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Sex, Motivation, and Reversal Learning in the Common Marmoset (*Callithrix jacchus*)

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Sex, motivation, and reversal learning in the common marmoset (*Callithrix jacchus*)

A Thesis Presented

by

ALYSSA CARLOTTO

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

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Sex, motivation, and reversal learning in the common marmoset (*Callithrix jacchus*)

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ABSTRACT

SEX, MOTIVATION, AND REVERSAL LEARNING IN COMMON MARMOSET (*CALLITHRIX JACCHUS*)

MAY 2019

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Directed by: Professor Agnès Lacreuse

This study examined the relationships between motivation and cognitive performance in male and female common marmosets (*Callithrix jacchus*). This question was driven by prior data from the Lacreuse lab showing a robust female impairment in reversal learning, as assessed by the number of trials needed to acquire a reversal following a simple discrimination between two stimuli. This thesis tested the hypothesis that the female impairment in reversal learning was mediated by deficits in motivation. Two sets of measures were used to test this hypothesis. I evaluated physical effort via testing on the progressive ratio (PR), a test that requires animals to produce an increasing number of responses to get a reward. Cognitive effort was evaluated through the number of refusals (aborted trials) produced during performance of a reversal. Because estrogen replacement was previously shown to impair reversal learning in ovariectomized females, I also examined whether PR performance was affected by estrogen levels in a subset of female subjects.

Contrary to my hypothesis, reversal learning was not significantly associated with cognitive or physical effort in either males or females. Estrogen levels did not significantly affect physical effort, but there was too much variability in a small sample of females for these results to be compelling. We conclude that the sex difference in

reversal learning performance is unlikely to be mediated by sex differences in motivation. Instead females may be more likely than males to engage in habitual processes implicating the dorsal striatum, likely through the action of estrogens on this brain region.

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CHAPTER 1

INTRODUCTION

Motivation is the process that guides goal-directed responses to changes in the external (e.g., incentives) or internal (i.e., drive) environment (Koob, 2013). Studies of motivation are historically grounded in the animal-learning field and have strongly focused on homeostatic drive accounts, in which shifts in motivational state are triggered by physiological deviations from an internal set point (Bindra, 1974; Hull, 1943; Toates, 1986). Contemporary approaches emphasize rather the incentive value of an action (Berridge, 2004) and state that the modulation of expectancies regarding the outcome of an action motivates behavior. In the domain of systems neuroscience, motivation is construed as having both activational functions, which refer to the response rate or intensity of responding, and directional functions, which refer to specific response biases (choice or place preferences) (Braver et al., 2016).

Research has recently shown that providing reward incentives for tasks is linked to increased performance in other cognitive processes, including judgment, memory, and attention (Locke & Braver, 2010; Maddox & Markman, 2010; Pessoa, 2009). It is suggested that the positive reinforcement given by the reward drives changes in decision-making (Berridge, 2007; Daw & Shohamy, 2008). This study focuses on effort-related decision-making, one aspect of motivation that evaluates how the decision to engage in a task relates directly to the reward and amount of effort needed to complete the task. An important distinction is between cognitive vs. physical effort (Dayan, 2012; Kurzban et al., 2013; Shenhav et al., 2013). The present study contrasts performance on a cognitive (reversal learning) task, which requires both cognitive and physical effort, to performance

on a Progressive Ratio (PR) task, which involves only physical effort with minimal influence from cognitive effort (ie. task engagement, prolonged attention). I will ask whether cognitive or physical effort is related to cognitive performance and whether females differ from males in this regard as a means to explain sex differences in reversal learning task performance.

Neuroanatomical Bases

Reward is the main incentive for motivated behavior, along with the avoidance of punishment. Reward processing is associated with several main brain regions that together constitute reward pathway. DA is released from the ventral tegmental area (VTA) to the globus pallidus and released into the nucleus accumbens (NAcc) in the striatum. One distinguishes the mesolimbic DA system (VTA, NAcc, septum, amygdala, hippocampus) involved in reward anticipation and learning, and the mesocortical DA pathway (medial prefrontal cortex mPFC, anterior cingulate cortex ACC and perirhinal cortex), associated with reward value encoding and goal-directed behavior (**Figure 1**). The orbito frontal cortex (OFC), NAcc and amygdala are the main brain regions consistently activated during reward processing (Haber and Knutson, 2010). While the NAcc is activated whenever a reward is received or anticipated, the OFC seems to encode the associative value of a reward and is critical for updating this value for future decisions (Roesch, 2006).

Motivation and Cognition

Cognition is a general term for multiple mental processes, including attention, language use, memory, perception, judgement, problem solving, creativity, and critical thinking (Sternberg, 2012). Modern research has referred to cognition as all processes

that include sensory input and its perception, transformation, elaboration, storage, recovery, and usage (Sternberg, 2012). What typically drives behavior is motivation directed to a specific goal, which means that the organism is influenced by the outcome of the behavior (Dickinson & Balleine, 1995); this is called incentive learning. By changing the level of food deprivation, Balleine was able to show that influence of deprivation on behavior was dependent on learning in specific deprivation states. (Balleine, 1992).

Cognitive and physical effort have been implicated in the ability to regulate cognitive control and motivation while trying to achieve a goal (Dayan, 2012; Kurzban et al., 2013; Shenhav et al., 2013). Currently, the bases underlying someone's decision to put forth effort into one task and disengage from another are unknown. Subjects' performance in a task may be affected by their ability or inability to stay motivated to complete the task based on amount of effort needed to be implemented (Westbrook & Braver, 2015).

Effort-related decision-making is defined as evaluations of relative costs compared to benefits that are the result of actions to complete the task (Bryce & Floresco, 2016). Psychiatric symptoms such as anergia, and fatigue, which cross multiple pathologies, including depression, schizophrenia, and Parkinson's disease affect effort-related decision-making (Salamone et al., 2016). Cost/benefit decision-making plays a critical role in a subject's ability to stay motivated to engage in a task. People with schizophrenia may experience a decrease in motivation because of their inability to calculate "effort costs" (Gold et al., 2015). Effort costs are defined as estimating the cost of effort someone is expending in comparison to the reward that will be given. This

results in someone over-estimate the amount of effort needed to obtain the reward and leading to decreased effort the person is willing to put into engaging in the task.

Inversely, problems with motivation can be associated with executive functioning deficits due to the inability to process a stimulus as a potential reward, causing them to undervalue a reward (Crocker et al., 2013). Depression is linked to motivation-related deficits, with affected patients showing a decreased responsivity to rewards and a decrease in approach behaviors (Fernandes and Miller, 1995, Pizzagalli et al., 2011). Those with major depressive disorder showed little response to cues that would signal potential rewards (Pizzagalli et al., 2009) and decrease in response when receiving an actual reward (Henriques and Davidson, 2000).

At the beginning of learning, behavior and cognition are goal-directed processes, where the performance of the animal is driven by the outcome of the response. Therefore, changes in the value of the outcome will alter the behavior. Using the outcome devaluation procedures, which decreased the value of reward to test whether motivation to perform to receive the reward will also decrease, Dickinson was able to show that the higher the incentive, the more likely the animal was motivated to perform a behavior (Dickinson & Balleine, 1994). Another test to show motivation-related changes in behavior was with the use of a Pavlovian-instrumental transfer (Dickinson & Balleine, 1994; Estes, 1943), in which response can be altered when paired with a Pavlovian cue (reward prediction not linked to behavior). Other forms of motivational incentives include water and food restriction, both increases responses for food reward (Dickinson & Dawson, 1987).

Sex Differences

Cognitive sex differences

In humans, sex differences in several cognitive domains are well documented. Typically, men tend to excel in tests involving visual-spatial or navigational skills, while women outperform men in several language tasks (Hampson and Kimura, 1988). Interestingly, there are also robust sex differences in PFC-dependent tasks, such as Reversal Learning and Iowa Gambling tasks for which males have an advantage, as highlighted in a recent review (Evans and Hampson, 2015).

Cognitive sex differences are under the influence of androgens and estrogens, which have both organizational effects, which permanently affect brain function early in development, and activational effects, which refer to effects later in life (e.g., puberty). Androgens masculinize the brain early in life, and some of these changes are associated with sex differences in cognitive function (e.g., visuospatial function) later in life (e.g., Williams et al, 1991; Hampson, 2002, 2018; McCarthy, 2012). The contribution of adult sex hormones is more controversial. There is evidence that a single dose of testosterone improves spatial performance in women (Aleman et al, 2004) and transgender males (Gomez-Gil et al, 2008) but studies on testosterone and cognition in adult men have produced inconsistent results (Hausman et al 2009, Cherrier et al., 2001). Though the role of adult testosterone is unclear, an activational effect of estradiol is supported by many studies. For example, higher estradiol levels (mid-luteal or ovulatory phases of the cycle) seem to improve working memory and impair mental rotation (Hausman et al, 2000; Hampson, 2018; Hampson and Kimura, 1988).

Sex differences in motivation?

Whether sex steroids also affect motivation is not as clear. In a study in children aged 4 to 14, Chelonis and colleagues (2011), reported that boys, independent of age, had higher breakpoints than girls in a progressive ratio task where they had to produce an increasing number of responses to obtain a reward. It is not known whether the same pattern of performance is maintained in adulthood. Dreher et al (2007) used functional MRI and a monetary reward paradigm to study women across the menstrual cycle and compared their performance to that of men. They found increased activation of the OFC and amygdala during the midfollicular phase (elevated estradiol) compared to the luteal phase (elevated estradiol and progesterone). Moreover, they found sex differences in brain areas activated during anticipation of uncertain rewards, with women activating the anterior medial PFC at the time of reward delivery while men activated the ventral putamen.

There is also evidence that testosterone affects sensitivity to rewards. A study showed that testosterone treatment in women increased risk taking in the IOWA Gambling task, which could be explained by increased sensitivity to reward and decreased sensitivity to punishment (Van Honk et al, 2004). Testosterone was also shown to increase striatal activity during anticipation of reward in women performing a monetary incentive delay task (Hermans et al, 2010). Several studies in adolescents are consistent with these results by showing that testosterone increases striatal activity during reward anticipation (e.g., Forbes et al, 2011). Rodent data confirm this pattern by showing that testosterone increases rats' willingness to tolerate punishment for greater reward (Cooper et al, 2014). Estrogens have also been shown to have similar effects on

reward sensitivity in several studies in women (Reimers et al, 2014; Diekhof, 2015).

These results suggest that sex steroids affect several aspects of reward processing both in men and women, but the specific mechanisms underlying these findings remain unclear.

The Marmoset Model

Marmosets are becoming increasingly popular as models for neuroscience research (Prins et al, 2017; Okano, 2012). Marmosets have large brains relative to their small body weight (300-500 g) and are able to perform complex cognitive tasks (Spinelli et al. 2004). Their brain shows many similarities with the human brain, for example in resting brain networks (Belcher et al. 2013), and in use of the OFC in reversal learning tasks (humans, Hornak et al. 2004; marmosets: Dias et al, 1996, 1997). Marmosets have the shortest lifespan of all anthropoids (10-12 years) and are therefore particularly useful for studying aging (Tardif, 2011; Ross et al, 2012).

The common marmoset undergoes a menstrual cycle that lasts between 24 to 30 days, similar to the human average of 28 days (Hearn, 1982; Kendrick & Dixson, 1983). However, the marmoset cycle presents a number of differences with women's menstrual cycle: they do not show overt signs of menstruation (Hearn & Lunn, 1975; Rothe, 1975; Brand, 1981), their follicular phase is reduced (8 days) compared to their luteal phase (20 days) and they exhibit very high levels of sex steroids (Dixson, 2012). When group housed, non-dominant female marmosets are sexually suppressed (Arruda et al., 2005). Estradiol fluctuations in female marmosets affect sexual behavior (Kendrick et al., 1983), but no study has examined whether they also affect cognitive functioning. Estradiol treatment in ovariectomized females is associated with deficits in reversal learning (Lacreuse et al., 2014).

Sex differences in reversal learning in the marmoset

Research in our lab focuses on sex differences in cognitive performance during aging in the common marmoset. Data collected from the past two years point to females having a deficit in reversal learning tasks compared to males (Workman et al, 2018). Importantly, this sex difference is similar to that reported in humans (Evans and Hampson, 2015). In reversal learning, subjects have to adapt to changing stimulus/reward contingencies. Monkeys in the study were presented with three stimulus pairs shown in **Figure 2**. For each pair, subjects had to perform a simple discrimination task (SD), in which they had to determine which of the two stimuli was always rewarded, followed by a simple reversal task (SR), in which the reward was switched to the other stimulus. In each task (SD or SR) each subject was given 40 trials per session. In simple discrimination, subjects had to reliably choose the correct stimuli until a 90% correct learning criterion, after which the stimulus associated with the reward was switched (simple reversal). When the 90% correct learning criterion was reached on the reversal, a new pair of stimuli was presented. Monkeys were presented with a total of 3 pairs of stimuli each year of testing. As can be seen in **Figure 3**, in year 1 (Y1) and year 2 (Y2) female marmosets showed impaired acquisition of the reversals, as assessed by a significantly higher number of trials to criterion compared to males.

The Progressive Ratio task to assess motivation

The progressive ratio (PR) task is commonly used to assess motivation in animal models. During the PR task, subject's motivation is measured by their willingness to produce multiple responses to a stimulus to receive a single reward. The ratio of responses needed for a reward increases progressively, allowing to measure the amount

of effort the subject is willing to produce to get the reward, in the absence of a cognitive load. The final completed ratio (FCR) is called the “break point.” Experiments that involved food restriction with rats and humans have been shown to have higher breakpoints than when subjects had no food restriction (Barbano et al., 2009; Chelonis, 2011). Multiple studies conclude that reinforcement is influenced by quality and quantity of reward in animals, similarly to humans, making the PR a suitable task for studying motivation (Chelonis, 2011). As mentioned earlier, Chelonis et al. (2011) reported sex differences in children aged 4-14 performing a PR task. They were rewarded with a nickel using a PR 1 +10 schedule (number of responses needed for reward increased by 10 after each reward was given). The results showed that, typically, boys had higher breakpoints than girls, and this stayed mostly consistent with increasing in age, and there was effort vs. value differences across sex.

Marmosets have previously been tested on PR to assess motivation (Spinelli, 2004; Kangas, 2014). Spinelli’s research focused on marmosets’ abilities to perform the PR on the CANTAB (Cambridge Neuropsychological Test Automated Battery), a computerized touch screen system that can be used with humans and nonhuman primates. They used 9 common marmosets ranging from 2 to 5 years old. They found that eating before testing reduced the amount of rewards the subjects were willing to respond for (Spinelli, 2004). It was concluded that the common marmoset is a viable subject to test motivation using the PR from the CANTAB. Kangas (2014) also used the CANTAB in 4 male marmosets and varied the amount of milkshake that the subjects were rewarded with. Results showed that the break point did increase as milk volume did. Both these studies indicate that marmoset responses on the PR change as a function of the incentive.

However, in these two studies, sex differences were not taken into account. A few studies involving food search tasks have suggested that females may be more motivated than males in these tasks. One study examined sex differences in obtaining food in heterosexual pairs of marmosets presented with food that was either easy or difficult to obtain (Michels, 1998). The author concluded that females were more successful in obtaining food than males, due to greater aggression and “apparent greater motivation” to search for food. These results are consistent with those of a prior study observing that females were more responsive than males to the presentation of an unfamiliar food (Box, 1995). A more recent study required male and female subjects to gain access to food through opening up a plastic container in a maximum of 15 trials. All females opened the container on day one and consistently performed more efficiently than their male counterparts (Yamamoto, 2004). It is unclear from this study whether the female advantage was due to motivational factors or problem-solving skills.

Altogether, although a few studies suggest that female marmosets may be more motivated than males by food incentives, these studies were mostly descriptive and the motivational basis for the sex difference was not clearly established. The PR is a valuable task to more rigorously assess motivation in this species, but sex differences have not been examined. Finally, very little is known on the relationships between motivation and cognitive performance in males and females. My research attempts to clarify this issue by comparing sex differences in a cognitive task and a motivational task.

Research Hypothesis and Study Objectives

My research tests whether deficits in motivation underlie the female impairment in reversal learning in the marmoset. Motivation was assessed through 2 indices allowing

us to evaluate cognitive vs. physical effort: the number of aborted trials in the reversal learning task (“Refusals”), encompassed both physical and cognitive effort, while performance on the PR task evaluated physical effort in the absence of an influential cognitive component.

We also collected urine samples across a 4-week period to examine potential relationships between estrogens levels across the cycle and female PR performance. We predicted that females would have fewer touches, rewards, and/or FCR compared to males in the PR task, indicating that females would be less willing to exert physical effort for a reward than males. A secondary hypothesis was that this reduced motivation in females may be mediated by estrogens. We predicted that touches, rewards, and/or FCR would be inversely correlated with E2 levels across the cycle.

CHAPTER 2

METHODS

Subjects

Sixteen (nine female) adult common marmosets (*Callithrix jacchus*) were used in this experiment. Their ages ranged from 5 to 7.5 years old at study entry (**Table 1**). All animals were housed in female/male pair maintained at a 12:12h light/dark cycle. During the experiment, animals were food and water restricted for a minimum of 2 hours and a maximum of 5 hours daily. They were fed ZuPreem Marmoset Diet, various breads, fresh fruits, and vegetables. Every evening, they received enrichment in the form of peanuts, mealworms, grapes, apples. Every animal was treated humanely, in accordance with the American Society of Primatologists policy of Principles for the Ethical Treatment of Non-Human Primates. This study was approved by the University of Massachusetts Amherst Institutional Animal Care and Use Committee.

Apparatus

Animals were tested using the CANTAB, an automated touchscreen system that includes several tasks, including the PR and Reversal learning tasks. The CANTAB consists a touchscreen (22.5" W x 15.5" H) attached to a computer. A spout in the middle of the screen delivers the reward (banana milkshake, 2 ml; see **Figure 3**). The marmosets had been previously trained in using the CANTAB and were proficient with the touchscreen.

Reversal Learning task

All subjects performed the Reversal Learning task using the CANTAB machine. Monkeys were presented with two tasks, a simple discrimination task and a simple

reversal. In the simple discrimination, the screen displayed two stimuli (**Figure 2**), on random locations on the screen, one of which being associated with reward delivery (milkshake). Each subject was given 10 seconds to respond. If they chose the “correct” stimuli, they received a banana milkshake reward (2 ml) accompanied by a high tone. If they chose the incorrect stimulus, a low tone was played and no reward was delivered. Once the subjects reliably chose the target stimulus (90% correct) in the simple discrimination portion, the “correct” stimuli was switched to the alternate stimulus (simple reversal). The number of trials to criterion to achieve 90% accuracy on the reversal was recorded. A total of three pairs of stimuli were given to the subjects. The dependent variable we analyzed is called the reversal index, RI, computed as follow: $RI = (\text{mean } SR1 + SR2 + SR3) / \text{mean } (SD1 + SD2 + SD3)$. The RI evaluates reversal performance relative to pre-reversal performance and circumvents problems due to individual differences in discrimination abilities (Rumbaugh and Jeeves, 1966).

Progressive Ratio Task

The PR task has been described in Spinelli et al. (2004). For this task, monkeys were presented with a large blue square (6” x 6”) at the middle of the screen (**Figure 3**). For the first trial, the subject had to touch the square. This touch was rewarded by the immediate delivery of milkshake (2ml) accompanied by a high tone. Following 1 sec intertrial interval, the blue square reappeared on the screen. The monkey had to touch the square twice to be rewarded. Trial 3 required 3 touches and so on, with the amount of touches required increasing by 1 until trial 8. From trial 8 to trial 16, the number of touches required increased by 2, then by 4 until trial 23, then by 8 until trial 30. Monkeys were given a maximum of 15 minutes to respond to the square as many times as they

wanted, but the program ended after 5 minutes of no response. The data that collected included: time to complete each trial, number of touches, and number of rewards given. The final correct ratio (FCR), the maximum number of responses that the subject is willing to produce to receive a single reward was computed for each marmoset. Monkeys were tested 5 days a week for approximately 20 testing days over a 4 to 5-week period. If a subject failed to respond in 4 different testing days, they were removed from the experiment. If a subject stopped responding after completing a minimum of 4 days of testing, their data were included in the analysis.

Urine Sampling

During the course of a subject's PR testing, lab members attempted to collect urine each day using the morning void procedure described in Saltzman et al. (2004). At 8:30 am, when the light first came on, the experimental subject voluntarily entered a transport box attached to its home cage. If the subject urinated, they were given a marshmallow as reward and let back into their home cage. Both males and females were used in this procedure. However, only the female samples were collected and stored for subsequent analysis of estradiol levels. Urine was pipetted into 1.5 ml vials, spun for 8 minutes at 1400 rpm and then frozen at -20°C. Estradiol assays were performed by the Assays services of the Wisconsin National Primate Research Center, University of Wisconsin-Madison, Madison WI, USA (Toni Ziegler, PI), using a "in house" enzyme immunoassay (EIA). To control for differences in fluid intake and output, hormone concentrations were corrected using creatinine concentration.

CHAPTER 3

STATISTICAL ANALYSIS

Sex differences in Reversal learning and PR

The main dependent variables used to evaluate performance on Reversal Learning were the RI, the percentage of refusals and the mean response times during the reversals. These data were analyzed in one-way ANOVAs with Sex as factor. For PR, female and male performance were compared using repeated measures ANOVA with Sex and Session as factors and the number of touches, number of rewards, time to completion and FCR as dependent variables.

Estrous Cycle and Female Performance

Since each female monkey had multiple E2 measures, linear mixed models (unstandardized correlation that accounts for multiple measures nested within each monkey) were used to test the association between E2 and each of the outcomes (FCR, time to completion, number of touches, number of rewards). This analysis was underpowered due to the small number of females ($n = 5$) who performed for this portion of study. These results are presented graphically for each individual.

Progressive Ratio and Reversal Learning

Our main objective was to detect potential relationships between motivation and cognition and specifically, determine whether cognitive and/or physical effort was associated with performance on reversal learning. For these analyses, a linear regression was performed on RI, with Sex, number of refusals and FCR as predictors.

CHAPTER 4

RESULTS

Reversal Learning

In this subset of 16 monkeys, we replicated our previous finding that RI is significantly greater in females ($M = 2.43$, $SEM = 0.16$) than in males ($M = 1.78$, $SEM = 0.20$; $F(1, 15) = 6.34$, $p = .025$), indicating lower performance of the females in SR (**Figure 4A**). Prior to analysis, the latencies were log transformed for normalization of the data. There was no sex difference in the mean latencies ($F(1, 15) = 1.67$, $p = 0.22$; **Figure 4B**) or percentage of refusals on the reversals ($F(1, 15) = 1.16$, $p = .30$; **Figure 4C**). Therefore, it was unlikely that the sex difference in Reversal Learning acquisition was related to sex differences in cognitive effort.

To examine reversal performance in more details, we examined performance as a function of sessions of 40 trials. **Figure 5A** depicts the number of correct responses as a function of sessions of 40 trials in males and female marmosets during SR3. As can be seen from the figure, in SR3 males reach criterion (90% correct or 36/40) much earlier than females (session 21). Interestingly, females continue performing at about 75% correct for another 20 sessions before reaching criterion at session 41. Thus, the female impairment emerges only at the latest stages of learning, when the response to stimuli is likely to be performed in a reflexive manner, that is, during habitual behavior. In addition, the number of refusals shown in **Figure 5B** during the same sessions shows that males and females follow a similar pattern, ruling out refusals as a main contributor of the sex difference in reversal performance.

Progressive Ratio

The PR measures physical effort, which was evaluated specifically by the FCR. Our subjects performed 62 responses, received 12 rewards and reached a FCR of 16 on average. We first investigated performance on the PR as a function of testing days, using repeated measures ANOVA with Session as repeated Factor and Sex as between-subject Factor for each dependent variable. As can be seen in **Figure 6**, females spent a greater amount of time ($m = 285.4$ s, $SEM = 23.4$) in PR each day compared to males ($m = 197.7$ s, $SEM = 25.6$; $F(1, 9) = 6.39$, $p < .032$), but produced a number of responses ($m = 67.71$, $SEM = 15.76$) that was not significantly different from that of males ($m = 56.20$, $SEM = 17.26$; $F(1, 9) = 0.24$, $p = 0.63$). A significant interaction between Sex and Session indicated that there was an effect of sex on the number of responses for some sessions ($F(19, 171) = 1.87$, $p = .029$). The responses times were longer in females ($m = 9.08$, $SEM = 3.18$) than in males ($m = 7$, $SEM = 3.18$), but this difference did not reach significance ($F(1, 9) = 0.21$, $p = .065$). The number of rewards obtained was similar between males ($m = 12.11$, $SEM = 1.7$) and females ($m = 12.4$, $SEM = 1.5$; $F(1, 9) = .017$, $p = 0.90$), but tended to increase as a function of Session ($F(19, 171) = 1.64$, $p = .052$). A Session x Sex interaction indicated that the effect of sex on the number of rewards varied according to session ($F(19, 171) = 1.74$, $p = .034$). Importantly, the FCR did not differ between males ($m = 15.14$, $SEM = 3.66$) and females ($m = 17.21$, $SEM = 3.34$; $F(1, 9) = .0187$, $p = 0.68$). There was also a marginal effect of session $F(19, 171) = 1.61$, $p = .058$) indicating that the FCR tended to increase with repeated testing and a significant Sex x Session interaction ($F(19, 171) = 1.83$, $p = .023$), indicating that males and females differed on some sessions.

Estrogens and motivation in females

Linear mixed modeling was used to examine potential relationships between E2 levels and each PR dependent variable in five females for which at least 6 days of E2 data were available. This analysis did not reveal any significant result, likely due to the small number of females involved (**Table 2**). **Figure 7** depicts the relationships between E2 levels and FRC for each of the 5 females.

Regression between indices of motivation and reversal learning

A linear regression was performed on RI, with Sex, number of refusals and FCR as predictors. This model explained 49.5 % of the variance in RI and was significant ($F(3, 15) = 3.92, p = .037$). Sex was the only significant predictor in this model ($\beta = 0.49, t = 2.26, p = .043$). FCR ($\beta = -0.29, t = -1.42, p = .018$) and the number of refusals were not significant predictors ($\beta = -0.31, t = -1.45, p = .017$) of RI.

CHAPTER 5

DISCUSSION

This study examined whether sex differences in motivation, as assessed by measures of physical and cognitive effort, mediated sex differences in the acquisition of the reversals, with males outperforming females. We found no evidence for sex differences in the percentage of refusals in the reversal learning task (a measure of cognitive and physical effort) or in the FCR in the PR (a measure of physical effort), suggesting that the sex difference in reversal acquisition was not likely to be related to measures of cognitive or physical effort. A regression analysis confirmed this assumption by indicating that sex, but not the FCR or the percentage of reversals, significantly contributed to reversal performance. We conclude that sex differences in reversal learning do not stem from sex differences in motivational factors. We discuss these results in more detail below.

Lack of sex differences in motivational measures

Contrary to our predictions, we found that both the percentage of refusals in the reversal learning task and the FCR in the PR task were similar in males and females. This indicated that there was no significant difference in males and females in cognitive or physical effort expenditure on the tasks. Interestingly however, the analysis of other dependent variables in the PR revealed that females spent significantly more time in PR than males. As can be seen in **Figure 4A**, the sex difference was established very rapidly and remained stable following the first two sessions. Because all the other outcomes were similar between males and females, including the number of touches, the number of rewards obtained and the FCR reached, this finding suggests that females had slower

responding than males in the PR. This was indeed the case, although the sex difference did not reach significance.

Estrous Cycle and Female PR Performance

We had predicted that estrogens levels would affect female performance on the PR task throughout the 4 weeks of data collection. Unfortunately, only 5 females provided urine samples across multiple days, leading to an underpowered analysis and important limitations for the interpretation of the data with regards to estrogen effects. Yet, the individual profiles between estrogen levels and FCR described in **Figure 8** suggest potential associations between higher estrogen levels and reduced performance on the PR in females. These relationships should be investigated further as they may contribute to the sex differences found at the session level. Future studies should not only increase the number of female subjects but also assess PR performance and Reversal Learning simultaneously across multiple cycles.

Comparison with prior PR studies in marmosets

Two prior studies used the CANTAB system to test motivation in the common marmoset (Spinelli, 2004; Kangas 2016). Spinelli et al. (2004) reported that food-restricted marmosets averaged 18 rewards per session, produced an average of 282 responses and obtained an FCR of 40. Although we used the PR with identical parameters, our subjects obtained an average of 12 rewards, produced 62 responses, and reached an FCR of 16. At least two major differences between the studies can explain these discrepancies. First, the amount of food restriction is likely a factor. Because of practical considerations, the amount of food restriction varied in our study, as monkeys were food restricted for 2 to 5 hours before the PR testing. Spinelli (2004) tested the

marmosets in 3 conditions, with a differential amount of food available, from “a normal condition”, where animals were deprived of on type of food (mash-diet) 3 hours before testing, a pre-feeding condition (10 ml milkshake given 10-15 min pre-testing) and a food-deprivation condition (no food 4 hour before testing). They found that the amount of reward obtained varied significantly between the 3 conditions, from 15 rewards in the normal condition, to 10 in the pre-feeding condition, and 18 in the no food condition. According to these data, it is likely that a 2 vs. 5-hour amount of food restriction would affect the number of rewards obtained and contribute to variability across sessions. Interestingly, the other parameters in Spinelli (2004) did not differ significantly according to feeding conditions, but were still much higher than the ones obtained in our study (Number of touches and FCR: 196 ± 52 and 29 ± 6 (normal feeding), 129 ± 63 and 20 ± 8 (pre-feeding), 282 ± 63 and 40 ± 8 (food restriction). This suggests that other factors are likely to contribute to the lower level of responding of our study.

One important difference between Spinelli (2004)’s study and the present study is the age of the subjects. Spinelli used 9 young adults between the ages of 2 and 4, while our 16 subjects were ranging from 5 to 7 years old (middle-age). The effect of aging on motivation has been investigated in several studies. Ennis et al. (2013) found that older adults (ages 64-85) tended to withdraw more than younger adults from a memory-search task varying in difficulty across trials, suggesting that the cost of cognitive engagement increased with age. Interestingly, little is known about the effect of aging on the PR task. A study testing young, middle-aged and aged mice in a PR task reported that both middle-aged and older mice had a lower breakpoint than younger mice (Bordner et al,

2011). Based on these findings, the older age of the subjects may have led to lower levels of motivation to perform the PR task.

Sex, Motivation and Reversal Learning

We found no evidence for a relationship between cognitive and physical effort and performance on reversal learning in either males or females. This strongly suggests that the sex difference favoring males in the Reversal Learning task is not associated with sex differences in motivation. As stated in the introduction, men also have an advantage over women in Reversal Learning tasks (Evans & Hampson, 2015). This sex difference may be best explained in the framework of goal-directed vs. habit systems in the brain (Balleine & Dickinson, 1998; Balleine & O'doherty, 2010). The goal-directed system encodes the relationship between action and outcome in order to select actions that are relevant to the subject's desires. The habit system encodes stimulus-response associations, which increase efficiency but decrease the flexibility of the responses. These two systems depend on different neural substrates. Evidence from rodent studies indicate a dorsomedial striatal (DMS)/OFC system for goal-directed learning (Gremel & Costa, 2013), and a dorsolateral striatal (DLS) system for habit learning (Yin, Knowlton, & Balleine, 2004). In primates, the DMS roughly corresponds to caudate and putamen, and the DLS to the posterior putamen. Findings in rodents are echoed in several human fMRI studies implicating the ventral medial prefrontal cortex (vmPFC) in encoding the value of a predicted reward linked to a specific action (Grabenhorst & Rolls, 2011; Tanaka, Balleine, & O'Doherty, 2008), whereas posterior putamen and caudate have been involved in habit learning (Tricomi, Balleine, & O'Doherty, 2009). A recent fMRI study in humans revealed the central role of the medial prefrontal cortex in goal-directed

learning and implicated the insula and dorsal striatum in habit learning (Eryilmaz et al., 2017). Interestingly, a recent study in the rat using a devaluation procedure showed that female rats engage in habit learning earlier in training than male rats (Schoenberg, Sola, Seyller, Kelberman, & Toufexis, 2018). Accordingly, we may posit that females engage overly into the habit system, perhaps by engaging the insula/striatum at the expense of the OFC earlier in training than the males. It is well known that dopaminergic activity in the striatum is sensitive to estrogens (Di Paolo, 1994; Shams, Sanio, Quinlan, & Brake, 2016). In addition, estrogen administration in the striatum biases navigational strategies of rats towards response learning (e.g, always turn to the right, as opposed to place learning; Korol, 2004; Quinlan, Hussain, & Brake, 2008). Our previous results in ovariectomized female marmosets showed impairing effects of estrogen administration on reversal learning acquisition (Lacreuse et al, 2014). In light of all these results, we propose that estrogens in female marmosets are likely to enhance habit formation by modulating dopaminergic striatal activity. The enhancement of habit formation during learning, detrimental to cognitive flexibility, leads to a sex difference in the speed of acquisition of the reversals. Future studies will need to elucidate the exact mechanisms by which estrogens may enhance habit formation.

Table 1: Age at test (years) for all marmosets

Animal #	Sex	Age at Test	Hormonal Data
1	Male	5.38	N
2	Male	5.71	N
3	Male	5.92	N
4	Male	5.94	N
5	Male	6.32	N
6	Male	6.68	N
7	Male	7.07	N
8	Female	5.08	N
9	Female	5.18	N
10	Female	5.20	Y
11	Female	5.21	Y
12	Female	5.29	N
13	Female	5.79	Y
14	Female	5.96	Y
15	Female	6.15	Y
16	Female	7.03	N

Table 2: Results of mixed model analysis of PR performance as a function of E2 levels in 5 females

Dependent Variable	Df	F value	p
Time in PR	35.45	0.042	0.84
Number touches	39	0.10	0.75
Number rewards	38.94	0.33	0.57
FCR	38.59	0.017	0.89

Figure 1: Schematic of the motivation circuit. From Kim (2013) Front. Psychol., 04

<https://doi.org/10.3389/fpsyg.2013.00098>

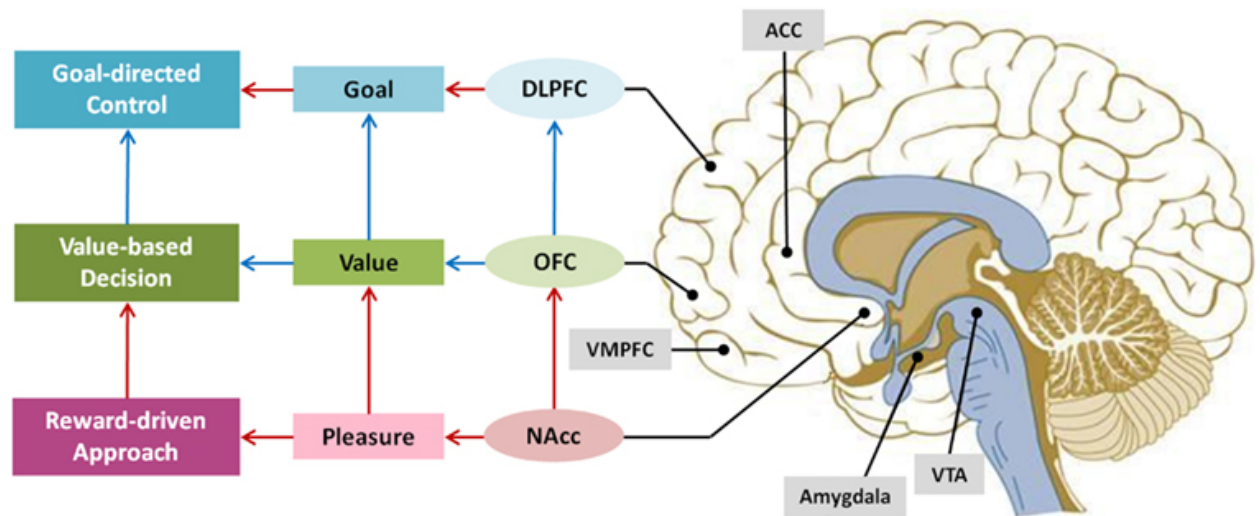


Figure 2: A. Stimuli presented to subjects during reversal learning procedure; B. Trials to criterion in the simple discriminations and simple reversals for year 1 and 2 Reversal Learning Task.

A.



B.

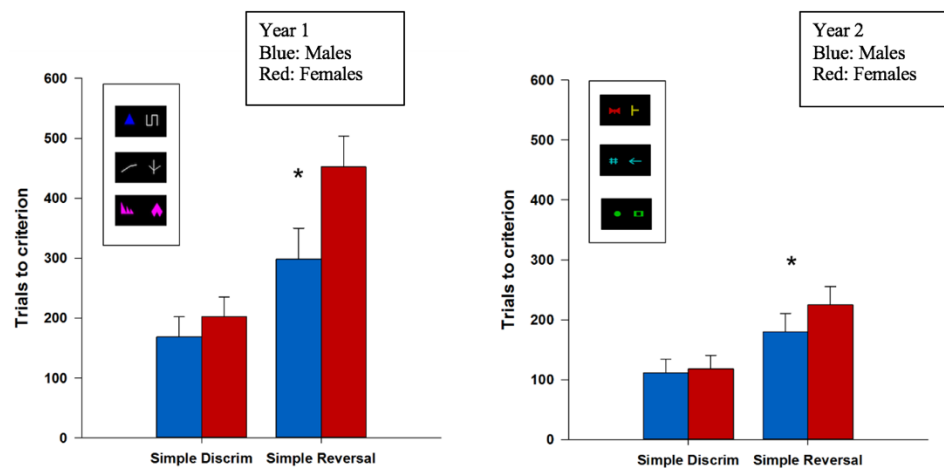


Figure 3: A. CANTAB machine used to perform PR and cognitive experiments. The stimulus used in the PR (blue square) is shown. The metal spout in the center of the screen dispenses the milkshake reward; B. Marmoset interacting with the CANTAB on the PR.

A.

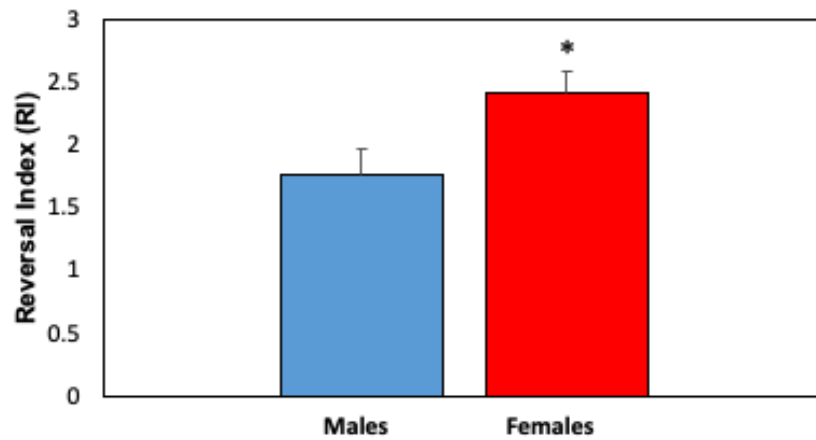


B.

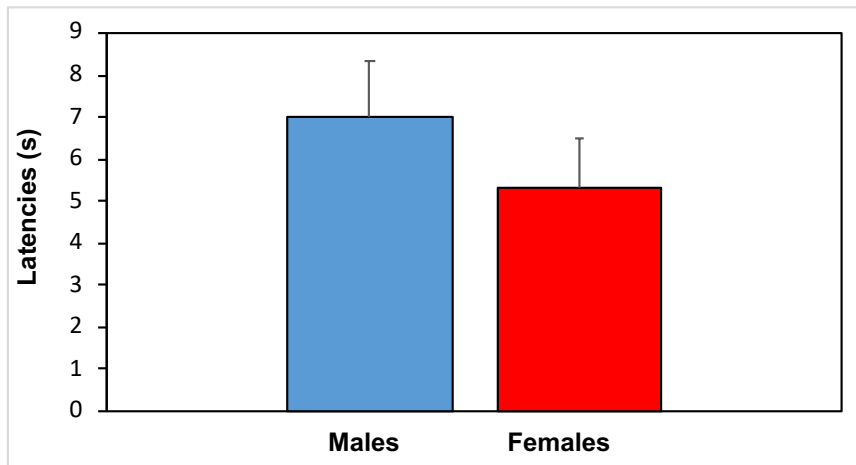


Figure 4: Reversal Index (A), latencies (B) and percentage of refusals (C) as a function of sex in the reversal learning task; * $p < .05$

A.



B.



C.

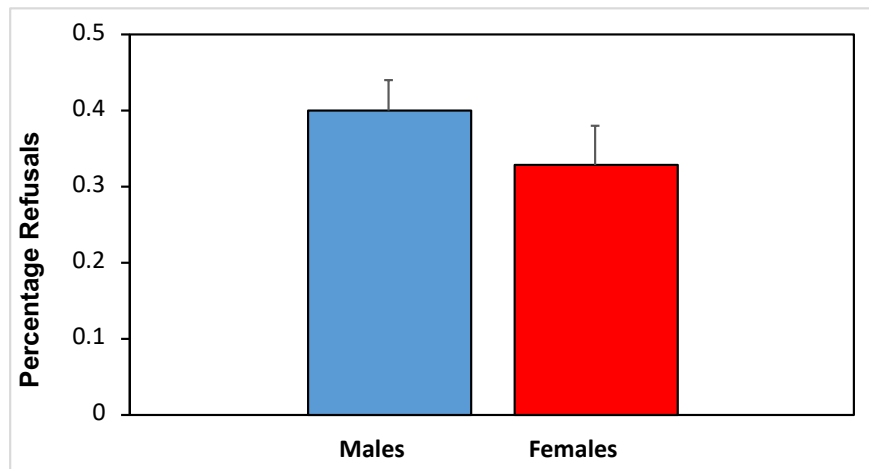
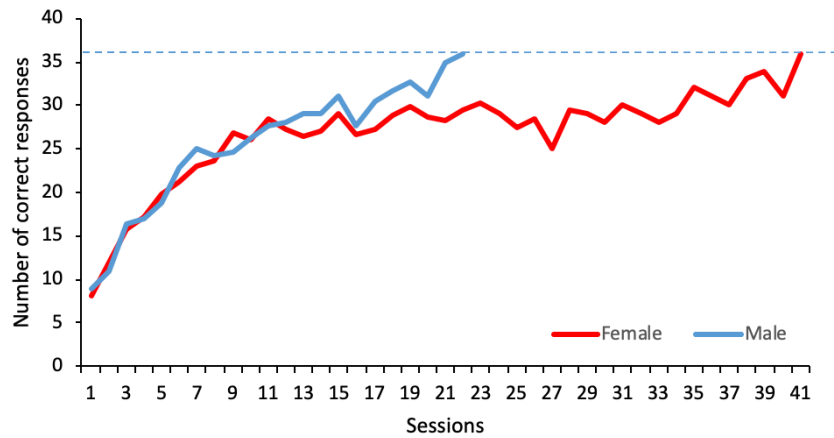


Figure 5: A. Number of correct responses as a function of sessions of 40 trials in the reversal learning task B. Number of refusals as a function of sessions of 40 trials in the reversal learning task.

A.



B.

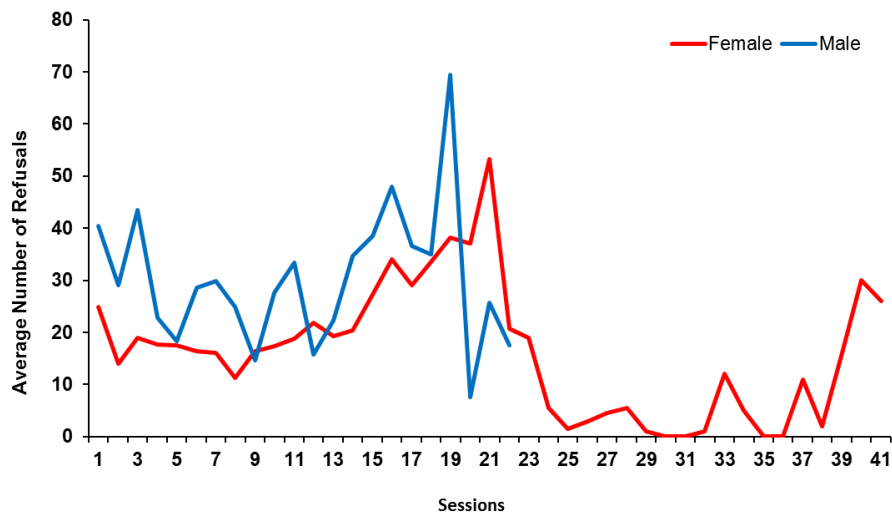


Figure 6: Time spent in PR (A), number of touches (B), number of rewards obtained (C) and average FCR (D) as a function of session and sex in the PR

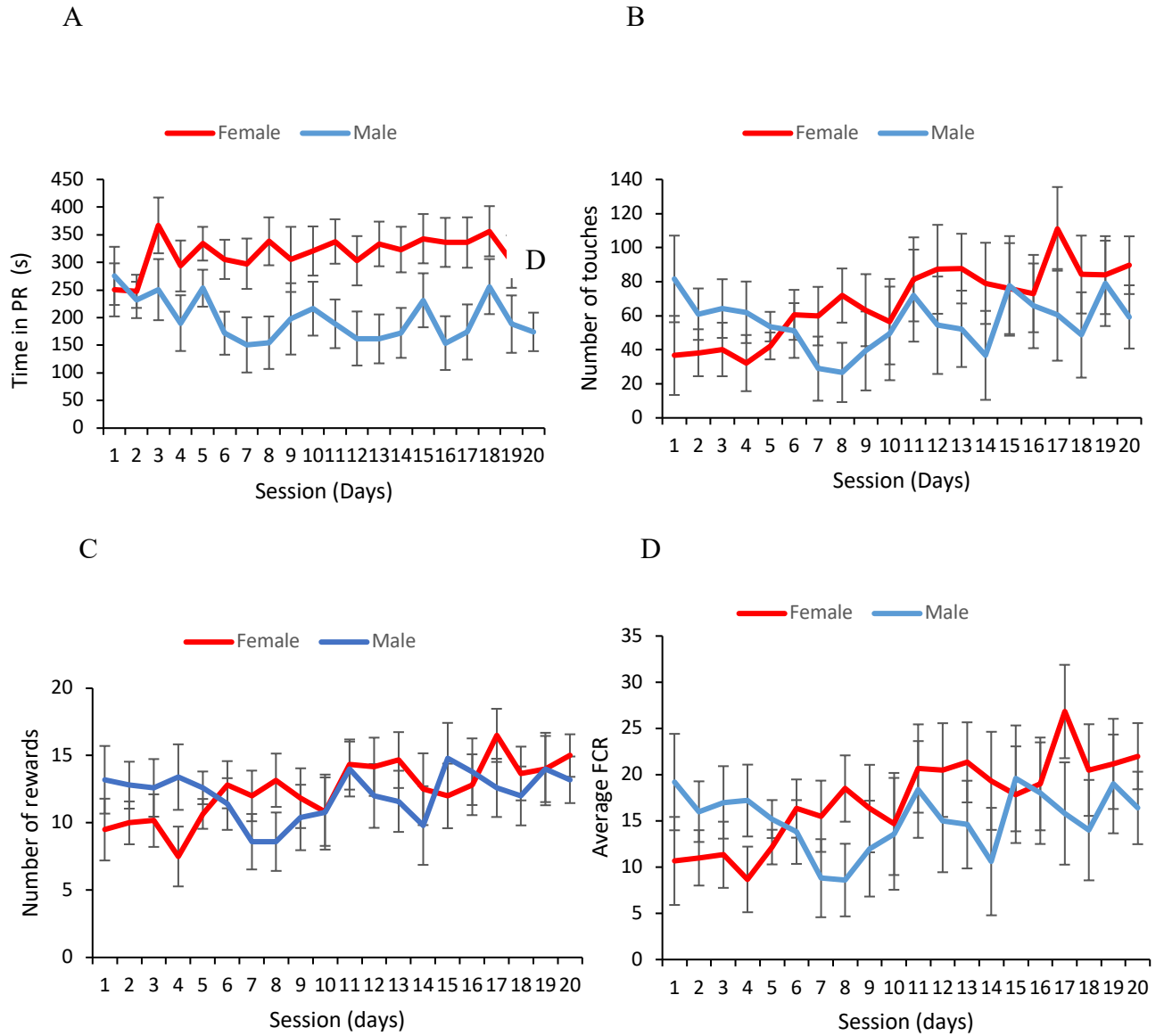
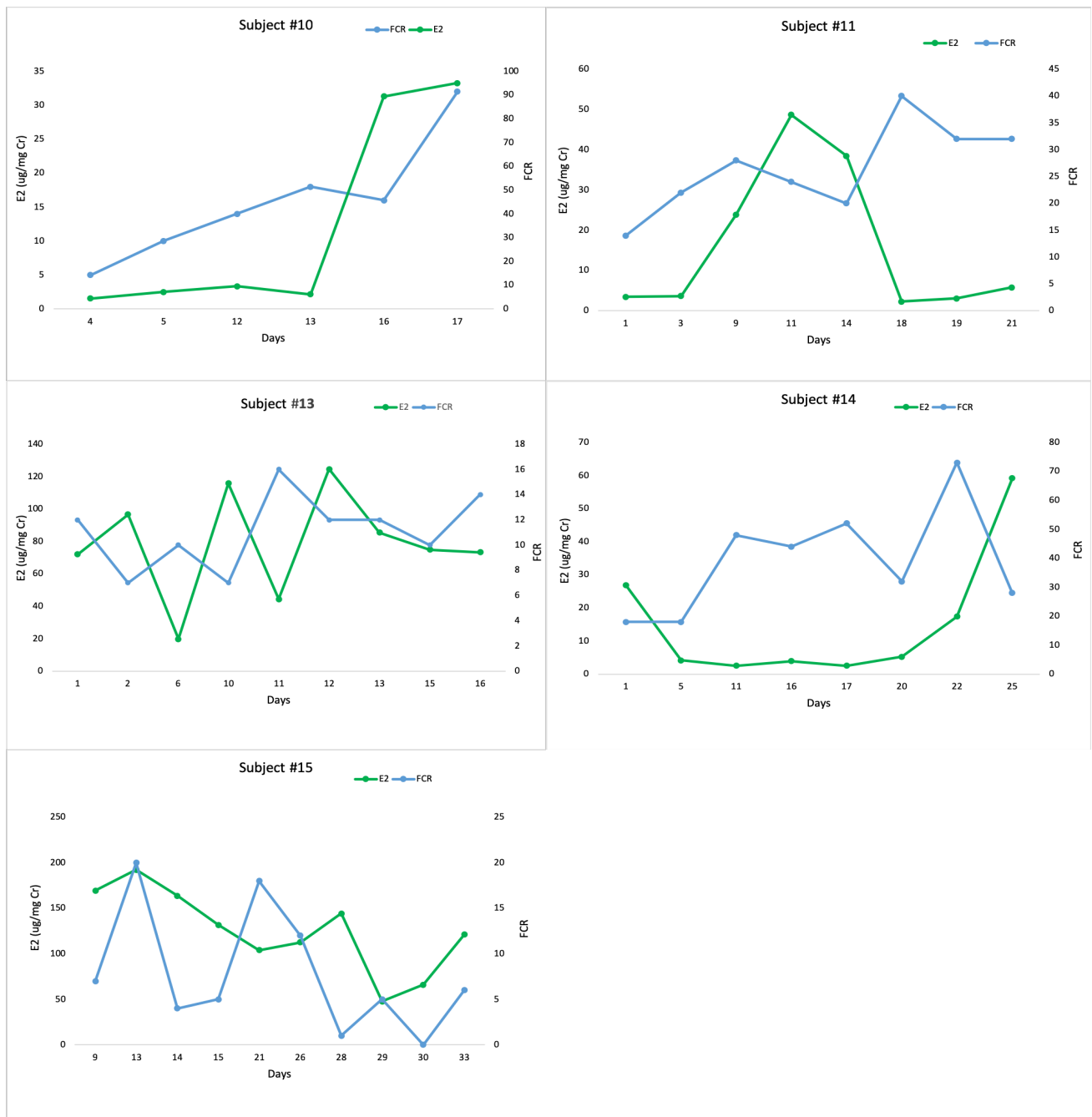


Figure 7: E2 levels and FCR as a function of testing session in 5 female marmosets



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