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Neural correlates and effect of jealousy on cognitive flexibility in the female titi monkey (*Plecturocebus cupreus*)

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Abstract

Jealousy is a social emotion that manifests as behavioral reactions from an individual toward a threat to a valuable relationship. Monogamous species exhibit jealousy-type behaviors as an adaptive response to preserve the relationship. Jealousy is also a complex, negatively-valenced emotion which may include fear of loss, anxiety, suspiciousness, and anger. Negative emotion may impair cognitive processes such as cognitive flexibility, an ability important for coping with new situations. However, little is known about how complex social emotions influence cognitive flexibility. To understand the interaction between jealousy and cognitive flexibility, we examined the neural, physiological, and behavioral factors involved in jealousy and cognitive flexibility in female titi monkeys. We presented subjects with a jealousy provoking scenario, followed by a reversal learning task and a PET scan with a glucose-analog radiotracer. We found that female titi monkeys reacted to a jealousy provoking scenario with increased locomotor behavior and higher glucose uptake in the cerebellum; however, hormone measures and were not affected. As only two females demonstrated cognitive flexibility, the effects of jealousy were difficult to interpret. Locomotion behavior was also negatively correlated with glucose uptake in brain areas linked with motivation, sociality, and cognitive flexibility. Surprisingly, glucose uptake in the orbitofrontal cortex (OFC) was significantly decreased during jealousy scenarios, while uptake in the anterior cingulate cortex (ACC) was decreased during reversal tasks. Our findings suggest that the presence

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Authorship
Study design: KLB, PZT, LES
Experimentation: PZT, LES, AJC, BAH, and LRW
Data analysis and interpretation: PZT, SMF, EF
Writing and Reviewing: PZT, LES, LRW, EF, AJC, BAH, SMF, KLB,

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of an intruder produces less visible behavioral reactions in female titis than in males, while still reducing activity in the OFC.

Keywords

jealousy; cognitive flexibility; emotion; PET-scan; primate

1. Introduction

Emotions and cognition are often studied as separate processes, which implies that emotions and cognitive processes are subserved by different brain areas. However, this view of an 'affective' and a 'cognitive' brain is no longer supported (Dolcos et al., 2011; Pessoa, 2008). There is a considerable amount of evidence showing that cognitive abilities—cognitive flexibility in particular—are connected to the emotional state of the individual and are supported by the same or by highly connected brain structures (Betzel et al., 2017; Dolcos et al., 2011; Hsieh and Lin, 2019; Wang et al., 2017; Wilson et al., 2018). In general, positive emotions and mood seem to improve cognitive performance (Wang et al., 2017), while anxiety and other negative emotions impair it (Hsieh and Lin, 2019; Wilson et al., 2018). Our understanding of the neural substrates that underlie these interactions is still in progress, and few of these studies have been conducted in complex social emotions such as "love", "social pain", or "jealousy" (for a review: Zablocki-Thomas et al., 2022).

Functional imaging is expanding the cognitive research landscape because it allows the measurement of neural activity longitudinally in living animals and humans. For example, the orbitofrontal cortex (OFC) is regularly found to be involved in cognitive flexibility (Rudebeck et al., 2013). The anterior cingulate cortex (ACC) is also considered active during cognitive flexibility processes (Ragozzino and Rozman, 2007) and emotion regulation (Domes et al., 2010). Researchers historically divided the ACC into an affective part (rostro-ventral) and a cognitive part (dorsal) (Bush et al., 2000), but this vision has been more recently contested (Pessoa, 2008). An fMRI study in humans showed the importance of the ACC for cognitive flexibility and that emotion that could generate conflicts in this area; during negative emotions, the ACC activity was increased and cognitive flexibility was negatively impacted, while during positive emotions, the ACC activity was decreased and cognitive flexibility was positively impacted (Wang et al., 2017). This study illustrates the potential for conflict between neural processes within the same brain regions or systems. In more naturalistic contexts, these areas are recruited in personal dilemmas involving the violation of personal morals (Greene et al., 2004).

Suspected infidelity, a case of violation of personal morals, can trigger emotional reactions such as jealousy. The term "jealousy" describes a specific emotional response of an individual when it perceives a threat to its relationships (Cubicciotti and Mason, 1978; Parrott and Smith, 1993), such as viewing a mate next to a rival; this elicits affective, cognitive, and behavioral reactions. Jealousy is qualified as a complex emotion, characterized by several "basic" emotions such as fear of loss, anxiety, suspiciousness, and anger about betrayal (Parrott and Smith, 1993). Due to its dependence on social

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relationships, jealousy is also considered a social emotion (Panksepp, 2010). An fMRI study in a Japanese cohort revealed some of the neurological underpinnings of jealousy by provoking the emotion. They found increased activation of the right amygdala in the case of sexual infidelity, and of the left and right cingulate cortex in the case of emotional infidelity (Takahashi et al., 2006). In another study (Sun et al., 2016), activation of the basal ganglia, the thalamus, and the middle cingulate was associated with romantic jealousy. While jealousy as an emotion is well known in humans (Panksepp, 2010) and can cause mental health disorders as depression (Mathes et al., 1985) and result in domestic violence (Kingham and Gordon, 2004), a similar emotion is also suggested by the behavioral and physiological reactions of non-human primates to threats to a valuable relationship (Cubicciotti and Mason, 1978). A better knowledge of the neural substrate of this social emotion could offer a better understanding of the mechanisms of pair bond maintenance in humans and other primates (Maninger et al., 2017c).

Since non-human primates are unable to verbally express their emotions, researchers infer their emotional state by changes in their behavior, physiology, and neural responses (Kremer et al., 2020). We define non-human primate emotion here as a “multicomponent response to a stimulus or event that is typically of importance to the individual, […] valenced (pleasant or unpleasant)” and that “can vary in activation/arousal and duration/persistence” (Paul and Mendl, 2018). For example, socially monogamous non-human primate species can display jealousy in the form of antagonistic behavioral reactions in the presence of an intruder (Rothwell et al., 2020a). During the jealousy response in male titi monkeys (*Plecturocebus cupreus*), PET neuroimaging revealed an increase in uptake of the glucose-analog radiotracer [^{18}F]-fluorodeoxyglucose (FDG) in the left ACC, the left posterior cingulate cortex (PCC) and the right lateral septum (LS) (Maninger et al. 2017). In male macaques (*Macaca mulatta*), a species that does not form monogamous bonds but does form short-term sexual consortships, the right superior temporal sulcus (STS), the right amygdala, and the insula showed increased [^{18}F]FDG PET uptake during the presentation of a visual stimulus involving their female consort next to a male competitor (Rilling et al., 2004). Primate models are thus extremely important to better understand the evolution of jealousy and its implication for humans, but only a handful of studies have been conducted on this topic (for a review: Zablocki-Thomas et al., 2022), especially in species that share monogamy with humans as a social mating system.

Titi monkeys form monogamous pairs that live in small family groups with their offspring. Partners display a strong preference for their mate (Carp et al., 2016) and engage in affiliative behaviors like tail-twining. Titi monkeys are an excellent model in which to study behavioral markers of jealousy, as they respond to the presence of strangers by an increase in arousal (tail-lashing, back-arching, movement), physically restraining the mate, and lip smacking (Fernandez-Duque et al., 2000; Mason, 1966; Rothwell et al., 2020b; Witczak et al., 2018). A male viewing his female mate next to a stranger male also shows an increase in testosterone, cortisol, and lip smacking behavior (Fisher-Phelps et al., 2016; Maninger et al., 2017c). The neural, behavioral, and hormonal reactions toward a jealousy-provoking scenario have been described in male titi monkeys, but not in female titi monkeys. In our study, we proposed first to examine behavioral, physiological, and neural correlates of jealousy in titi monkey females as a comparison to a previous study published in male

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titi monkeys (Maninger et al., 2017c). The second objective focused on whether jealousy affects cognitive flexibility in these individuals and investigates the neural correlates of this interaction. This study was the first to study the neural basis of cognitive flexibility in titi monkeys, and the first to do so in a jealousy-inducing context.

Sex differences are common among primate species, in morphology, physiology, and/or behavior (Clutton-Brock and Harvey, 1997; Lukas and Clutton-Brock, 2013). There are two hypotheses that are usually proposed to explain dimorphism for body size and potentially, other dimorphisms: (1) males and females occupy different ecological niches and (2) sexual dimorphism is the result of sexual competition to access a mate according to evolutionary theories (Clutton-Brock and Harvey, 1997; Lukas and Clutton-Brock, 2013). In males, jealousy behavior is hypothesized to have evolved to prevent his mate from getting pregnant from an extra-pair copulation, and the male then spending energy to raise offspring that is not his own (Panksepp, 2010). For females, infidelity risks the loss of resources provided for her and her offspring by her male mate – in titi monkeys, the male is the primary caregiver for the infant and thus a substantial resource, thus we might expect the mechanisms by which these affective states are initiated and expressed to differ (Fragaszy, Schwarz, and Shimosaka 1982). Previous studies have found that male and female titi monkeys had a different and sometimes opposite behavioral response in the presence of a same sex competitor (Cubicciotti and Mason, 1978). In the presence of a conspecific without the presence of their mate (non-jealousy conditions), female behavioral reactions are generally lower than those of males (Cubicciotti and Mason, 1978; Fernandez-Duque et al., 2000; Mercier et al., 2020). With this evidence in mind, we hypothesized that our jealousy condition would elicit a milder behavioral reaction in female titi monkeys than in males. However, this lack of behavioral response in female titi monkeys may not reflect a lower endocrine or neural response. We therefore expected to see a change in hormonal levels in cortisol and in androgens, as they are implicated in sexual behaviors processes in females (Staub and De Beer, 1997) and because human women experiencing jealousy showed an increase in salivary testosterone (Ritchie and van Anders, 2015).

Hormonal, neural, and behavioral aspects of jealousy do not always correlate: in humans, men and women showed no difference in self-rated jealousy, but they did present different responses in brain activation when presented to jealousy stimuli (Takahashi et al., 2006). Men showed activation of the amygdala and the hypothalamus, which are parts of the brain involved in appraisal of sexual salience and reproductive behavior, among other things. Conversely, women presented an activation of two regions, the thalamus and posterior superior temporal sulcus (STS), the latter being involved in detection of intention, deception, trustworthiness of others, and violation of social norms. Like in humans, male titi monkeys experienced a change in [^{18}F]FDG PET uptake in the right amygdala and the ACC in a jealousy context (Maninger et al., 2017c). But unlike humans, they also showed an activation of the right LS, which in titi monkeys contains both oxytocin and vasopressin receptors (Freeman et al., 2014) . We expected to detect similar sex specific variation in titi monkeys as was observed in humans, potentially in the thalamus and STS in female titi monkeys.

Finally, we predicted that jealousy would affect cognitive flexibility and this effect would be most profound in females displaying the largest behavioral response to the jealousy

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condition. Considering jealousy as a negative emotion related to anxiety, we expected that higher levels of jealousy will correlate with poorer cognitive flexibility, as is the case in humans (Wang et al., 2017; Wilson et al., 2018). Negative emotions are also known to reduce the "switching" cost and accelerate reversal (Hsieh and Lin, 2019). Thus, an alternative possibility is that jealousy evolved in concert with the monogamous social system and may improve cognitive processes in order to facilitate social cognitive solutions to maintain pair bonding.

2. Methods

All experimental procedures were approved by the Animal Care and Use Committee of the University of California, Davis, and complied with the National Institutes of Health ethical guidelines as set forth in the Guide for the Care and Use of Laboratory Animals.

2.1. Subjects

Subjects were seven captive-born and paired adult female titi monkeys (*Plecturocebus cupreus*) housed at the California National Primate Research Center (CNPRC). Females were selected because they were living with a vasectomized male (6 individuals) or because they had a tubal ligation (1 individual), ensuring they were non-pregnant, with intact ovaries, and not on hormonal birth control. Ages ranged between 3-6 years (mean = 4.5y).

2.2. Experimental Design and cognitive task

Visual discrimination training procedure.—All subjects were trained to perform a visual discrimination task by the lead experimenter in the front of their home cage and in the presence of their partner. To avoid any disturbance from the partner, the partner was simultaneously trained to sit in a specific spot of the cage (at the opposite side) by an assistant.

Titi monkeys are highly neophobic and need to be habituated to each procedure. Before proceeding to the visual discrimination training, all individuals were progressively trained to approach and sit at the front of the cage in proximity to the first experimenter, and then to touch a wooden shape, during five-minute sessions. The experimenter rewarded the subject's correct behaviors with an auditory stimulus paired with a small food reward. When individuals mastered the touching behavior, they were trained to discriminate between a shape paired with a reward (CS+) and a shape with no consequence (CS−). Visual discrimination tasks using these general procedures have been used previously in this species (Freeman et al., 2018). Some individuals had already participated in other cognitive experiments in the past, at least one year or more before the current project.

Discrimination training sessions consisted of up to five-minute trials for the subject to discriminate and select between two wooden shapes (square or circle or triangle painted in white, grey or black) placed on a board fixed on the front of the cage. A correct selection was followed by a clicker sound paired with a large food reward (peanut, dried papaya, grapes, or banana). During this phase of the training, the animals first performed ten forced choice trials and ten choice trials with rewards not exceeding limitations based on daily

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food requirements. Subjects performed one session per day maximum. Each monkey was randomly allocated a square, triangle, or a circle as a CS+ and a different shape as a CS−.

All individuals reached an accuracy level of 80% within 9-10 sessions of training. Next, they would perform the discrimination task with a food reward randomly delivered every minute on average and after a correct choice. These sessions lasted 10 minutes and were performed for 5 days before their move to the testing room. We designed these sessions with randomly distributed food rewards to train the subjects to do the task without food reward (only clicker sound), in preparation for the behavioral procedure to be followed by a PET scan, which requires fasted individuals. All individuals reached a ratio of 80% correct choices with random food reward over the 5 sessions. At this point, they were considered trained and ready to proceed to the behavioral testing phase.

Behavioral testing conditions and reversal learning

Reinforcement and habituation to the testing room.: All individuals were relocated to a testing room with their mate for two days. During these two days, they were trained again for visual discrimination with the clicker sound and a constantly distributed food reward (two days before the PET scan) and then randomly distributed food reward (one day before the PET scan). This additional training condition was necessary to habituate the subjects to do the task in new conditions in preparation of the test in the room dedicated to subjects receiving PET scans. All subjects reached the 80% criterion during this phase.

Behavioral experiment.: On the day of the experiment, subjects performed the behavioral experiment followed by an [^{18}F]FDG PET brain scan (Figure 1). This behavioral experiment lasted a total of 30 minutes. First, individuals were placed in a jealousy or control condition, then they either performed a reversal task or remained undisturbed during the last 10 minutes of the stimulus presentation. For all scenarios, the subjects were left without the presence of an experimenter for at least 15 minutes after the start of the experiment (Figure 2).

- ***Social conditions: Jealousy and no reversal task.*** As a replication of the previous study performed in males, Maninger et al. (2017), we presented two scenarios to the monkeys, one to elicit jealousy reactions and the other as a control.
  - During the control condition without the reversal task (Condition 1), the subject viewed a stranger couple.
  - During the jealousy condition (without the reversal task, Condition 2), the subject viewed her pair-mate next to a stranger female.
- ***Cognitive conditions: Reversal task with or without jealousy.*** For the reversal task, the predictive value of CS+ and CS− was reversed for each subject, and the subject performed the reversal with the clicker sound as the only reward for 10 minutes. The stimuli were left until the subject touched the new CS+.

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- During the control condition followed by the reversal task (Condition 3), the subject participated in the reversal task with her pair mate within visual range.*
- During the jealousy condition followed by the reversal task (Condition 4), the subject participated in the reversal task with her pair-mate next to a stranger female (Figure 2).**

All subjects underwent four PET scans preceded by these four different conditions presented in a counterbalanced order two weeks apart and with an alternation between reversal and non-reversal conditions (**See** Supplementary Table 1).

*In Condition 3, the pair mate was present with visual contact to minimize disruptive effects of separation from the attachment figure on cognition.

**Individuals were presented with two reversal tasks in total. Reversal tasks were spaced out by a minimum of four weeks and conducted with a different CS+.

2.3. Experimental design and [^{18}F]FDG PET imaging

We used [^{18}F]FDG PET brain scans to quantify glucose uptake in females viewing their mate close to a stranger female and during the performance of a reversal task. Forty-eight hours prior to each scan, the subject and her pair mate were moved to a testing room to reduce the effect of novel housing on brain metabolism (Hinde et al. 2016; Maninger et al. 2017b,a). Tested individuals were fasted 8-12h before the experiment with water allowed *ad libitum*. On the day of the PET scan, tested individuals were manually restrained and received a bolus injection of the [^{18}F]FDG radiotracer (PETNET Solutions Inc, Sacramento, CA, USA) (mean±SD: 37.8±4.6 MBq/kg ; SEM =.86 ; [min,max]=[23.2,48.4], administered intravenously in a volume of < 2 ml) into the saphenous vein before the behavioral experiment.

During the next 30 minutes of conscious uptake period, the individuals were placed in the test condition of the behavioral experiment (jealousy or control) followed by the cognitive condition (reversal or control). We placed a camera at the side of the subject's cage and a camera aimed at the stimulus monkeys for 30 min to record subject and stimulus monkeys' behaviors, while the humans left the room. After 15 minutes (for reversal task) or 30 minutes (for non-reversal condition), the experimenter reentered to perform the reversal task with the subject or to stop the experiment.

After the [^{18}F]FDG uptake period, the individuals were sedated with ketamine (25 mg/kg IM) and medetomidine (0.05 mg/kg IM). Then, a blood sample (1 mL) was collected from the femoral vein and put into a heparin-containing tube. Following collection of blood, an endotracheal tube was placed, and a catheter was placed in the saphenous vein to administer IV fluids. Atipamazole was used to reverse medetomidine, and anesthesia was maintained with isoflurane (1–2%), while the subject was positioned on the scanner bed feet first and the brain of the animal was positioned in the center of the scanner. PET imaging was performed on the πPET dedicated brain scanner (Brain Biosciences, Rockville, MD, spatial resolution ~2.0 mm). Image acquisition started 60 min post-[^{18}F]FDG administration and

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lasted for 1 hour. Anesthesia was maintained throughout the scan. Static PET images were reconstructed using the vendor-provided maximum likelihood expectation maximization method. Animals were housed in the testing cages for 24 hours after scanning to wait for the radiation to decay at a background level and being able to return animals in their home cages.

2.4. Structural MRI Scanning

We conducted structural magnetic resonance imaging (MRI) in a GE Signa LX 9,1 scanner (General Electric Corporation, Milwaukee, WI) with a 1.5 T field strength and a $3''$ surface coil. Subjects were fasted 5-12h before the scan. Subjects were sedated with ketamine (10/mg/kg IM) and Midazolam (0.1mg/kg IM) prior to the placement of the endotracheal tube. A catheter was placed in a peripheral vein to provide vascular access. Anesthesia was maintained with isoflurane (1-2%), and the animal was positioned in the MRI scanner. The scan took approximately 25-30 minutes and consist of a 3D T_1-weighted spoiled gradient echo pulse sequence in the coronal plane. Images of the entire brain were collected using the following parameters: echo time TE = 7.9ms, repetition time TR = 22.0ms, flip angle = 30.0°, field of view = 8cm, number of excitations = 3, matrix = 256 × 256, and slice thickness = 1mm. The subject's vital signs and physiologic parameters (EtCO2, oxygen saturation, heart rate and blood pressure) were monitored throughout. Following the scan, recovery was monitored, and once alert and responsive, the animal was transported back to their home-cage.

2.5. PET and MRI Co-registration, Quantification of [^{18}F]FDG Uptake

Based on previous studies in non-human primate and human jealousy, we selected the following regions of interest (ROIs).

1. From the male titi monkey study on jealousy (Maninger et al., 2017c): LS, ACC and PCC.
2. From the male rhesus monkey study on jealousy (Rilling et al., 2004): STS, ACC, PCC and amygdala.
3. From human studies on jealousy and social pain (Steis et al., 2021): STS, thalamus, hypothalamus, amygdala, ACC, nucleus accumbens (NAcc), ventral pallidum (VP), caudate nucleus, hypothalamus, and pulvinar and putamen.
4. From studies in cognition and cognitive flexibility: orbitofrontal cortex (OFC), ACC, globus pallidus (GP) (Rudebeck et al., 2013; Wang et al., 2017). (Figure 3)

We drew ROI structures on each subject’s MRI image using the PMOD software (v. 3.9, PMOD Technologies Ltd, Zurich, Switzerland). We drew ROIs prior to co-registration of the MRI with PET scans in order to ensure blinding in PET signal assessment. The same ROIs were used for all experimental conditions. The PET images were co-registered to the MRI and mean [^{18}F]FDG PET uptake was determined within each ROI. Data were normalized to the mean [^{18}F]FDG PET uptake of the whole brain, and presented as the standardized uptake value ratio (SUVr). ROI delineation, including the location of the PCC, in the present study was selected to standardize methodology across this study and previous studies in titi moneys (Maninger et al., 2017b, 2017d) and on the Marmoset atlas (Yuasa et al., 2010).

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Some anatomical structure were used as landmarks to select slice reliably across studies and subject (for example: the anterior commissure is generally well define and visible on one slice).

2.6. Blood Sampling and Hormone Analysis Blood

After the behavioral experiment and sedation, a blood sample of approximately 1 mL was collected in heparin-containing syringes. Blood sample was immediately placed on ice in tubes and centrifuged at 1,610 x g for 15 minutes at 4°C. Plasma was aliquoted and placed at −70°C until assay. We used an enzyme immunoassay to measure plasma androgens (using antibody R156/7, UC Davis Endocrinology Laboratory; cross reactivity : Testosterone 100%, dihydrotestosterone 57%, Androstenedione 0.27%, DHEA and all other steroids tested <0.05%) and cortisol (with antisera R4866, produced by UC Davis Endocrinology Laboratory) using a method validated for female titi monkeys (Witczak et al., 2021), described in detail in the referenced publication. Inter- and intra-assay c.v.s were 0.804% and 16.64% for cortisol; intra-assay c.v. for androgens was 9.50% as all samples were run in a single assay.

2.7. Behavioral Coding

We recorded behaviors from the test subject and her mate stimulus with a camera during the 30-minute behavioral experiment period, and we scored them using the same ethogram as Maninger et al. 2017b (Table 1).

We used Behavior Tracker software (v1.5, behaviortracker.com) to code each video and recorded the duration of all the behaviors. The videos were scored by a trained coder who was unaware of the experimental condition and validated against previous scoring done in the laboratory. We performed data analysis on the total duration or frequency of each behavior.

2.8. Timeline

The full course of the experiment lasted approximately 2 months for each individual, starting with the visual discrimination training and ending with the fourth PET scan (Supplementary Figure 1).

2.9. Data analysis

All computations were performed in R (R Development Core Team 3.0.1., 2013) and the scripts are available upon request. All p-values were considered significant when less than α=.05.

Creation of Composite variables—To reduce the number of outcome variables in the analyses, we created composite variables by grouping brain areas that were presumed to be part of the same systems or share similar functions. For this, we assigned brain regions to four groups, where they were all considered under the same label: Group 1, Group 2, Group 3 and Group 4. As a result, all subjects for each condition obtained more than one data point in each Group (i.e., number of data points per Group and per individual and condition = number of brain areas included in that Group X multiplied by two hemispheres).

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- Brain Group 1 =“Motivational areas”: Caudate, Putamen, Nucleus accumbens, Substantia nigra (Acevedo et al., 2012; Resendez et al., 2016)
- Brain Group 2 = “Social areas”: Lateral Septum, Amygdala, Posterior cingulate cortex, Hypothalamus (Bales et al., 2007; Maninger et al., 2017c; Rilling et al., 2004)
- Brain Group 3 = “Female jealousy”: Superior temporal sulcus, Insula, Pulvinar (Steis et al., 2021; Takahashi et al., 2006)
- Brain Group 4 = “Flexibility areas” (Anterior cingulate cortex, Orbitofrontal cortex, Globus pallidus) (Rudebeck et al., 2013; Wang et al., 2017)
- The Cerebellum and the Whole Brain were not included as factors but were analyzed as control areas.

Comparison of jealousy and non-jealousy conditions—To compare between the two jealousy conditions, we ran linear mixed models on the behaviors with nlme and lme4 packages, (Bates et al., 2015, p. 4; Pinheiro et al., 2015), the two hormonal measures, and each brain group as outcome variables. We checked for residuals’ normality with the qqnorm function. We ran two sets of models:

- With a Jealousy or Non-Jealousy factor as a two-level fixed effect (meaning considering the data from C2 and C4 with Jealousy together and the data from C1 and C3 without Jealousy together), and the identity of the individuals as a random effect.
- We also ran the same models but with the four conditions as a four-level fixed effect (C1, C2, C3 and C4 taken separately), and the identity of the individuals as a random effect (**Results shown in** Supplementary Table 2).

Relationships between behavioral, hormonal, and neural data

Averaging Brain Values: To obtain one single value per brain grouping, for each condition and each subject (so that they correspond to associated unique behavioral and hormonal measures for each test condition), we averaged the value per brain grouping by individual and condition (‘summarize()’ function of tidyverse (Wickham et al., 2019). We scaled behavioral and hormonal data using the ‘scale()’ function.

Selection of test hypothesis: Given the large number of neural, hormonal, and behavioral measures, we focused on theoretically driven questions to reduce the number of models. This led to five hypotheses, which we tested using eight different models:

1. Model 1: Given the difference in locomotion in response to jealousy, we tested for the effects of androgens and cortisol on locomotor behavior, to see if this behavior changed as a response to hormonal changes.
2. Models 2.1 and 2.2: We tested for the effects of locomotion, androgens and cortisol on Group 1 (Model 2.1). Because only locomotion significantly explained Group 1 activation, we ran another model with Group 1 as the response variable, and an interaction between Locomotion and Condition as

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a fixed effect in order to see if this relationship was dependent on particular conditions (Model 2.2). Specifically, we tested for the effect of behaviors and hormones on Group 1 ("motivational areas"), to see if behavior and hormones affected this composite variable.

3. Models 3.1 and 3.2: We tested for the effects of locomotion, androgens and cortisol on Group 2 (Model 3.1). Because only locomotion significantly explained Group 2 activation, we ran another model with Group 2 as the response variable, and an interaction between locomotion and condition as a fixed effect in order to see if this relationship was dependent of particular conditions (Model 3.2). We tested for the effect of behaviors and hormones on Group 2 ("social areas"), to understand the relationship between expressed hormonal changes and the activation of social areas.

4. Model 4: We tested for the effect of behaviors and hormones on Group 3 ("judgment areas").

5. Models 5.1 and 5.2: We tested for the effects of locomotion, androgens and cortisol on Group 4 (Model 5.1). Because only Locomotion significantly explained Group 4 activation, we ran another model with Group 4 as the response variable, and the interaction between locomotion and condition as a fixed effect, to see if this relationship was dependent on particular conditions (Model 5.2). We tested for the effect of behaviors and hormones on Group 4 ("cognitive flexibility").

Effect of Jealousy on Cognitive Flexibility—To examine the effect of jealousy on cognitive flexibility, we ran linear mixed models on: a) the number of trials (i.e., the number of correct answers + 1, Poisson distribution) during the reversal test, b) the number of touches (active choice of a shape from the monkey by touch, Poisson distribution) and, c) the latency to start the first trial, with condition (here only for the two conditions with reversal test) as a fixed effect and individual as a random effect.

We also ran linear models on the three specific areas from brain areas from Group 4 specifically (OCF, ACC and Globus Pallidus), with non-reversal (Condition 1 and Condition 2) versus reversal (Condition 3 and Condition 4) as a 2-levels fixed effect and individual's identity as a random effect, in order to detect if the cognitive task was involving these areas in our study. We also ran similar models with the four conditions as four level fixed effects (**See** Supplements).

3. Results

3.1. Research question 1: neural, hormonal, and behavioral correlates of jealousy in female titi monkeys and comparison with male titi monkeys

a. Behavioral description—Female titi monkeys presented four measurable behaviors during the behavioral experiment (Supplementary Figure 2): locomotion (all individuals across four conditions), directed gaze (all individuals across four conditions), lip smacking (only two individuals in two conditions) and arching (one animal in one condition). Due to

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the scarcity of lip smacking and arching behaviors we only discuss locomotion and directed gaze for the rest of the study.

b. Comparison of Control and Jealousy conditions—We found that only locomotion significantly differed across conditions, with females moving more during jealousy conditions as compared to non-jealousy conditions (Table 2, Figure 4). There was also a trend in cerebellar [^{18}F]FDG PET, which was lower in non-jealousy conditions (Table 2, Figure 5). When we ran a similar model with the four conditions as a fixed effect, only locomotion showed a significant difference in the jealousy condition C4 (as compared to C1), with individuals moving more in this condition than in the control condition (Supplementary Table 2). We also found that the OFC [^{18}F]FDG PET was lower in the two jealousy conditions (C2 and C4) as compared to the control condition (Supplementary Table 3, Supplementary Figure 3).

c. Relationships between neural, hormonal, and behavioral measures—We found that locomotion was not associated with hormones and directed gaze behavior. However, brain area Groups 1, 2 and 4 (motivational, social, and cognitive factors) were related to locomotion, showing lower [^{18}F]FDG PET uptake when locomotion is higher (Models 2.1, 3.1 and 5.1, Figure 6). The relationship between locomotion and [^{18}F]FDG PET uptake was mainly driven by the two conditions without the reversal tests, C1 and C2 (Models 2.2, 3.2 and 5.2; Table 3).

3.2. Research question 2: effects of jealousy on cognitive flexibility in titi monkeys and its neural basis

Only two females illustrated cognitive flexibility: two females selected the new stimulus twice (number of Trials = 3) in the control condition, and one of these two females selected the new CS+ twelve times (Number of Trials = 13) in the Jealousy condition (Figure 7A). We did not find any effect of jealousy condition on the other variables of the reversal task (Table 4; Figures 7B and 7C).

We found that the [^{18}F]FDG PET uptake of the ACC was affected by the reversal test condition, with lower uptake when there was a reversal test (Table 5, Figure 8). This result was driven by the two conditions with reversal test (C3 and C4, Supplementary Table 3).

4. Discussion

To our knowledge, only two previous studies have investigated the neural, behavioral, and physiological correlates of jealousy in nonhuman primates, and those studies were on male titi monkeys and male rhesus macaques (Maninger et al., 2017c; Rilling et al., 2004). We argue in accordance with other researchers (Beery and Zucker, 2011; Woitowich et al., 2020) that there is a particular need to study females in the neuroscience field. In addition, we aimed to describe the importance of a complex social emotional state, “jealousy”, and its interaction with a cognitive process. This study was the first to examine the neural basis of cognitive flexibility in a non-human primate while in a potentially jealousy-inducing context, and the first study to describe the neural correlates of jealousy in a female monogamous primate.

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4.1. Neural, hormonal, and behavioral correlates of jealousy in female titi monkeys and comparison with male titi monkeys

We found that female titi monkeys reacted to the jealousy-provoking scenario by increasing their locomotor behavior as compared to non-jealousy scenarios, which contrasts with male titi monkeys that spent more time gazing at their mate next to the stranger (Maninger et al., 2017c). We compared four groups of brain areas regularly involved in motivation and social interactions (group 1 and group 2), and groups of brain areas involved in women jealousy (group 3) and cognitive flexibility (group 4), but were unable to detect a difference in glucose uptake between the four scenarios for these groups. In contrast with males, [^{18}F]FDG PET uptake in females in the LS, PCC, ACC and amygdala did not change significantly; however, the cerebellum showed higher [^{18}F]FDG PET uptake during jealousy in females. Another difference is that we did not find significant changes in the androgen and cortisol levels, as were found in males. Finally, [^{18}F]FDG PET uptake in the OFC decreased significantly during the two jealousy scenarios, which was not investigated in males.

The lower [^{18}F]FDG PET uptake in the OFC in the jealousy scenario is surprising because this cortical region is generally not associated with jealousy to our knowledge and has been associated with behavioral inhibition, outcome expectancies, and adaptive behavior when facing unexpected outcomes (Schoenbaum et al., 2011). It has also been implicated in other processes, such as emotion regulation (Golkar et al., 2012). One study implicated the OFC in the feeling and anticipation of regret (Coricelli et al., 2007). Because of the role of the OFC in adaptive behavior, its decreased activation in jealousy scenarios as compared to non-jealousy scenarios is interesting and suggests an interaction with this emotion. This observation seems similar to the decrease of the ACC during positive emotions, where decreased activity in the ACC (assessed through fMRI) is hypothesized to improve cognitive flexibility in humans by allowing the ACC to be more available for cognitive processes (Wang et al., 2017). The decrease of the OFC during jealousy could potentially facilitate cognitive flexibility in female titi monkeys. However, the design of the current study could not directly assess this idea.

In a previous study in male and female titi monkeys (Cubicciotti and Mason, 1978), subjects were presented with a same-sex stranger at various distances to the pair mate of the subject. Similar to our findings, males and females responded differently; males approached their pair mate more when the same-sex stranger was closer to her (0.5m) than further (4.5m) away, while females approached less when the same sex stranger was closer to their pair mate. In our study, stimulus monkeys were consistently close to each other (~0-1m depending on their respective location in their stimulus cages). We could possibly interpret the higher locomotion of our female subjects as agitation or an attempt to avoid the situation. In the cited study, males also tended to display more agonistic behavior than females. Our subjects and the stimulus monkeys did not show any agonistic behaviors (i.e. aggression).

In addition, locomotion and cerebellar [^{18}F]FDG PET uptake were not correlated in our study (not shown), suggesting that the higher activation of the cerebellum during jealousy would not be solely explained by the increase in locomotion. The functions of the cerebellum are still debated, but research has mainly been restricted to motor functions,

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especially implicating the vermis (Jahn et al., 2004). Studies of emotion that implicate the cerebellum are now more common; brain imaging research has shown for example that negative emotions have a stronger impact on the cerebellum than positive emotions (Adamaszek et al., 2017). Our study showed that cerebellar glucose uptake was higher in the jealousy condition. Further studies would be necessary to investigate which subdivision of the cerebellum is responsible of this change in glucose uptake. Indeed, in our study we considered the entire volume of the cerebellum as we did not dispose of more detailed information of the cerebellum sub-regions in the titi monkey. By considering the entire volume of the cerebellum, we ensured to have enough voxels to detect a change in glucose uptake between conditions.

Other brain areas were related to locomotion: brain areas groups 1, 2, and 4 (motivational, social, and cognitive factors) had a lower [^{18}F]FDG PET uptake when locomotion was higher across conditions and thus were negatively associated with locomotion. This result partially converges with a study in humans showing that basal ganglia were less activated during walking than during standing (Jahn et al., 2004).

Regarding the association between hormones and behaviors, we found no correlation between hormonal measures and behavioral or neural measures. In males, the change in testosterone had a small effect size (Maninger et al., 2017c), so it is likely that we were not able to detect a change in females because the effect size was even smaller. Both hormonal measures were correlated with gazing behavior in males, a behavior which was influenced by jealousy in males but not in females. Altogether, the relative absence of lip-smacking behavior, arching, and hormonal changes seem to suggest that the presence of an intruder produces less detectable behavioral and physiological reactions in female titis than in males.

We chose to assay androgens over estrogens because of our prediction that female jealousy would be related to androgen levels (Ritchie and van Anders, 2015) and to compare our results with the previous study in male titi monkeys (Maninger et al., 2017c), where males showed an increase in plasma testosterone and cortisol when purportedly experiencing jealousy. Testosterone levels in women were increased when they imagined their partner flirting with another woman (romantic jealousy) compared to a control condition involving a neutral conversation with a co-worker. This increase was even higher in the situation where they had to imagine that their partner was actually kissing another women, while there was no impact of jealousy at all in male testosterone levels (Ritchie and van Anders, 2015). Some research has shown estrogens can have an impact on jealousy behavior: women taking hormonal birth control tended to be more sensitive to sexual jealousy and to present more intense affective reaction than women who are not taking birth control (Geary et al., 2001). Further analysis will be conducted using mass spectrometry in order to quantify the relative importance of the different androgens in female titi monkeys.

From an evolutionary perspective, it is surprising to see so little difference in behavior between the jealousy and the control conditions. Male titi monkeys indeed represent an important resource for female fitness, because they are the primary caregivers for offspring (Fragaszy et al., 1982), and we might expect that selection would have favored behaviors that increase bonding (affiliative behaviors toward the male like lip smacking, or agonistic

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behaviors like tail lashing), especially during situations when the pair bond might be challenged. Only one female exhibited these kinds of behaviors and only in rare occasions. We tested if pair affiliation (measured by the occurrences of contacts between the pair in their home cage, see supplements) influenced behavior during the experiment, be we found no relationship between affiliation and locomotion behavior, and the female who presented lip smacking and back arching behaviors was not among the most affiliative pairs. It could be that the scenario was not challenging enough for the subject, and because the pair mate could not interact with the stranger female, the subject females did not react strongly. It may also be relevant that tested females were paired with vasectomized males, and thus have never reproduced with those males. Future experiments should include older subjects that had previously had offspring with their pair mate and study the effect of previous reproductive experience of the couple (Hinde et al., 2016a). Observations in wild populations corroborate this idea; females have not been observed to interfere with extra-pair copulation of their mate with a stranger female (Mason, 1966). Cubiccioti and Mason (1978) argue that extra-pair copulation of the male does not represent a high cost for the female. Since a female resource is highly valuable, the evolution of pair bonding positively selects males that will present a high level of bonding behavior, which in turn reduces the selective pressure on female behavior and, possibly, the apparent absence of a jealous reaction.

4.2. Effect of jealousy on cognitive flexibility in titi monkeys and its neural basis

We could not be sure that the jealousy scenario had an influence on performance during the reversal task. Indeed, in the control and the jealousy conditions, only two females out of the seven subjects managed to show cognitive flexibility. The possible absence of a jealousy effect on cognition could be attributed to the relatively low level of a jealous reaction in our subjects. It is also likely that we were unable to detect an effect due to low participation rates in both conditions. Despite their ability to perform complex cognitive tasks once trained (Fragaszy, 1980; Freeman et al., 2018), this is the first time participation in a reversal task has been published in this species. The lack of previous data made it particularly challenging to estimate how much time subjects would need to reverse their learned behavior during the test trial (i.e., selecting the other shape instead of the learned shape), and future experiments could allow more time for the reversal task. Although animals were not receiving food rewards during testing, we do not believe the lack of participation was caused by a lack of motivation. For example, one of the females showed a high participation rate and kept touching the new CS+ stimulus during the whole trial, indicating that receiving only a clicker sound as a reward was sufficient to maintain motivation in the subjects.

The decrease in [^{18}F]FDG PET uptake in the ACC during reversal task scenarios was unexpected; an increase in ACC activity is generally found with cognitive tasks (Wang et al., 2017). In our case, the main difference between reversal task conditions and non-reversal conditions was the presence of two experimenters (one interacting with the monkey and the other scoring the behavior of the subject) and almost of the subjects participated in the cognitive task during the experiment (mainly failing to find the correct answer). One hypothesis for this result is the positive effect on subject's emotional state provoked by the presence of the experimenters and the anticipation of a food reward. It has been previously shown in the laboratory that titi monkeys can recognized researchers based on their uniform

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color (Arnaud, *unpublished data*). This anticipation may result in a positive mental state and then decrease the activity of the ACC (Wang et al., 2017). Indeed, it has been shown in many species that cognitive training and food anticipation is beneficial for animal wellbeing by eliciting positive affective states (Boissy and Erhard, 2014).

4.3. Technical considerations

From a technical point of view, the reversal-learning task represented a good option for our purposes because the reversal test is relatively quick, and therefore meets the timing requirement of the [^{18}F]FDG PET uptake necessary for the PET scan. In addition, visual discrimination learning is relatively easy to implement in this species. From a theoretical point of view, reversal learning measures the cognitive flexibility of an individual and thus its capacity to adapt its behavior to a new situation despite adverse effect of emotions. Behavioral flexibility may be a key factor for adaptation to new environments, such as the transition from a rural environment to an urban environment or changing climate conditions (Federspiel et al., 2017).

A potential limitation of the present study is limited sampling of the brain regions in question. This decision was driven by previous data and published works (Hinde et al., 2016b; Maninger et al., 2017b, 2017d) using these areas such that direct comparison could be drawn. Development of a titi monkey, 3D, anatomical atlas may overcome this limitation in the future.

Other control conditions could have been proposed in this experiment, but as argued by Rilling et al. (2004), there is no single perfect control for this kind of experiment. Our control condition C1 provides the advantage of presenting the same number of individuals as in test condition C2 and replicating the conditions in the study in male titi monkeys. We also conducted a control with the partner male alone, similar to Rilling et al. (2004). This condition had the advantage of controlling for a possible effect of separation from the pair mate during the cognitive test (Cronin et al., 2017; Hinde et al., 2016a).

Finally, it is not surprising to find large variability in individuals' reactions to the cognitive task. Individual titi monkeys have different personalities as in most primate species (Blaszczyk, 2020), meaning that they will present consistent variation in their behavioral response and also in their cognitive style (Cauchoix et al., 2018). In our study, some individuals were naïve to cognitive testing; however, our training should have provided sufficient habituation to the cognitive test to allow all individuals to participate to the task, regardless of personality. The weeks of training are assumed sufficient for all females with different personalities to successfully complete the visual discrimination task and to benefit from a similar level of habituation to perform cognitive tasks in the presence of two human experimenters. The seven subjects indeed presented a large variation in their behavior. Personality is an inherent feature of each individual and for researchers studying cognitive processes it can represent an unwanted source variation. However, personality also presents the opportunity to describe various levels of reactions and correlate these variations to other factors (hormones, physiology, and genetics for example). In our case, even though we did not possess reliable personality ratings at the time of the study and because the sample size was small, we suggest that differences in personalities might explain the variability of the

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behavioral, cognitive, hormonal, and neural reactions, and suggest adding personality ratings in future cognitive and behavioral experiments, especially with small sample sizes.

5. Conclusions

This study is the first to test the behavioral, hormonal and neural reaction of a female primate facing a jealousy provoking scenario, and to investigate on the potential impact of the emotional reaction of jealousy on cognitive flexibility. Despite no clear effect of jealousy on cognitive flexibility has been identified in this study, we were able to show a behavioral and neural reaction in female titi monkeys, which was clearly different from that of male titi monkeys. We suggest that future studies on animal emotions include both male and female subjects when possible, as well as continuing to have an integrative approach combining physiological and behavioral data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Raw data are available in the supplements as Supplementary Table 5.

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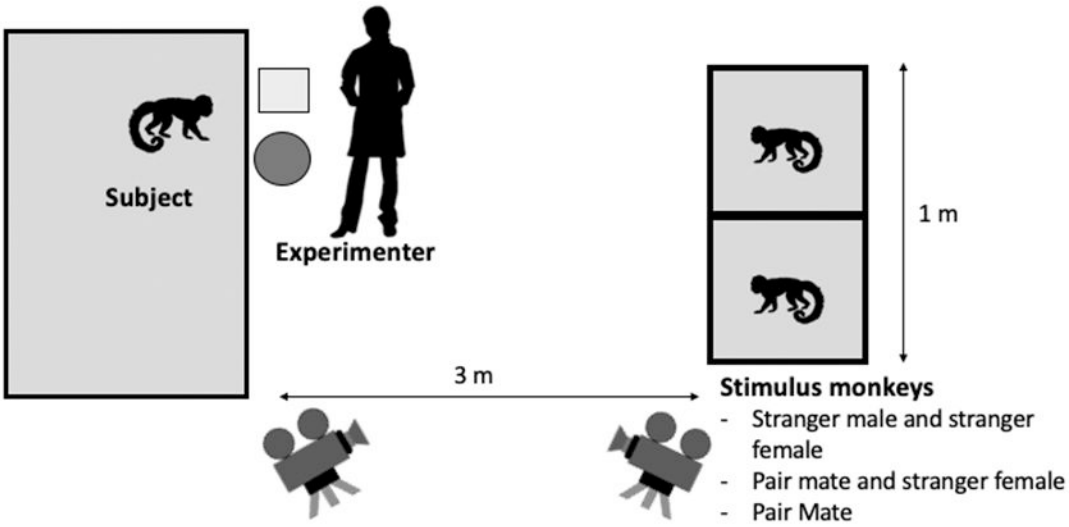

Figure 1.
Set up for experimental testing including the reversal test.

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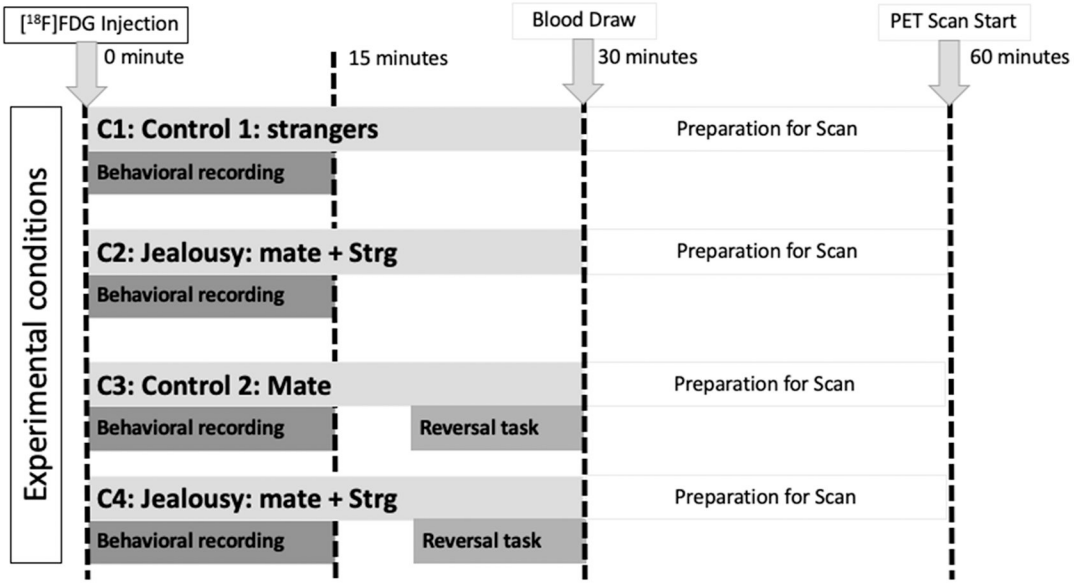

Figure 2.

Jealousy and control conditions without reversal task. Details of experimental design and details of the four conditions: the first 15 minutes after radiotracer injection are only observational (recorded by camera, no experimenter in the room). After 15 minutes, the two experimenters enter the testing room in conditions C3 and C4 and start the reversal task 10 minutes before the end of the behavioral experiment. Stimulus monkeys are presented to the subjects during the 30 minutes of the behavioral experiment for all four conditions.

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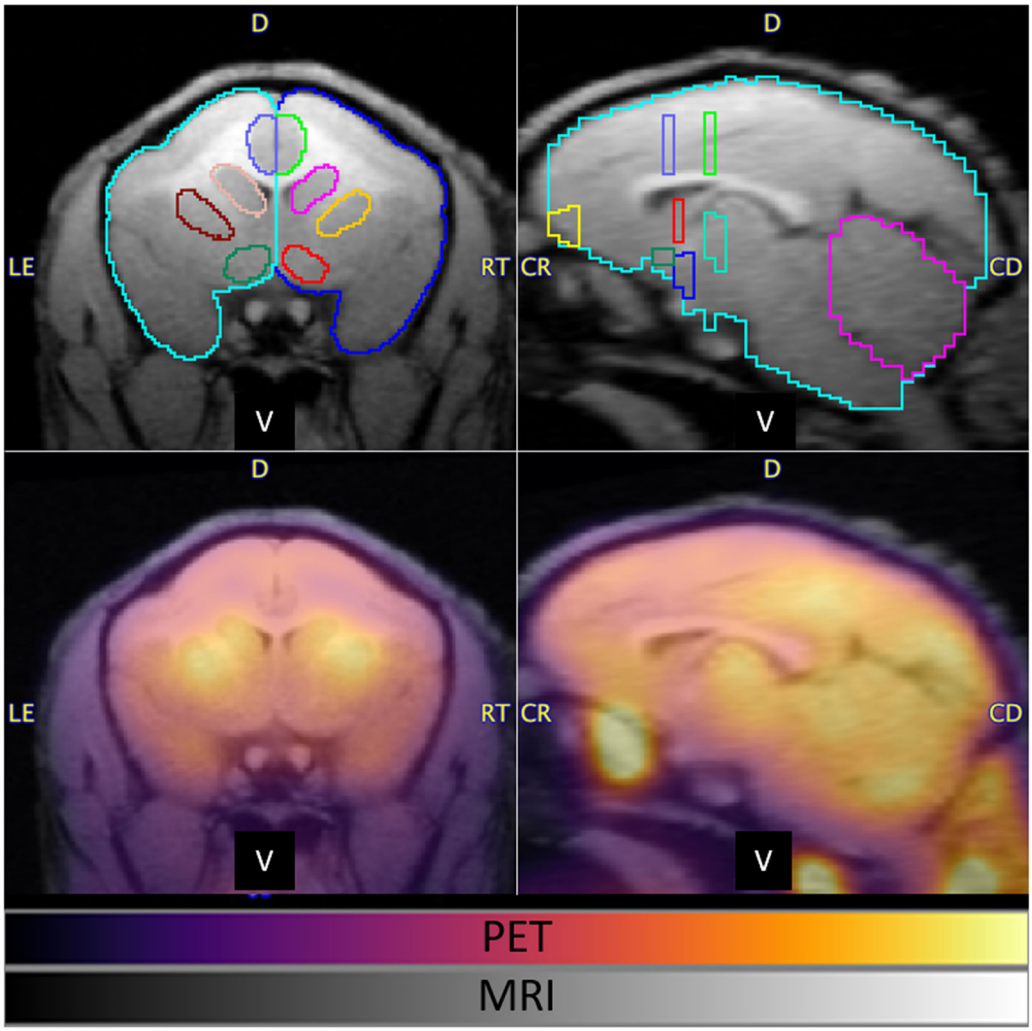

Figure 3:

Scans of a 5.4 y/o titi monkey from the study. Top row: T1-weighted MR image showing the regions of interest analyzed. Bottom row: PET (color) co-registered with MRI (grayscale) showing regional uptake of [18F]FDG. Regions (right and left) represented from top to bottom on coronal section (top left panel) are: ACC, Caudate, Putamen, NAcc. Brain areas left to right sagittal section (top right panel): OFC, NAcc (dark green), ACC (purple), lateral septum (red) and hypothalamus (blue), PCC (green) and thalamus (turquoise), cerebellum. The whole brain hemispheres are delimited in cyan and blue. Note: not all regions of interest are visible on this figure.

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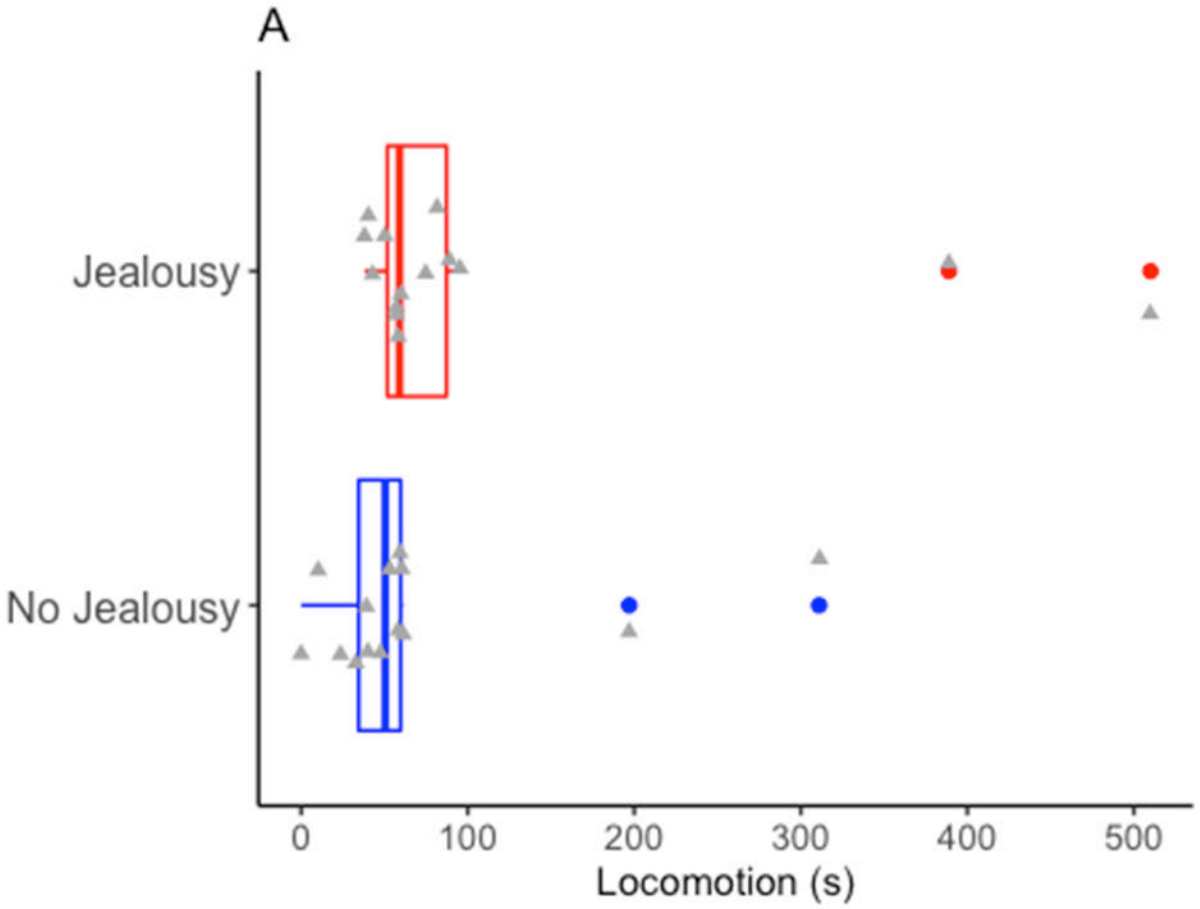

Figure 4:
Locomotion behavior of the 7 females during jelouasy vs non-jealousy scenarios compared. Each data point is represented by a grey triangle. Additionnal filled cirles tag outliers data points. Boxplots were generated with ggplot2 ; the external sides of the box represent the first and third quartiles (the 25th and 75th percentiles) and the middle line represents the median.

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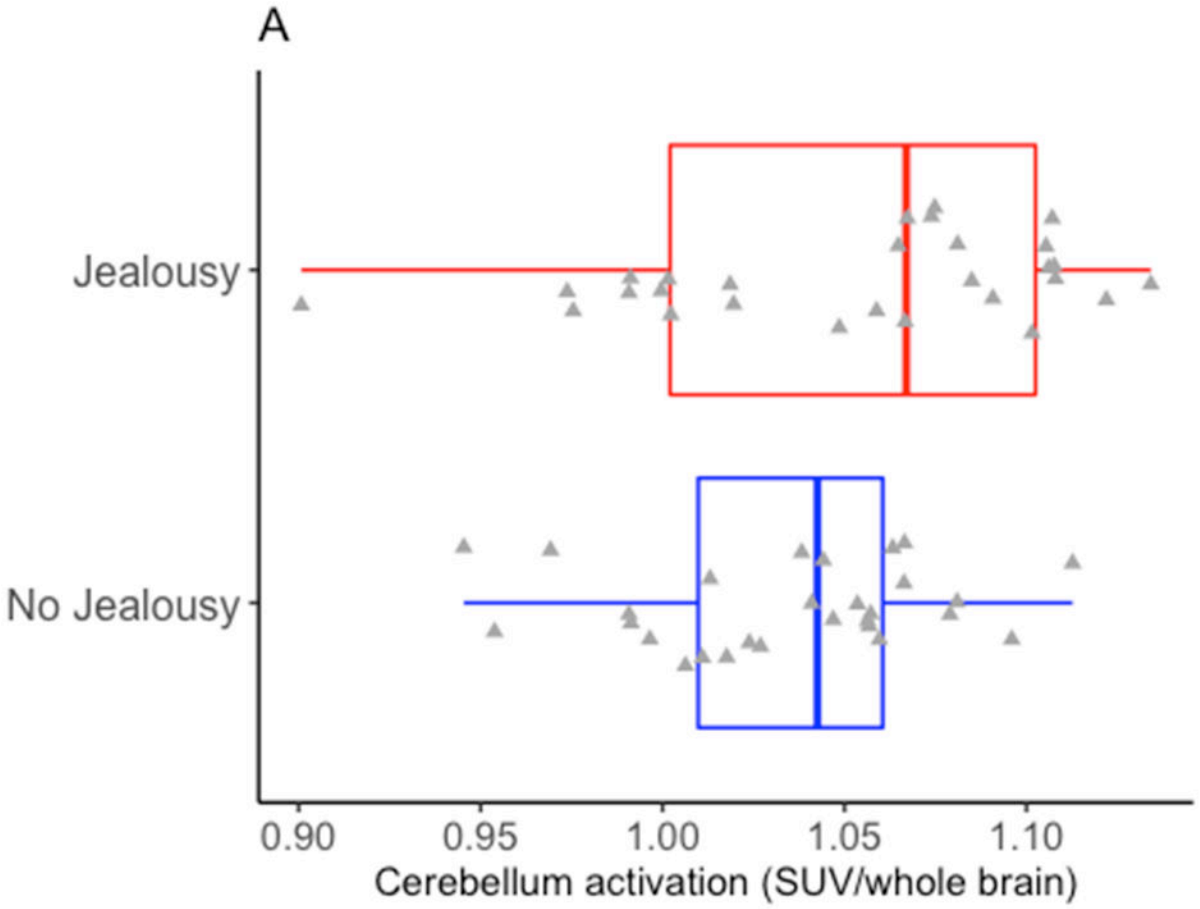

Figure 5:
Cerebellar activity of the 7 females during jelouasy vs non-jealousy scenarios compared. Each data point is represented by a grey triangle. Additionnal filled cirles tag outliers data points. Boxplots were generated with ggplot2 ; the external sides of the box represent the first and third quartiles (the 25th and 75th percentiles) and the middle line represents the median.

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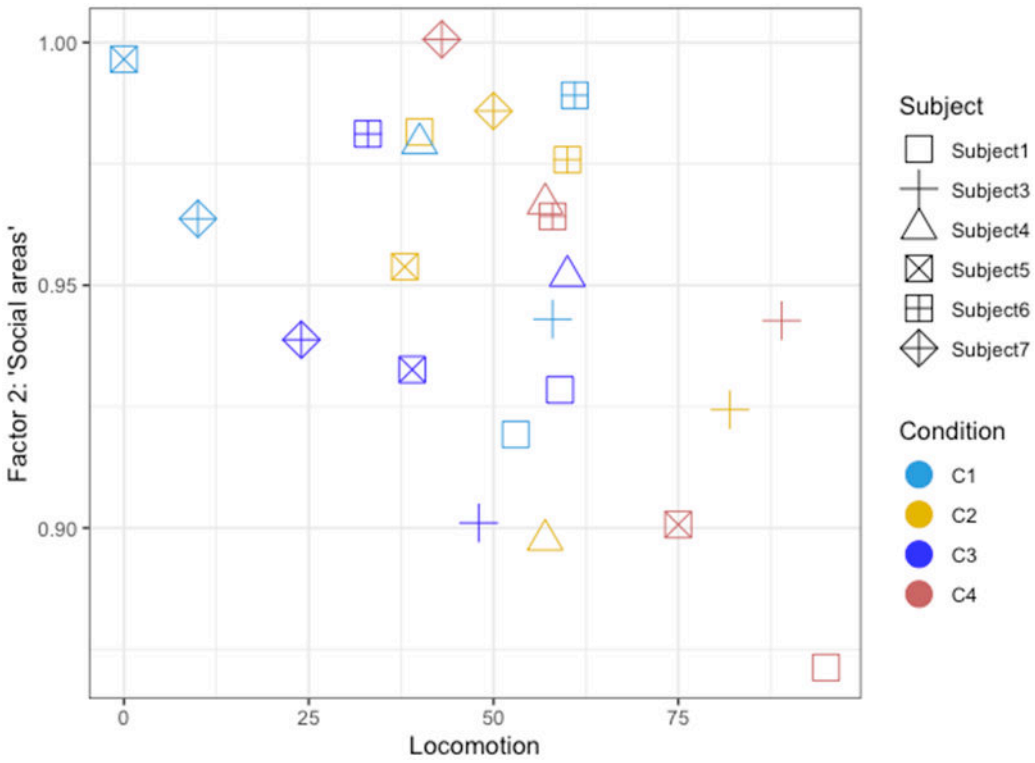

Figure 6:

Relationship between the activation of Brain Group 2 and Locomotion across conditions and accounting for individual effect. Subject 2 is not show here for clarity as her Locomotion scores are much higher than the other individuals (she was still included in the statistical models, See Supplements). See Table 3**, Model 2.1**, for details about the statistical output of the full model.

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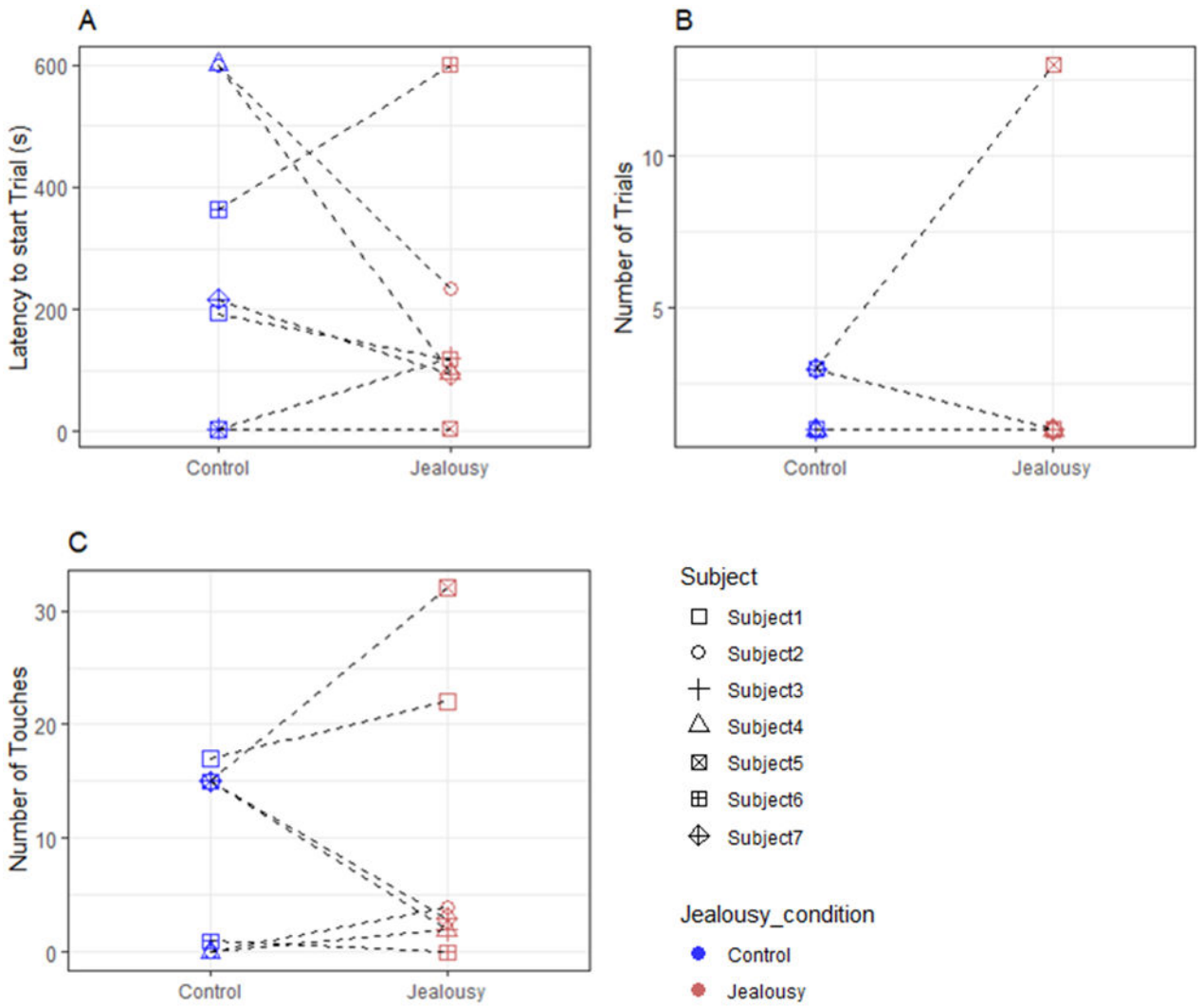

Figure 7:

(A.) Number of trials during the reversal task, (B.) the number of touches during the task (CS+ and CS−) and (C.) the latency to start participating to the reversal task for each of the 7 subjects in control and jealousy conditions with a reversal task (C3 and C4).

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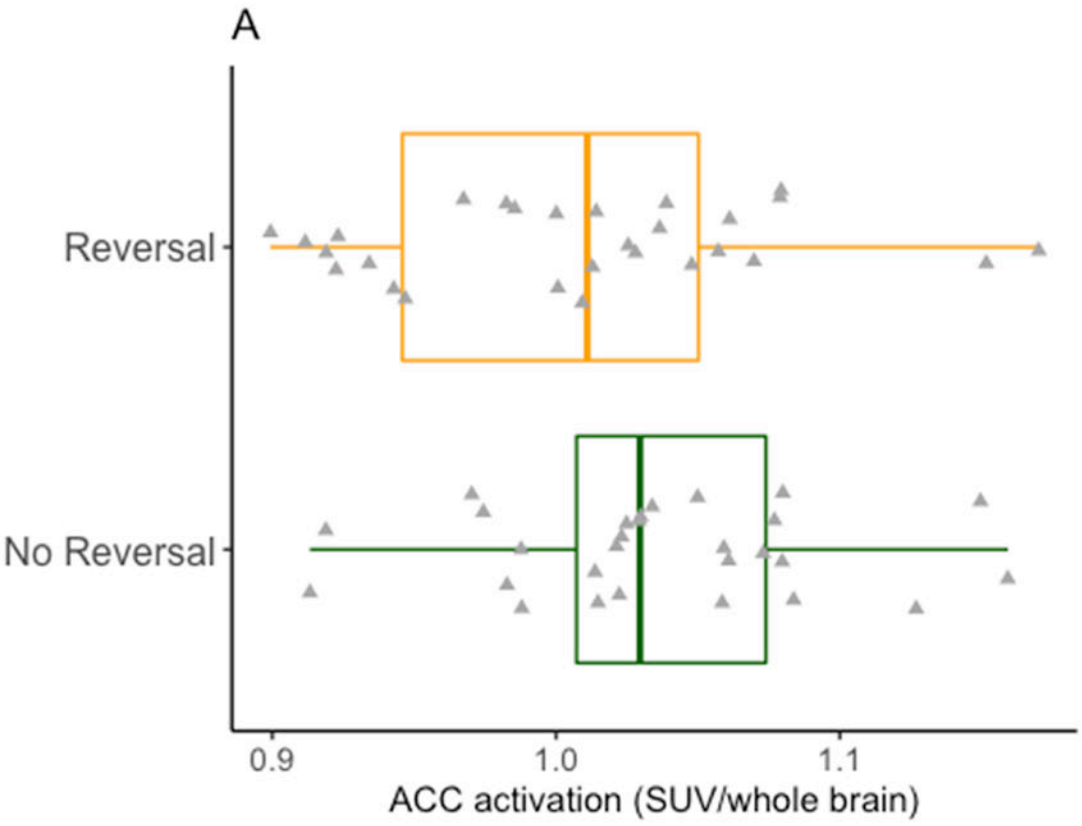

Figure 8:

ACC activity of the 7 females during jelouasy vs non-jealousy scenarios compared. Each data point is represented by a grey triangle. Additionnal filled cirles tag outliers data points. Boxplots were generated with ggplot2 ; the external sides of the box represent the first and third quartiles (the 25th and 75th percentiles) and the middle line represents the median.

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Table 1.

ethogram adapted from Maninger et al. 2017b

Behavior	Definition
Directed gaze	Individual's eyes gaze (or look across) in the direction of the stimulus cage. Duration.
Lip smack	Individual makes rapid lip movement accompanied by smacking sound. Count.
Arch Tail lash	Individual raises dorsal surface of his back and whips his tail back and forth laterally. May be accompanied by piloerection. Arousal behavior. Count.
Locomotion	Individual moves at least one body length. Duration.
Off camera	Individual is out of view of the camera. Duration.

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Table 2:

Comparison of neural, hormonal, and behavioral measures across the four conditions using linear mixed models, with Jealousy or Non-Jealousy (C2 and C4 vs C1 and C3) as a fixed effect and individual identity as a random effect.

Locomotion					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	70.93	44.12	20	1.61	0.12
Jealousy	46.43	17.80	20	2.61	**0.02** *
Directed gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	341.08	35.66	19	9.57	0.00
Jealousy	−18.16	24.89	19	−0.73	0.47
Androgens					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	418.94	51.63	20	8.11	0.00
Jealousy	71.00	45.18	20	1.57	0.13
Cortisol					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	1050.79	100.78	20	10.43	0.00
Jealousy	131.10	123.06	20	1.07	0.30
Brain Group 1					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.03	0.11	216	−0.27	0.78
Non-Jealousy	0.06	0.13	216	0.44	0.66
Brain Group 2					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.01	0.16	216	−0.05	0.96
Non-Jealousy	0.02	0.13	216	0.12	0.90
Brain Group 3					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.00	0.11	160	0.01	0.99
Non-Jealousy	0.00	0.15	160	−0.01	0.99
Brain Group 4					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.08	0.13	160	−0.61	0.54
Non-Jealousy	0.16	0.15	160	1.08	0.28
Cerebellum					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.18	0.30	48	0.62	0.54
Non-Jealousy	−0.37	0.20	48	−1.84	**0.07.**

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Whole Brain

	β	Std. Error	DF	t.value	p.value
(Intercept)	0.00	0.19	48	0.00	1.00
Non-Jealousy	0.00	0.27	48	0.00	1.00

Significant results are indicated with in bold with a * and tendencies with a “.”.

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Table 3:

Summary of the eight linear models to test for the effect of hormones and direct gaze on locomotion (Model 1) and on behaviors and hormones on the Brain Factors (Models 2 to 5). Hormonal and behavioral data were scaled.

Model 1: Locomotion ~ Androgens + Cortisol + Directed_gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.02	0.32	17	−0.05	0.96
Androgens	−0.02	0.14	17	−0.12	0.90
Cortisol	0.02	0.12	17	0.19	0.85
Direct gaze	−0.25	0.15	17	−1.63	0.12
Model 2.1: Group 1 ~ Locomotion + Androgens + Cortisol + Directed_gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.00	0.20	16	0.01	0.99
Locomotion	−0.51	0.23	16	−2.27	**0.04***
Androgens	0.25	0.18	16	1.40	0.18
Cortisol	−0.22	0.17	16	−1.26	0.22
Directed gaze	−0.17	0.22	16	−0.77	0.45
Model 2.2: Group 1 ~ Locomotion:Condition					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.04	0.27	17	−0.16	0.88
Locomotion:C1	−0.80	0.41	17	−1.94	**0.07.**
Locomotion:C2	−0.28	0.35	17	−0.79	0.44
Locomotion:C3	−0.70	0.66	17	−1.06	0.30
Locomotion:C4	−0.31	0.25	17	−1.23	0.24
Model 3.1: Group 2 ~ Locomotion + Androgens + Cortisol + Directed_gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.00	0.15	16	0.00	1.00
Locomotion	−0.72	0.19	16	−3.91	**0.001***
Androgens	0.12	0.15	16	0.81	0.43
Cortisol	−0.10	0.16	16	−0.62	0.55
Directed gaze	−0.02	0.19	16	−0.10	0.92
Model 3.2: Group 2 ~ Locomotion:Condition					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.04	0.16	17	−0.28	0.79
Locomotion:C1	−1.43	0.29	17	−4.87	**0.0001***
Locomotion:C2	−0.80	0.25	17	−3.22	**0.005***
Locomotion:C3	−0.48	0.48	17	−1.00	0.33
Locomotion:C4	−0.31	0.18	17	−1.72	0.10
Model 4: Group 3 ~ Locomotion + Androgens + Cortisol + Directed_gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**

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(Intercept)	−0.02	0.34	16	−0.05	0.96
Locomotion	−0.14	0.27	16	−0.54	0.60
Androgens	0.29	0.19	16	1.55	0.14
Cortisol	−0.06	0.16	16	−0.41	0.69
Directed gaze	0.27	0.22	16	1.23	0.23
Model 5.1: Group 4 ~ Locomotion + Androgens + Cortisol + Directed_gaze					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.00	0.20	16	−0.02	0.98
Locomotion	−0.63	0.23	16	−2.78	**0.01***
Androgens	−0.11	0.18	16	−0.64	0.53
Cortisol	−0.19	0.17	16	−1.13	0.28
Directed gaze	−0.30	0.22	16	−1.38	0.19
Model 5.2: Group 4 ~ Locomotion:Condition					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.06	0.21	17	−0.29	0.77
Locomotion:C1	−0.79	0.37	17	−2.12	**0.05***
Locomotion:C2	−0.84	0.31	17	−2.66	**0.02***
Locomotion:C3	−1.04	0.61	17	−1.71	0.11
Locomotion:C4	−0.20	0.23	17	−0.87	0.40

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Table 4:

Summary of the generalized and linear mixed models on the number of trials during the reversal task, the number of touches during the task (CS+ and CS−) and the latency to start participating to the reversal task.

Number of Trials (Poisson) – GLMM (lme4)				
	Estimate	**Std. Error**	**z.value**	**Pr…z..**
(Intercept)	0.12	0.44	0.28	0.78
Condition C4	0.55	0.38	1.44	0.15
Number of Touches (Poisson) - GLMM (lme4)				
	Estimate	**Std. Error**	**z.value**	**Pr…z..**
(Intercept)	1.57	0.49	3.21	0.00
Condition C4	−0.11	0.19	−0.57	0.57
Latency to start				
	β	**Std Error**	**DF**	**t.value**	**p.value**
(Intercept)	283.29	84.96	6.00	3.33	0.02
Condition C4	−102.00	98.11	6.00	−1.04	0.34

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Table 5:

Comparison of OFC, ACC and Globus Pallidus activation across conditions without (C1 and C2) and with (C3 and C4) reversal test using linear mixed models, with individual identity as a random effect.

OFC					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.00	0.30	48.00	0.02	0.99
Reversal	−0.01	0.20	48.00	−0.05	0.96
ACC					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	0.22	0.32	48.00	0.68	0.50
Reversal	−0.43	0.18	48.00	−2.45	**0.02***
Globus Pallidus					
	β	**Std. Error**	**DF**	**t.value**	**p.value**
(Intercept)	−0.16	0.29	48.00	−0.53	0.60
Reversal	0.32	0.20	48.00	1.55	0.13