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Research report

Sex differences in inhibitory control in socially-housed baboons (*Papio papio*)

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HIGHLIGHTS

- 13 socially-housed baboons performed the Stop-Signal task on touchscreen stations.
- Males had slower response execution, slower response inhibition and were better at the task.
- Female's performance did not vary as a function of menstrual cycle phase (ovulatory/luteal).
- Males maximized reward, females emphasized speed. This pattern of responses may be due to testosterone effects on reward sensitivity in males.

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ABSTRACT

Inhibitory control is an important component of executive function. An emerging literature in humans suggests that inhibitory control is sexually dimorphic and modulated by sex steroids, but evidence for such a link in nonhuman animals is scarce. In this study, we examined the effects of menstrual cycle and biological sex on response inhibition, as measured by a Stop-Signal task, in the baboon (*Papio papio*). The monkeys (n = 13) were socially-housed, with voluntary access to multiple touchscreen computerized stations. The task required monkeys to inhibit prepotent responses (touching a target, "Go" trials) following the appearance of a visual stop signal on 25% of the trials ("Stop" trials). The cognitive data, consisting of computerized records of the monkeys' performance on the Stop-Signal task over a year of testing, were matched to records of female sexual swellings. Same-day menstrual and cognitive data were available for 5 females, aged 5–18 years. These data were compared to those of 8 males (5–14 years old) performing the Stop-Signal task over the same time period. Contrary to our hypothesis, performance on the task was not significantly affected by the phase (ovulatory vs. luteal) of the cycle in females. However, males were slower than females on Go trials and were less efficient in inhibiting responses on Stop trials. Slower responses in males were indicative of a speed-accuracy trade-off, as overall accuracy was also better in males than in females. Analyses of trial history indicated that males did not speed as much as females following a successful Go trial, but did not differ from females in post-error slowing or post-inhibiting responses. Overall, the data show that biological sex modulates Stop-Signal performance in the baboon, with males exhibiting slower response execution overall, less efficient inhibition, but greater accuracy than females. This pattern of sex differences may reflect motivational sex differences in which males emphasize accuracy rather than speed. Interestingly, these sex differences do not seem to vary as a function of ovarian hormones in females. Males' greater focus on accuracy is possibly due to enhanced sensitivity to reward mediated by testosterone levels.

1. Introduction

Executive function encompasses several processes including memory updating (e.g., N-back tasks), task-switching (e.g., Wisconsin Card Sort test, reversal learning), planning (e.g., Tower of Hanoi) and response inhibition (e.g., Stroop task or Stop-Signal task; [1]). In both nonhuman and human primates, the prefrontal cortex (PFC) has been shown to play a unique role in supporting executive function. In particular, neurophysiological studies in macaques have identified neurons in the dorsolateral PFC (DLPFC) that fire during the delay interval in working memory tasks such as the Delayed Response task [2] and neurons in the ventrolateral PFC (VLPFC)

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that contribute to behavioral inhibition in Go/NoGo tasks [3]. Importantly, humans and Japanese macaques have been shown to activate homologous regions of the VLPFC during the performance of set-shifting tasks [4], supporting the idea that nonhuman primates are excellent models for human PFC function [5]. Functional Magnetic Resonance Imaging (fMRI) studies in healthy humans consistently report Blood-Oxygen-Level-Dependent (BOLD) signal increases in PFC when participants are engaged in tasks requiring executive processes [6,7] and have identified a set of regions within the PFC being crucial for inhibitory control, including the dorsal anterior cingulate cortex, the lateral PFC, insula and lateral parietal cortex [8–10].

Growing evidence suggest that estrogens modulate PFC function (see for review [11]). Indeed, several studies in young women have indicated that the menstrual cycle phase affects performance on working memory [12,13] and response inhibition tasks [14]. These findings are echoed by the growing number of neuroimaging studies that report menstrual cycle-dependent patterns of PFC activation in women, even in the absence of behavioral effects [13,15–18]. A role for estrogens in the modulation of PFC function is also supported by findings of improved working memory in premenopausal women with higher levels of estradiol (E2) [19], postmenopausal women on hormonal therapy [20,21] and data showing that hormonal depletion in young women [22,23] and hormonal replacement in postmenopausal women [18,24–26] modulate patterns of PFC activation.

Fewer studies are available in nonhuman primates, but they also point to an effect of estrogens, in particular E2, on several aspects of PFC function. Working memory in nonhuman primates has traditionally been assessed through the Delayed Response (DR) task or Delayed Non Matching or Matching-to-Sample (DNMS or DMS tasks), which require the animals to hold in mind information for a certain duration and compare this information to incoming information. The Delayed Recognition Span Test (DRST) is an attempt to more closely model human working memory (which includes a maintenance and a manipulation component), by requiring monkeys to update working memory via tracking new stimuli at each trial. Performance on the spatial version of the DRST [27], but not on the DMS [27,28], has been shown to be modulated by menstrual cycle phase in female macaques. In young adult ovariectomized (OVX) females, E2 administration seems to have little effect on working memory tasks (spatial or object versions of DRST, DMS and DR) [29,30], except when emotional information is presented [29]. In contrast, in aged OVX macaques, cyclic E2 administration was associated with improved performance on the DR [31] and increased dendritic spine density in area 46 of the DLPFC [32]. Less is known about the effects of estrogens on other aspects of executive function, such as task-switching or response inhibition in nonhuman primates, and findings are also mixed. Performance on a modified Wisconsin Card Sort test, which provides a measure of task switching, was not altered in aged OVX female rhesus monkeys receiving ethinyl E2 or placebo [33]. In contrast, impaired reversal learning, a measure of cognitive flexibility, was found in E2-treated OVX marmosets, relative to middle-aged control monkeys [34]. Finally a recent report found that reversal learning performance was enhanced during the late follicular phase relative to the luteal or early follicular phase in intact female macaques, suggesting that high E2 facilitated acquisition of this PFC-dependent task [28].

There are also reports of sex differences in executive function [35,36]. In the Iowa Gambling task, which requires subjects to identify which of four decks is more advantageous based on feedback received, a male advantage has consistently been found (e.g., [35,37–39]). In contrast, females appear to be advantaged in working memory tasks that emphasize monitoring and updating [40,41]. Other tasks that require inhibitory control such as the Stroop color-word task or the Stop-Signal Task have usually failed to find sex differences in performance (e.g., [42–44]), even though sex differences may be observed in brain activation patterns [43].

To our knowledge, no study has yet investigated the effects of estrogens or biological sex on response inhibition in nonhuman primates. The present study focused on Stop-Signal task performance in a social group of Guinea baboon (*Papio papio*) proficient in using automatic touchscreen stations within their enclosure to freely perform cognitive tasks [45]. This unique set up, which yielded a very high participation and excellent levels of performance, allowed us to collect a large number of trials over a year of testing. To analyze potential menstrual cycle-dependent performance fluctuations among females, the Stop-Signal data were matched, whenever possible, to same-day menstrual phase, as assessed from records of sexual swellings. These data were compared to those of males performing the Stop-Signal task over the same time period.

2. Methods

2.1. Subjects

The participants were 5 females and 8 male Guinea baboons (*Papio papio*) ranging from 5 to 18 years old (mean age female = 7.5 ± 3.9 years; mean age male = 7.6 ± 1.3 years), housed at the CNRS Primate Center in Rousset, France. Five females and 4 males were housed with 15 additional individuals (including other males, females, and their offspring of varying ages) in a 25 m × 30 m outdoor enclosure connected by tunnels to indoor housing (6 m × 4m) used at night. Four other males were housed together in a 4.7 m × 6.4 m outdoor enclosure connected to indoor housing (2 m × 4m). Both groups had visual and auditory contact with each other. Water was provided *ad libitum* within each enclosure. Feeding (fruits, vegetables, and monkey chows) occurred once daily at 5PM. All baboons had free and voluntary access to several computerized test stations (10 stations for the large group and 3 stations for the smaller group). All research adhered to the American Society of Primatologists Principles for the Ethical Treatment of Nonhuman Primates and received approval from the Provence Alpes Côte d'Azur ethics committee for animal experimental research.

2.2. Apparatus

The computerized task was administered via an Automated Learning Devices for Monkeys (ALDM) described in detail elsewhere [45,46]. Briefly, the ALDM consisted in 13 operant conditioning testing stations equipped with 19" touchscreens and food dispensers. A critical feature of ALDM system is that each baboon was automatically identified by a microchip controlling the initiation of the test program depending on the animal identity. Baboons could therefore participate to the task at will, without capture, and on a 24 h basis, within their social group. Grains of dry wheat were delivered as rewards after each correct response.

2.3. Stop-signal task

The Stop-Signal paradigm was based on Logan and Cowan's task of inhibitory control [47]. In this paradigm, subjects are presented with a stimulus that calls for a particular response (touch), and this stimulus may or may not be followed by a Stop signal that calls for termination of this response. The paradigm allows for an assessment of the individual's ability to inhibit a prepotent response and provides an estimate of response inhibition via the Stop-Signal Reaction Time (SSRT). The Stop-Signal task was one of three fill-in tasks that were systematically proposed to the baboons when there were not engaged in other experiments. Although the Stop-Signal