briefly, 4-week old virgin female rats were fed a control (AIN93G with 1,000 I.U. vitamin D3, Specialty Feeds, WA) or a vitamin D deficient diet (AIN93G with 0 I.U. vitamin D3) 6 weeks prior to conception and throughout gestation, and housed under incandescent lighting to avoid exposure to UVB radiation. At birth, all dams and corresponding whole litters (i.e. there was no culling) were placed on a standard diet formulation (Grower and Feeder diet, Specialty Feeds, WA). Using this method, maternal and immediate post-natal vitamin D is depleted, however there is no effect on maternal bodyweight or litter size and offspring have vitamin D levels that return to control levels by two weeks of age and normal calcium, phosphorous and parathyroid hormone levels as adult rats (Eyles *et al.*, 2011b). Rats were maintained on standard diet formulation and food restricted to ~90% of free-feeding weight prior to behavioural testing. Water was provided in home cages *ad libitum.* Animals were weighed prior to each test session and daily food allocation was determined based upon percentage of free feeding body weight.

2.2. Testing and apparatus

Behavioural testing was conducted in a set of six operant chambers, which were individually housed in sound attenuating and ventilated cubicles (Med-Associates, VT, USA). Each chamber consisted of a curved aluminium front wall with five square apertures (2.0cm in diameter) equally spaced horizontally, 2.0cm above a stainless steel grid floor. A yellow light-emitting diode (LED) stimulus light (6.4mm in diameter) was located at the

base of each aperture, and an infrared detector located 1.0cm from the front of the aperture. A food magazine (5.0cm in diameter) connected to a 45mg pellet dispenser was located on the back wall of the chamber. A light (1.0cm in diameter) was located inside the magazine and an infrared detector was situated horizontally across the magazine. A house light was located at the top of this wall, in the centre above the magazine. A background white noise (70dB) generator was situated at the top right of this wall. Behavioural testing was conducted between 0800 and 1700 h under dim light. Animals were housed in a separate room to the behavioural apparatus and were habituated to the behavioural room 30 min prior to each test session. Between test runs, chambers were cleaned with 70% v/v ethanol and dried with paper towel.

2.3. Rat Gambling Task

The protocol followed for the rGT in this study was adapted from that described by Zeeb *et al.* (2009), and consisted of 4 separate phases; fixed ratio (FR)1 training, habituation, forced-choice rGT and free-choice rGTsessions. Briefly, rats were first trained to make nose poke responses in the operant chambers, before moving to a forced choice protocol where they experience each of the 4 different contingencies through single option trials. These contingencies vary in the number of rewards delivered, the duration of punishment and the probability of receiving a reward or punishment. After seven forced choice sessions, rats move to a free choice protocol where they may now choose between the four different contingencies on each trial. The parameters used to evaluate performance are listed in Table 1.

2.3.1. FR1 training and habituation

Animals were first trained to respond to an illuminated food magazine under an FR1 schedule of reinforcement in order to obtain single 45 mg grain food pellet rewards

(BioServ, Frenchtown, NJ, USA) for 3-5 days. Once animals were consistently completing >80 trials in the 30 minute time period they were then habituated to the array wall of the operant chambers for two daily 30-min sessions with single food pellets placed in array wall apertures 1, 2, 4 and 5 and in the food magazine. Hole 3 of the response wall was never illuminated nor recorded as the central position may bias performance. Animals were trained to nose poke an array wall aperture within 20s of illumination to obtain a food reward, similar to the training for the 5 choice serial reaction time task (described by Winstanley *et al.* (2003)). Stimulus light location varied between trials and between apertures. Each session had a maximum of 100 trials or 30 min. Rats remained on this training stage until they were completing ≥70 trials.

2.3.2. Fixed-choice rGT

Following criteria fulfillment for habituation training, rats received seven consecutive sessions of a forced-choice version of the rGT, to expose animals to all rGT pellet options and to avoid simple aperture biases occurring. During each trial of the forced-choice rGT session a single response aperture was illuminated and this varied between apertures and between trials. A head entry into an illuminated aperture resulted in either food pellet delivery for successful trials, or a time out period (where the light in the chosen hole flashed at 0.5Hz) for punished trials. Punishment resulted in the absence of a food reward, the mildly aversive flashing light and a variable delay to begin the next trial that corresponded to the aperture conditions. A response into a non-illuminated aperture resulted in a 5s time-out after which a new trial could be initiated.

2.3.3. Free-choice rGT

Each session lasted 30 min and began when the magazine light illuminated. A head entry into the illuminated magazine extinguished the light and triggered a 5s inter trial interval (ITI). During this ITI, a head entry in any response aperture was recorded as premature and signaled by 5s of house light illumination, after which the magazine light was re-illuminated and the trial could be re-initiated. Following the ITI, array apertures 1, 2, 4 and 5 were illuminated for 10s. If no head entry was recorded within 10s, the trial was scored as an omission and the magazine light re-illuminated. A head entry into an illuminated response aperture extinguished all lights and led to either magazine light illumination and pellet delivery for successful trials, or the start of a punishing time-out period in which the stimulus light of the selected aperture flashed at 0.5Hz for a period of time correlating with the punishment duration designated to that hole. Perseverative responses at the array wall during both punishment and rewarded trials were recorded but were not punished.

The pellet choice options (P1-P4) differed in terms of the number of pellets delivered (1, 2, 3, or 4, respectively), probability of a trial being rewarded (0.9, 0.8, 0.5, 0.4, respectively), and duration of punishing time-out periods (5, 10, 30, 40s, respectively). Although there are a number of variables, there are only 4 combinations of pellets, reward probability and time-out period, which give relatively more or less rewards. (P1, P2, P3 and P4) differed in terms of the number of pellets delivered (1, 2, 3, or 4, respectively), probability of a trial being rewarded (0.9, 0.8, 0.5, 0.4, respectively), and magnitude of punishing time-out periods (5, 10, 30, 40s, respectively). Consistent choice of P1 or P2 coincided with more frequent pellet delivery and was considered advantageous overall. Consistent choice of P3 or P4 coincided with larger rewards per response, however at a lower success rate and were considered disadvantageous overall. The optimal decision-making strategy in this paradigm is consistent choice of P2 (i.e. 2 pellets delivered with a probability of 0.8 and 10s time-out), leading to the highest overall pellet gain. Two spatial

versions of the rGT were used, with half of animals tested on rGT version-A and the other half on rGT version-B. According to the 5-hole array in the operant chamber (left to right: 1, 2, 4, and 5) spatial locations of pellet options in version A was P1, P4, P2, P3, and in version B was P4, P1, P3, P2. All rats acquired the learning task and they received daily testing sessions for a minimum of 12 sessions. Rats were able to obtain a large number of pellets by choosing P2 over 100 trials, however the amount of food consumed remained well below the daily ration of food required to maintain an individual at ~90% of their free-feeding body weight.

2.4. Statistical analysis

Operant chamber data was recorded by Med-PC IV software and exported to Microsoft Excel. All statistical analyses were performed using IBM SPSS statistics (version 20.0). To examine rGT performance measures (Table 1), the mean ± SEM of test days 9, 10 and 11 were calculated and multivariate ANOVA performed. In an assessment of choice preferences, two-way repeated measures ANOVA with choice (four levels, P1-4) as the within-subjects factor and Diet (two levels, DVD-deficient or control) as the between-subjects factor. The choice preference data analysed here were mean percentages of the last three days of rGT testing. Independent samples t-tests were used to examine group-related differences in baseline choice. Other measures of interest included choice accuracy (in forced-choice sessions), pellets earned, trials completed, premature responses, perseverative responses and the percentage of omissions, as well as the number of days to reach criteria and percent of free-feeding body weight.

3.0. Results

3.1. rGT training

No effects of sex or diet were evident during FR1 training for the rGT. Analysis of rGT nose-poke training revealed a significant main effect of sex on days to reach rGT criteria ($F_{1,45}$=18.31, p<0.001), with female rats (n=27) reaching criteria sooner than male rats (n=22). A significant main effect of diet ($F_{1,45}$=6.32, p=0.016) was also evident with DVD-deficient animals (n=26) requiring fewer training sessions to reach rGT criteria as compared to control animals (n=23). No sex*diet interaction was evident ($F_{1,45}$=0.027, p=0.871) (Table 4).

Male and female DVD-deficient and control rats performed forced-choice rGT with high levels of accuracy (Table 4). Male control rats (n=12) were more accurate than male DVD-deficient rats (t_{20}=2.20, p=0.04). Female DVD-deficient rats (n=13) had a lower percentage of omissions (t_{25}=3.06, p=0.005) than control rats (n=14). No effects of sex or diet on premature or perseverative responding were observed.

3.2. Rat Gambling Task

There was a significant main effect of choice on the rGT, with animals (n=49) preferring the optimal option P2, as compared to P1, P3 and P4 ($F_{3,135}$=16.01, p<0.001; P2 vs P1, t_{48}=6.31, p<0.001; P2 vs P3, t_{48}=4.59, p<0.001; P2 vs P4, t_{48}=6.34, p<0.001) (Fig. 1). No choice*diet interaction ($F_{3,135}$=0.42, p=0.74), choice*sex*interaction ($F_{3,135}$=1.73, p=0.17), or choice*sex*diet interaction ($F_{3,135}$=0.90, p=0.45) was observed at baseline (Fig. 1). The establishment of preference for P2 occurred early in testing and remained throughout the extent of testing sessions and strengthened as sessions continued.

DVD-deficient animals (n=23) received significantly more pellets per session than control animals (n=26) (t_{47}=-2.57, p=0.01; Male, t_{20}=-2.52, p=0.02; Female, t_{25}=-1.21, p=0.24), and performed significantly fewer omissions than control animals (t_{47}=3.08, p=0.003, Table 2).

4.0. Discussion

DVD deficiency was associated with subtle alterations in rGT performance in the current study. DVD-deficient rats earned more food rewards per session in the rGT, suggesting an overall performance improvement on this task, however no significant changes in choice-preferences were evident. This increase in food-pellet gain in DVD-deficient animals is likely attributed to a non-significant increase in the number of trials completed per session as well as a non-significant increase in the preference for the most optimal choice-option, P2, in DVD-deficient animals. DVD-deficient rats required fewer training sessions to fulfil criteria for the rGT as compared to control rats. During forced-choice rGT testing, male DVD-deficient rats were significantly less accurate than male control rats. Food-restriction is required in many operant paradigms to encourage

performance and may effect motivation or locomotion. Importantly, no diet-related differences in free-feeding or food-restricted body weights were apparent (Table 3)

No baseline alterations of choice-preference were observed in DVD-deficient rats and it is possible that forced-choice rGT training eliminates differences in early acquisition of optimal choice during first exposure to the task contingencies. Early life exposures such as social isolation and enriched housing (as compared to pair-housed), which are linked to cognitive function (Cacioppo & Hawkley, 2009) and schizophrenia (Paus *et al.*, 2008), have been shown to impair early rGT acquisition (Baarendse *et al.*, 2013a; Zeeb *et al.*, 2013). Based upon this, the 'free-choice sample session' used by (Baarendse *et al.*, 2013b) more closely reflects the initial stages of the human IGT, which is also when schizophrenia patients are impaired (Shurman *et al.*, 2005) and should be investigated in future studies in DVD-deficient rats prior to forced-choice training.

The rGT is a relatively new paradigm, and has been demonstrated in males from a variety of rat strains (Zeeb *et al.*, 2009; Baarendse *et al.*, 2013b; Paine *et al.*, 2013), but to our knowledge has not been performed in female rats. The current study demonstrates female rats performing the rGT for the first time, and found that they are capable of developing a stable, optimal pattern of choice-preference comparable to that of male rats. It also demonstrates that female rats are faster to progress through training stages of the rGT, however this does not appear to have any effects on the development of stable choice or decision-making. In line with previous studies, rats developed a preference for the most optimal option, P2, and female rats developed choice-preferences comparable to male rats. Since rGT development (Zeeb *et al.*, 2009), data on pharmacological and lesion manipulations is growing and future experiments should continue to investigate possible neural networks that may underlie how male and female rats develop optimal choice, and how this correlates with the deficits observed in human patients performing the IGT.

In conclusion, we showed that DVD deficiency has a subtle impact on the training stages of the rGT, evident as differences in the number of days required to reach training criteria as compared to control rats, however this did not alter decision-making processes in rats performing the rGT. The DVD-deficient rat model is characterised by a number of behavioural alterations and while these results do not suggest significant impairments in decision-making, demonstrate subtle performance alterations on rGT training and performance. Finally, this is the first study to examine female Sprague-Dawley rats performing the rGT and we found that, once established, they made equivalent choices to male rats.

Table 1. Description of dependent variables used for analysis of the rGT and how they were calculated.

Measure	Representation
Choice-preference	(No. of responses of particular option/Total No. of choices)*100
Pellets earned	No. of pellets earned
Trials initiated	No. of trials initiated
Premature responses	No. of premature responses
Perseverative responses	No. of perseverative responses
Percentage of omission	(No. of omissions/No. of trials)*100

Table 2: Rat gambling task settings

Level	Trial	Session m	Stim Dur	ITI s	LH s	Time out	Criteria	# Days
FR1	-	30	-	-	-	-	Food pellets in magazine and response apertures	2
Habituation	100	30	20	5	20	-	>= 80% correct, <=20% omissions	Minimum of 5
Forced-choice	100	30	10	5	10	5		7 consecutive
Free-choice	100	30	10	5	10	5		12

Table 3. Adult male and female DVD-deficient and control SD rats free-feeding body weight, and food restricted percentage of free-feeding body weights

	Male		Female	
	Control (n=12)	DVD-deficient (n=10)	Control (n=14)	DVD-deficient (n=13)
Free-feeding weight (g)	578 ± 16	573 ± 27	297 ± 5	301 ± 9
% Free-feeding weight for FR1	93 ± 1	92 ± 1	91 ± 1	91 ± 1
% Free-feeding weight for habitation	92 ± 1	92 ± 1	91 ± 1	91 ± 1
% Free-feeding weight for forced-choice rGT	88 ± 1	89 ± 1	89 ± 1	90 ± 1
% Free-feeding weight for free-choice rGT	88 ±1	90 ± 1	90 ± 1	90 ± 1

Table 4. rGT training

	Male		Female	
	Control (n=12)	Deplete (n=10)	Control (n=14)	Deplete (n=13)
Forced-choice accuracy (%)	93.2 ± 1.3	88.8 ± 1.5 *	91.3 ± .7	90.8 ± 1.2
Forced-choice omission (%)	11.0 ± 2.3	10.8 ± 4.1	12.8 ± 1.9	6.1 ± 1.0 **
Forced –choice premature responses	9.8 ± 3.1	10.9 ± 2.0	9.9 ± 1.3	14.5 ± 2.8
Forced-choice perseverative responses	77.8 ± 7.6	70.2 ± 7.3	85.9 ± 7.1	91.0 ± 7.0
** Habituation training days to criteria	11.4 ± 0.9	9.1 ± 1.0	7.6 ± .8	5.5 ± .8

In forced choice rGT testing; DVD-deficient male rats were less accurate than control male rats (p=0.04), female DVD-deficient rats had a lower percentage of omissions than control female rats (n=14) (p=0.005), and made non-significantly (p=0.140) more premature responses than control female rats.. During rGT nos-poke training; male rats took a greater number of training sessions to reach rGT nose-poke training criteria as compared to female rats (p<0.001). Additionally, DVD-deficient rats took fewer training sessions to reach rGT nose-poke training criteria as compared to control rats (p=0.016*)*. Data are expressed as mean ± SEM.

Table 5. rGT performance in DVD-deficient and control, male and female rats

	Males		Females	
	Control (n=12)	Deplete (n=10)	Control (n=14)	Deplete (n=13)
(A) Choice of advantageous options (%)	58.0 ± 5.1	69.0 ± 5.6	62.5 ± 6.6	64.9 ± 5.6
(B) Choice of disadvantageous options (%)	42.0 ± 5.1	31.0 ± 5.6	37.5 ± 6.6	35.1 ± 5.6
(C) Choice of P1 (%)	19.2 ± 3.4	17.1 ± 4.3	15.7 ± 3.1	17.1 ± 3.0
(D) Choice of P2 (%)	38.8 ± 5.0	51.9 ± 7.7	47.0 ± 8.6	47.9 ± 5.8
(E) Choice of P3 (%)	16.8 ± 4.6	15.4 ± 5.2	26.3 ± 5.9	20.9 ± 5.3
(F) Choice of P4 (%)	25.2 ± 4.5	15.6 ± 6.3	11.1 ± 2.9	14.2 ± 4.9
(G) Pellets earned (no.) *	85.6 ± 4.5	112.2 ± 10.3	86.0 ± 5.9	97.2 ± 7.3
(H) Trials completed (no.)	65.3 ± 3.1	79.3 ± 5.3	66.5 ± 4.0	69.6 ± 4.4
(I) Premature responses (no.)	14.4 ± 2.8	16.8 ± 2.8	11.0 ± 1.9	17.9 ± 4.0
(J) Perseverative responses (no.)	45.8 ± 4.4	40.9 ± 7.5	45.8 ± 8.9	43.7 ± 3.3
(K) Omissions (%) **	6.9 ± 1.6	3.6 ± 1.2	10.8 ± 2.4	3.6 ± 1.0

(A) to **(K)** Baseline rGT performance by DVD-deficient, male and female rats. ***(G)** DVD-deficient rats earned more pellets (*p<0.05) per session than control rats, which likely resulted from a non-significant increase in preference for the optimal P2 choice **(D)** and a non-significant increase in trials initiated **(H)**. ****(K)** DVD-deficient rats had a lower percentage of omissions than control rats (**p<0.01). Data are expressed as mean of days 9, 10 and 11 free-choice rGT testing ± SEM.

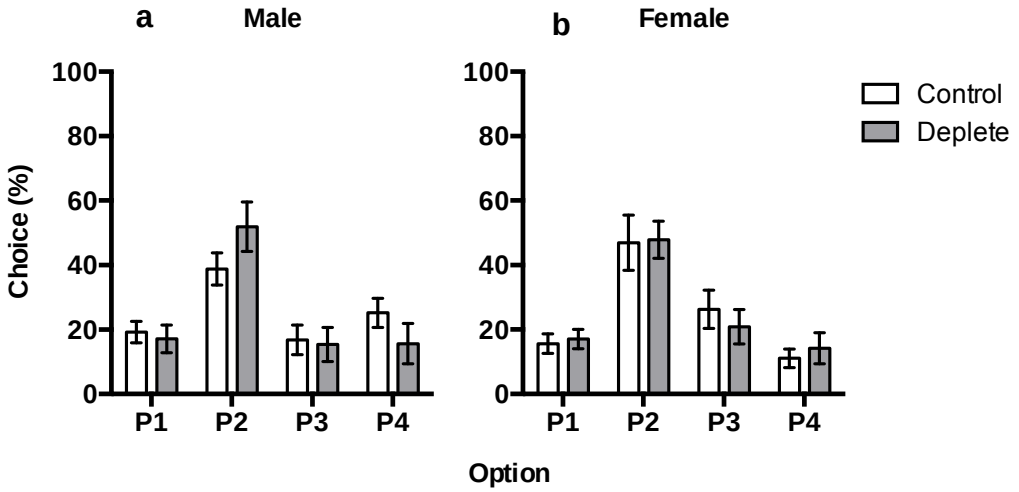

Figure 1. rGT choice behaviour in male (a) and female (b) DVD-deficient and control rats. All rats favoured P2 choice as compared to the other three options. Data are expressed as the mean± SEM of the last three days (days 9, 10, 11) of consecutive rGT testing.

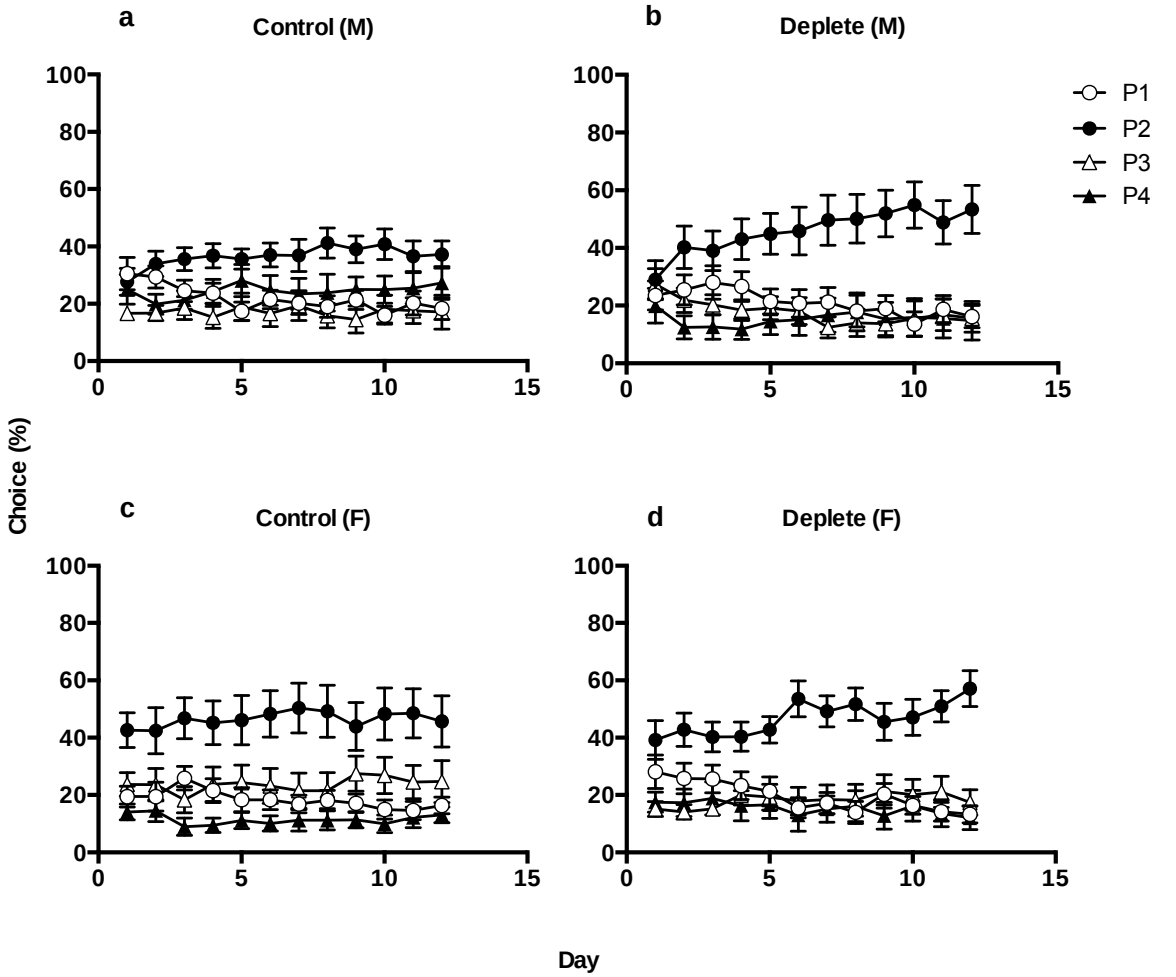

Figure 2. Acquisition of choice-strategy in the rGT in male (a) and female (c) control and, male (b) and female (d) DVD-deficient rats. Each group developed a stable preference for P2, which was the optimal choice. Data are expressed as mean ± SEM.

5.0. References

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