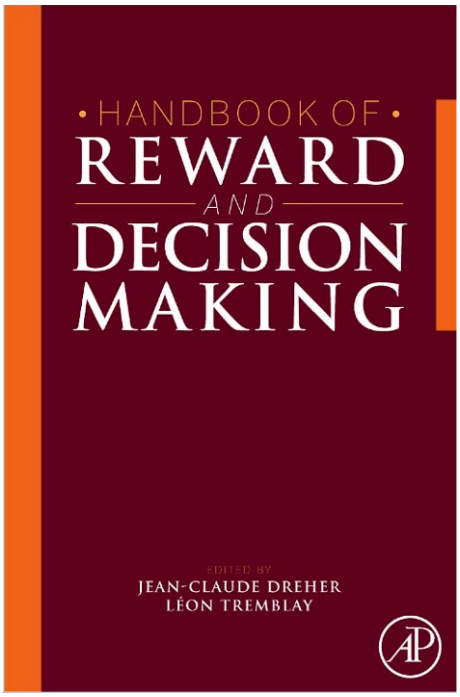

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Part Four

Genetic and Hormonal Influences on the Reward System

14 Gonadal steroid hormones' influence on reward and decision making processes

Xavier Caldú and Jean-Claude Dreher

Reward and Decision Making Group, Cognitive Neuroscience Center, CNRS-Lyon 1 University, 67 Bd Pinel 69675 Bron, France

Abstract

Current research combining endocrinology and functional neuroimaging starts to unveil the neural influences of gonadal steroid hormones on brain and cognition. This chapter focuses on the effects of gonadal steroid hormones on reward processing and decision making, which critically depend on dopaminergic neurotransmission. Evidence from animal and human studies are reviewed that indicate the important roles played by variations of gonadal steroid hormones on a number of cerebral inter-individual differences (e.g., between men and women, between hypogonadal patients and healthy subjects) and intra-individual differences (e.g., differences across phases of the menstrual cycle or at different stages of the lifespan, such as menopause or andropause). Taken together, these studies help to understand the impact of gonadal steroids on vulnerability to drug abuse, neuropsychiatric diseases with differential expression across males and females, and hormonally mediated mood disorders.

Key points

1. Estrogen and progesterone not only influence ovulation and reproductive behavior but also affect cognitive functions, affective state, and vulnerability to drug abuse.
2. The dopaminergic system is sensitive to circulating gonadal steroid hormones in animals and in humans (evidence from behavioral and neuroimaging experiments).
3. Testosterone modulates reward processing and decision making in men and women.
4. Estradiol and progesterone modulate reward processing and decision making (effects of menstrual cycle and pharmacological manipulations).
5. Hormone replacement therapy affects cognitive functions in women with menopause and in elderly men.

Handbook of Reward and Decision Making

14.1 Introduction

Gonadal steroid hormones modulate the activity of several neurotransmission systems, including the dopaminergic system [1–5]. These effects extend beyond the tuberoinfundibular dopaminergic system, involved in the control of the anterior pituitary and important for reproductive behavior, to the mesolimbic and mesocortical dopaminergic systems, relevant for cognitive activities [6–9], affective state [10–12], and reward processing [13].

Receptors for gonadal steroid hormones have been detected in dopaminergic neurons of the ventral tegmental area and the substantia nigra [5,14,15]. Androgen and estrogen receptors are also expressed in target areas of dopaminergic neurons, such as the amygdala and the prefrontal cortex. Dopamine and circulating estrogens and androgens are known to interact in these brain structures [5,16–18]. In other structures, such as the striatum, autoradiography studies have shown that very few neurons, if any, possess nuclear estrogen receptors [4,17,19]. However, gonadal steroid hormones may also affect dopaminergic activity in the striatum through their action on membrane neuronal G-protein-coupled receptors that activate intracellular signaling systems [1,20]. The striatum has received special attention, because it is a key component of the dopamine-dependent reward system.

In the striatum, there are sexually dimorphic actions of estrogens and progestagens that involve both pro- and antidopaminergic effects that depend on the dose and time of estrogen administration and that are manifested in both the nigrostriatal and mesolimbic dopaminergic systems [21]. For example, estrogen and progesterone exert rapid effects on the amphetamine-induced dopamine increase in the striatum [22]. Also, there is an estrous cycle-dependent variation in the amphetamine-induced increase in striatal dopamine, with greater increases during estrous than during other days of the cycle in rats [23]. After ovariectomy, amphetamine-induced striatal dopamine release is attenuated, but dopamine levels can be restored to normal by repeated administration of estrogen treatment. Similar effects on dopaminergic activity in the striatum have been reported following long-term testosterone treatment in male rats [2]. Moreover, gonadal steroid hormones also influence dopaminergic transmission by affecting the activity and expression of dopamine receptors [24–26].

Gonadal steroid hormone receptors can be activated by other compounds, such as neurotransmitters and growth factors [27]. Indeed, dopamine has been shown to activate gonadal steroid hormone receptors. In particular, dopamine D_1 agonists have been found to mimic the effects of progesterone in facilitating sexual behavior in female rats. This facilitatory effect of dopamine is blocked by administration of progesterone receptor antagonists, indicating that dopamine may regulate behavior by means of cross-talk with steroid receptors in the brain [28,29].

Historically, the study of sex differences has been reduced to sexual behavior, its regulation by gonadal steroid hormones, and their effects on the main brain structure considered responsible for this behavior, that is, the hypothalamus [21]. Today, an increasing amount of data from animal and human studies confute this conception and point toward a more ample vision of between-sex differences, including differences in brain anatomy, chemistry, and function [30]. Sex differences extend far beyond mating behavior and reproduction, and beyond the neural circuits that govern them, to reach the domain of cognition. For instance, it is currently accepted that women outperform men in verbal skills and short-term memory, while men outperform women in spatial abilities [4]. Sex differences are due to a combination of genetic and hormonal events that begin early during development. Behavioral sex differences in humans are also cultural and arise from learning. However, in the sphere of cognitive abilities, the differentiation between nature

and nurture becomes less clear. The challenge for researchers is to draw the boundaries between the cultural and biological influences on human behavior and cognition.

One source of biological influence on cognitive performance is gonadal steroid hormones, which, due to their chemical properties, are capable of crossing the blood-brain barrier to exert prominent effects in the brain. Men and women possess the same type of hormones, but their respective amounts are critically different. This has led to the hypothesis that the effects of gonadal steroid hormones, either during early development of the brain or during adulthood, may explain part of the between-sex differences in behavior and cognitive abilities observed in humans. Thus, variations in hormones levels may contribute to the large inter- and intra-individual differences observed during reward processing and decision making [31,32]. Comparing cognitive performance and brain function across or between conditions associated with different levels of gonadal steroid hormones may not only help explain inter-individual differences (e.g., between men and women, between men with different levels of testosterone, or women with different levels of estrogen, etc.) but also intra-individual differences that result from different hormonal status experienced through life (e.g., menstrual cycle, menopause, andropause, etc.).

Since dysfunction of the dopaminergic system seriously impairs reward processing, motivation, and decision making in many neurological and psychiatric disorders (e.g., pathological gambling, drug addiction, schizophrenia, Parkinson's disease), a better understanding of the influences of gonadal steroid hormones on human neural functions would have crucial implications for sex-related differences and menstrual cycle effects on prevalence, course, and treatment response characteristics of neuropsychiatric disorders, as well as on vulnerability to drug abuse. For example, such information could elucidate the mechanism by which women experience greater subjective response to both cocaine [33] and amphetamine [34] during the follicular phase of the menstrual cycle as compared with the luteal phase, and by which women with schizophrenia have later disease onset and less severe course of illness than men [35]. These clinical observations provide evidence that neurosteroids modulate the dopaminergic system in women, but they leave open the question of gonadal steroid hormone modulation on the human reward and decision-making neural circuitry.

14.2 Effects of testosterone on cognitive capacities

The testes secrete several male gonadal steroid hormones, including testosterone, dihydrotestosterone, and androstenedione. Of those, testosterone is the most abundant [36]. Besides its androgenic and anabolic effects, testosterone also exerts influence on brain development and functioning, thereby influencing behavior and cognition. In animals, testosterone increases aggressive behavior [37,38]. However, in humans this effect is more controversial and the effects of testosterone on aggressive behavior appear to be positive, but weak [39–43]. It has been suggested that testosterone is related to dominance in humans, that is, the enhancement of one's status over other people's, which does not necessarily involve aggression [37,39,44,45]. The effects of testosterone on aggressive behavior could be mediated by its fear-reducing properties [46,47] and its relation to selective attention to threat [48]. In females, testosterone induces faster responses to angry faces [49] and enhances the responsiveness of the neural circuits of social aggression, which include the amygdala and the hypothalamus [50].

The higher level of performance shown by men compared to women in some cognitive tasks raises the possibility that testosterone might be involved in the development and

maintenance of some cognitive abilities. Perhaps the most studied of these male-advantageous abilities are spatial abilities. A positive relationship between testosterone levels and performance has been reported in tasks that engage spatial abilities [51–54]. Other studies have assessed the activational effects of testosterone by directly manipulating its physiological concentrations. Current data suggest that the relationship between testosterone levels and spatial abilities may follow a nonlinear, inverted U-shaped function [4,55,56]. Thus, higher adult concentrations of testosterone would be associated with better spatial abilities in males, but only to a certain limit. Yet, beyond an optimum concentration, testosterone may diminish spatial abilities. In women, a single administration of testosterone also increases spatial abilities [57,58]. Another approach to study the effects of testosterone is based on biorhythms in testosterone secretion, since testosterone levels are higher in the morning than in the evening in men [59–61].

14.2.1 Effects of testosterone on reward processing and decision making

Animal studies. The affective rewarding properties of testosterone and its metabolites have been demonstrated in animal studies by using the conditioned place preference paradigm [62–65]. This paradigm allows inferring the rewarding properties of a drug by the observed tendency of the animal to approach an originally neutral environmental stimulus that has been paired with the positive affective consequences of drug administration. Further proof of the rewarding effects of a drug can be derived from the extent to which an animal self-administers it. Studies in rodents demonstrate that both males and females self-administer testosterone [66–68]. Two sites where testosterone and its metabolites exert their rewarding effects are the nucleus accumbens and the intramedial preoptic area of the hypothalamus [63,69,70]. As happens with other rewarding drugs, such as amphetamine [71] and morphine [72], dopamine release mediates the rewarding effects of testosterone, with both D_1 and D_2 receptors playing an important role [73].

Human neuroimaging studies. Recently, functional neuroimaging techniques have been used to explore the effects of gonadal steroid hormones on brain activity related to cognitive functioning, including the processing of different types of rewarding stimuli. In a positron emission tomography (PET) study carried out in hypogonadal and eugonadal control men, Redouté and colleagues [74] found differences in brain activation while processing sexual stimuli. The right orbitofrontal cortex, the insula, and the claustrum showed higher responses in untreated patients compared with controls and when they were compared to themselves after receiving hormonal replacement therapy (HRT). The left inferior frontal gyrus also showed a differential response, but in this structure a deactivation was observed in controls and in patients after treatment. The fact that the activity observed in these brain regions is modulated by testosterone levels supports the view that their activation or deactivation is related to sexual arousal and not merely to a state of general motivational arousal. The activation of the orbitofrontal cortex, a component of the reward system, may be interpreted as the neural correlate of an appraisal process through which visual stimuli are categorized as sexual incentives. The testosterone dependency of the activation of this structure suggests that testosterone may increase the motivational salience or subjective value of these stimuli.

In healthy men, processing of visual sexual stimuli has also been found to elicit activation in several structures of the reward system, such as the orbitofrontal cortex, the striatum, and the amygdala [75,76]. Also, differences and similarities between men and women in the response to visual sexual stimuli have been reported using functional magnetic resonance imaging (fMRI). Hamann and colleagues [76] found similar patterns

of activation in men and women with passive viewing of sexual stimuli, including common activation of the ventral striatum. However, differences were found in the activation of the amygdala and hypothalamus bilaterally, with men displaying greater activity. According to the authors, the amygdala mediates sex differences in responsiveness to appetitive and biologically salient stimuli, and could also mediate the greater role of visual stimuli observed in males. In order to disentangle whether activation of reward structures was driven specifically by the pleasantness of the stimulus or by its salience, Sabatinelli and colleagues [77] compared viewing of pleasant erotic and romantic couples with viewing of equally arousing unpleasant and neutral pictures. They observed an increased activation in the nucleus accumbens and the medial prefrontal cortex related to the visualization of pleasant images, while viewing of equally salient unpleasant or neutral pictures did not produce such an increase. Thus, these data suggest that these brain structures are reactive to the rewarding properties of stimuli and not to their salience [77].

In a recent fMRI study comparing monetary (secondary rewards) and erotic stimuli (primary rewards) in healthy young heterosexual men, we observed, for both types of reward, a common brain network composed of the striatum, the anterior cingulate cortex, the midbrain, and the anterior insula. In addition, we also found an anteroposterior dissociation in the lateral orbitofrontal cortex, monetary gains being specifically represented in the anterior part of the orbitofrontal cortex, while erotic pictures eliciting activation in its posterior part. This result indicates a new functional division within the orbitofrontal cortex, with more recent cortical circuits supporting symbolic representation of goods and evolutionarily more ancient orbitofrontal regions representing subjective value relative to primary rewards. Moreover, the amygdala was more activated for erotic rewards than for monetary gains [78] (see also Chapter 6).

Behavioral studies

Sex differences have been observed in different aspects of reward processing and decision making. The delay-discounting paradigm measures choice behavior when people are presented with a choice between a small immediate reward and a larger delayed reward. Delay discounting provides an account for impulsivity, which is a core deficit in several neuropsychiatric conditions such as attention deficit hyperactivity disorder or addiction. A delay-discounting factor can be estimated by making subjects choose between variable amounts of any reward delivered immediately and a variably higher amount of this reward delivered after a variable delay. In such a task, men show higher delay discounting rates than women for monetary rewards [79,80]. In other words, men devaluate rewards faster as the delay to the reception of reward increases, which leads them to choose more frequently low immediate over higher delayed rewards. These findings are interesting when considering the higher prevalence observed in men of a number of neuropsychiatric illnesses characterized by increased impulsivity [81–84]. Nonetheless, between-sex differences in decision making depend upon the specific paradigm that is tested. For example, Reavis and Overman [85] found that men performed better than women in the Iowa Gambling Task [85]. In this classic task, participants have to repeatedly choose cards from four decks with the goal of maximizing their earnings. Two disadvantageous decks provide immediate large rewards but also substantial money losses. The other two decks are advantageous, since reward is modest but consistent and punishment is low. Thus, consistent choice of cards from the advantageous decks will result in low short-term but high long-term gains, whereas consistent choice of cards from the disadvantageous decks will result in a long-term loss of

money. This task has been used in numerous neuropsychological studies showing impaired decision making after orbitofrontal cortex damage [86,87] (see also Chapter 13). The crucial importance of the integrity of the orbitofrontal cortex in decision making is further demonstrated by a number of gambling tasks involving choices between options that differ in terms of size and probabilities of their associated punishments and rewards [88–90].

A direct influence of testosterone on the development and on the decision-making function of the orbitofrontal cortex is demonstrated by a number of animal and human studies. For example, a surge in perinatal testosterone causes the orbitofrontal cortex to mature faster in male monkeys than in females, which is accompanied by better performance in an object reversal task. Also, early-life androgenized female monkeys perform similarly to normal males and better than normal females [91,92]. In adult humans, testosterone levels negatively influence decision making in both men and women [85,93], and an inverted U-shaped relationship has been found between delay discounting of gains and salivary testosterone levels in men [94]. Whether these effects derive from an increased sensitivity to gains, a lower sensitivity to punishment, or a lower sensitivity to future consequences remains unclear.

14.2.2 Testosterone effects on economic decision making

Little is known about the role of testosterone during economic decision making. However, a recent study demonstrates the involvement of testosterone on a decision-making task engaging players in the ultimatum game [95]. In this game, one player (the "proposer") makes an offer to a second player (the "responder") on how to share a certain sum of money. The word "ultimatum" reflects the non-negotiability of the offer, so the only options for the responder are to accept or reject it. If the responder agrees, the sum is divided as proposed. If there is no agreement, none of the players receives any money. The standard economic solution for the game is for the proposer to offer the smallest amount of money possible and for the responder to accept any offer, on the basis that any monetary amount is better than none. However, extensive behavioral data show that responders tend to accept offers that are considered fair (i.e., those splitting the amount around 50%) and that the rate of rejection increases as offers become unfair [96]. Burnham [95] found that men with higher levels of testosterone rejected more low offers than men with lower levels of testosterone. Furthermore, low second to fourth digit ratio, which has been suggested as a marker of high prenatal testosterone exposure [97,98], is associated with higher discount rates and more rejection of unfair offers in men, although this effect seems to be modulated by contextual cues, such as the status position of the responder or the presence of sex-related cues [99,100]. One possible explanation of this effect may relate to the role of testosterone in dominance. Low offers may be interpreted by responders as a challenge and the acceptance of the offers as harmful for their reputation. In the face of such a threat, men with higher levels of testosterone are more prone to react in a way that preserves their reputation and reasserts their dominance, even if this involves an economic cost.

Another behavioral study measured endogenous steroids in male traders under real working conditions [101]. Traders' morning testosterone levels predicted the profitability during the day, and traders' cortisol raised with both the variance of their trading results and the volatility of the market. These data indicate that higher testosterone may contribute to economic return, whereas cortisol is increased by risk. One drawback of this study is that sampling was done over only 8 days and was performed during a period of low volatility. This study suggests that if acutely raised steroids were to persist for several weeks or even increase as volatility rises, they might have cognitive and behavioral consequences, specifically by shifting risk preferences or disturbing the neural basis for rational choice.

The effect of incidental cues on decision making may be mediated, at least in part, by the activation of the nucleus accumbens. Activation of the nucleus accumbens has been found to predict shifts to high-risk options in an investment task [102]. Moreover, activation of the nucleus accumbens has been observed during anticipation of diverse types of rewards [76,77,103,104], so it may be considered as a neural marker of the positive arousal induced by these rewards [105]. Recent fMRI data indicate that viewing erotic stimuli influences risk taking in healthy young men, partially through the activation of the nucleus accumbens [105]. At a behavioral level, presentation of erotic pictures before decision making increased self-reported positive arousal and subsequent high-risk choices and shifts to the high-risk options. At a functional level, presentation of these erotic stimuli increased activity of several brain structures, including the mesial prefrontal cortex and subcortical regions such as the nucleus accumbens and the putamen. The nucleus accumbens activation partially mediated the influence of positive stimuli on shifts to the high-risk option. These results point toward the neural mechanisms through which anticipatory affect induced by incidental, irrelevant stimuli influence decision making.

14.3 Effects of estradiol and progesterone on cognitive capacities

Estrogens and progestagens are the two main gonadal steroid hormones in women. The most important of the estrogens is estradiol, whose functions include causing cellular proliferation and growth of the tissues of the sex organs and of other tissues related to reproduction, as well as development of secondary sexual traits in females. The main progestagen is progesterone, which is secreted by cells from the corpus luteum, which develops from an ovarian follicle during the luteal phase of the menstrual cycle. The corpus luteum is essential for preparing the uterus for ovum implantation and for maintaining pregnancy [36].

One of the prime site mediators of estrogen's effects on cognition in general, and decision making in particular, may be the prefrontal cortex, as revealed by an early PET study in young women under pharmacological ovarian suppression [106], by comparison between menopausal women with and without hormone replacement therapy [107,108], and by the fact that ovarian steroids are potent regulators of dopaminergic innervation to the prefrontal cortex. Ovariectomy reduces, and subsequent estrogen and progesterone replacement restores, the density of axons immunoreactive for tyrosine hydroxylase in monkey dorsolateral prefrontal cortex [8]. Estradiol treatment, which is associated with changes in dorsolateral prefrontal cortex structural plasticity, also reverses age-related impairment in prefrontal cognitive function in ovariectomized monkeys [109].

In women, the levels of estradiol and progesterone fluctuate through the menstrual cycle. Roughly, the first 14 days correspond to the follicular phase and are characterized by constant low levels of progesterone and a sudden increase of estradiol to reach a peak just before ovulation and decrease again to the initial levels. The next 14 days correspond to the luteal phase. Estradiol levels finish their fall at the beginning of this period and then gradually increase until the midluteal phase, when they start to gradually drop to start a new cycle. During the luteal phase, progesterone levels follow a similar fluctuation to estradiol levels, but always at lower quantities [4,110].

There is evidence in animals and humans that the menstrual cycle effects extend beyond those merely related to reproduction. The menstrual cycle phases influence spatial and verbal cognitive abilities [111–113], attention [114], mood [115], and vulnerability to drugs of abuse [34].

14.3.1 Menstrual cycle effects on reward processing and decision making

Animal and human studies have demonstrated the influences of menstrual cycle and of gonadal hormone levels on the psychological effects of stimulants. In rodents, females are more sensitive to these drugs than males, and estradiol seems to be involved in these sex differences [116], enhancing the effects of these stimulants and drug-seeking behavior [3]. There is also evidence for such an effect in humans. In women, the subjective positive response to stimulants is greater during the follicular phase, when estradiol levels are moderate and progesterone levels are minimal, than in the luteal phase, when both estrogen and progesterone levels are relatively high [33,34]. The rewarding properties of estrogen may involve actions at estrogen receptors in the nucleus accumbens [117,118]. In contrast, progesterone has been found to attenuate the subjective effects of stimulants in women [116,119].

We have recently identified, for the first time in humans, the effects of the menstrual cycle phases on the reward system [13]. Using fMRI, healthy young women were scanned during the midfollicular and luteal phases of their menstrual cycle while they performed a monetary reward task that distinguished the neural concomitants of anticipating uncertain rewards from those of reward outcome. In the midfollicular phase, women showed higher activation in the orbitofrontal cortex and the amygdala during anticipation of uncertain rewards, relative to the luteal phase (Fig. 14.1). At the time of reward delivery,

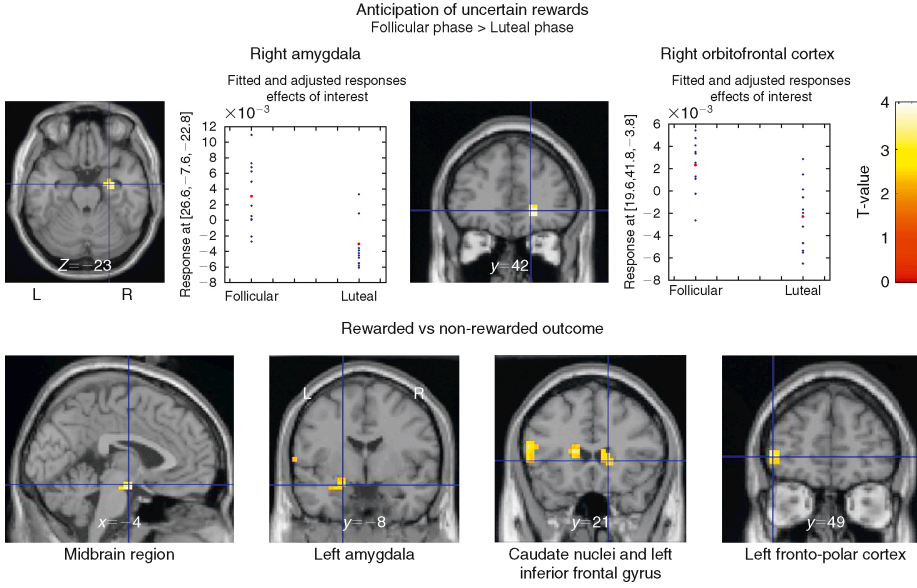

Figure 14.1 Cross-menstrual cycle phase differences in blood oxygen level-dependent (BOLD) response during reward anticipation and at the time of reward delivery. *Top*. During reward anticipation, higher BOLD responses were observed in the follicular phase than in the luteal phase in the right amygdala and orbitofrontal cortex. To the right of each map are shown distributions of BOLD signal response for each woman. *Bottom*. Cross-menstrual cycle phase differences in BOLD response at the time of reward outcome. Greater BOLD response during the follicular phase than during the luteal phase in midbrain, left amygdala, heads of the caudate nuclei, left inferior frontal gyrus, and left fronto-polar cortex [13]. See Plate 17 of Color Plate section.

higher activation was observed in midbrain, striatum, and frontopolar cortex during the follicular phase compared to the luteal phase. These data demonstrate that reactivity of the reward system is heightened in women during the midfollicular phase of the menstrual cycle, when estrogen is unopposed by progesterone. Furthermore, women were compared with a group of men matched for age and level of education. In men, a more robust blood oxygen level-dependent (BOLD) response was observed in the ventral putamen than in women during anticipation of uncertain rewards, whereas women showed stronger activation of the anterior medial prefrontal cortex during reward delivery (Fig. 14.2). Previous neuroimaging studies of reward that grouped men and women together proposed different functions for the ventral striatum and the anterior medial prefrontal cortex, linking the former to reward anticipation and the latter to the time of reward outcome [103]. Extending these reports to anticipation of rewards with maximal uncertainty, we recently found robust ventral striatum activation in a large group of subjects that included both men and women (scanned without monitoring their menstrual cycle) [13]. Our data suggest that these findings may, in part, be driven by sex-specific differences, with men showing higher ventral striatal activity and women exhibiting higher anterior medial prefrontal cortex activity. Thus, reward studies must consider

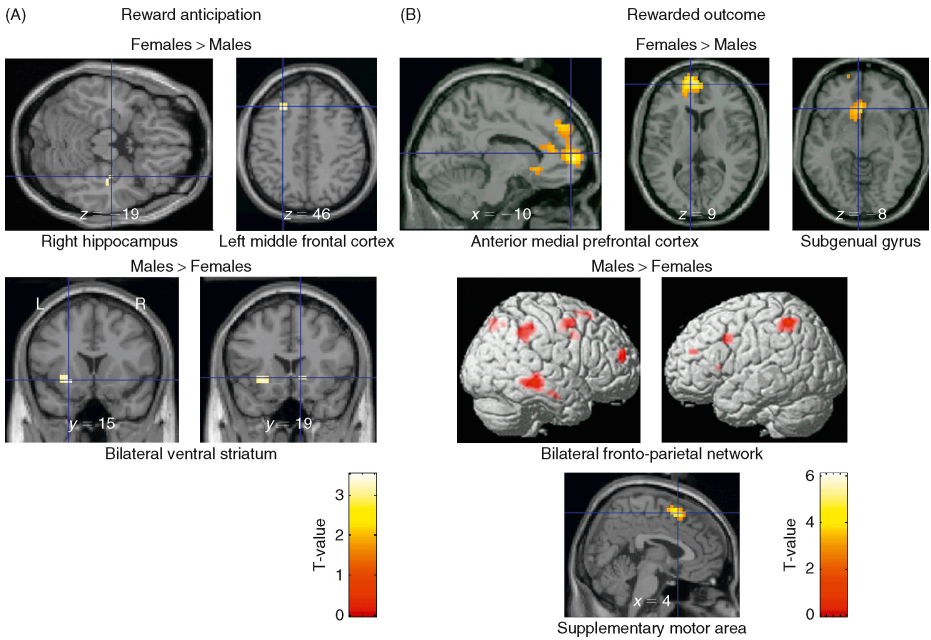

Figure 14.2 Between-sex differences in brain activity during reward anticipation and at the time of reward delivery. (A) During anticipation of uncertain rewards. Statistical maps showing greater right hippocampal and left middle frontal gyrus activity in women than in men, whereas men showed greater activation in bilateral ventral striatum. (B) At the time of reward delivery. Women showed more activation in anterior medial prefrontal cortex and subgenual gyrus compared with men, who, in turn, showed more activation in a bilateral fronto-parietal network, the right inferior temporal cortex, and the supplementary motor area [13].

both sex differences and gonadal steroid actions at the time of testing. Our findings extend to humans the previous observations in animals that the actions of estrogen and progesterone on midbrain dopaminergic projections to the striatum are sexually dimorphic and involve both prodopaminergic and antidopaminergic effects [23].

Finally, brain activity was correlated with gonadal steroid levels, and a positive correlation between activity in the amygdalo-hippocampal complex and estradiol levels was observed regardless of menstrual cycle phase. These results indicate that ovarian steroids modulate reward-evoked neural activity. This modulation may underlie differences observed between sexes and between different phases of the menstrual cycle in women, such as the greater subjective response to addictive drugs observed in women, especially during the follicular phase. The increased reactivity of the reward system during the follicular phase is meaningful also from an evolutionary perspective, since it may underlie the increased availability, receptivity, and desire during the ovulatory period that are thought to facilitate procreation.

Functional neuroimaging studies have also revealed changes in brain activation related to menstrual cycle phase, not only during processing rewarding stimuli but also during processing negative stimuli. In the anterior medial orbitofrontal cortex, activity increases premenstrually and decreases postmenstrually, whereas the lateral orbitofrontal cortex displays the opposite pattern [120]. Moreover, during the follicular phase, a set of areas involved in the response to stress, including the amygdala, the orbitofrontal cortex, and the anterior cingulate gyrus, are more responsive to negative, high arousing stimuli [121]. Although there is more evidence of estradiol modulation on motivational and emotional processes, recent neuroimaging studies also indicate a role for progesterone. For example, the neuroactive metabolite of progesterone, allopregnanolone, modulates memory for faces by influencing amygdala activity [122,123].

Behaviorally, some studies have investigated the menstrual cycle influence on women's social preferences and decision making. For example, women's preference for secondary sexual traits in male faces varies during the menstrual cycle, with women preferring more masculine traits during the follicular phase, when conception is more likely [124–126]. On the other hand, during the midluteal phase, women display higher attraction for apparent health and self-resemblance [126,127]. A woman's preference for testosterone markers on male faces may be influenced by her estrogen/progesterone ratio [128], although recent data suggest that this effect seems to be mediated by progesterone rather than estrogen levels [126,127], and even a role for female testosterone levels has been suggested [129]. Interestingly, similar effects have been reported for voice pitch [130], male odor [131], and male social behavioral displays [132].

These cyclical changes in male trait preferences are meaningful from an evolutionary perspective. More masculine traits are thought to reflect higher resilience to infectious disease but also unwillingness to invest in partners and offspring [128,133]. Thus, these shifts in preferences may represent adaptive trade-offs in mate choice. During ovulation, when chances of conception are high, women may increase their attraction toward men displaying more resistant features and cues to heritable immunity to infectious diseases, so that these positive characteristics may be inherited by the offspring. However, when women's hormonal profile is similar to that during pregnancy or when the body is preparing for pregnancy (e.g., during the luteal phase of the menstrual cycle), women may show stronger preferences for features that might be beneficial at this time, such as social and material support [134].

Some facial cues (e.g., squarer jaws, smaller pupil-to-brow distance) may be interpreted as signaling social dominance (i.e., enhancing one's status and control of resources over

conspecifics) and have been suggested to be indicators of a man's potential to achieve a high status [135]. Senior and colleagues studied whether variations in preferences for male traits due to menstrual cycle phases led to differences in decision making [136]. Women participated in a mock job scenario in which they had to assign minimum-, low-, high-, or maximum- status resources to several men previously rated to look either dominant or non-dominant. Women assigned resources of high status to dominant-looking men and resources of low status to non-dominant-looking men. Further analyses showed that during the follicular phase, more high-status resources were allocated to dominant-looking men than to non-dominant-looking men. Thus, the bias due to cyclic hormonal profiles observed in women toward male features that signal phenotypic and genotypic superiority has behavioral effects when making decisions.

Evolutionary psychology proposes that humans have evolved to perceive as attractive those characteristics that are displayed by healthy individuals [128]. These features of what are considered beautiful faces are important biological signals of mate value that motivate behavior in others. Functional neuroimaging studies have demonstrated that viewing beautiful faces activates components of the reward system, such as the ventral striatum and the orbitofrontal cortex, also engaged for different types of rewards, such as drugs and money [137–139]. A classic fMRI study provides an interesting finding for brain processing of facial attractiveness [138]. In this study, subjects were scanned while viewing unfamiliar faces, whose attractiveness they were asked to rate at the end of the session. Strikingly, no region in the brain showed any activation in response to facial attractiveness *per se*. These results led the authors to investigate a possible effect of gaze direction on brain activation related to the processing of facial attractiveness. Interestingly, perceived attractiveness was related to increased activity in the ventral striatum when the eye gaze of the observed person met the eyes of the observer, while when eye gaze was directed away, activity in this region decreased. Thus, the striatum is involved not only in the processing of basic reinforcing stimuli (e.g., food) but also in the evaluation of stimuli with relevance for social interaction. Moreover, the pattern of striatal activity observed in this study is concordant with prediction error signal coding (see Chapters 2 and 6). A returned eye gaze from an attractive face may be considered a better outcome than expected, leading to an increased response. On the other hand, failing to establish eye contact with an attractive face is a disappointing outcome, which leads to reduced striatal activity [138]. In summary, these results suggest that the modulation of the activity of women's reward system by gonadal steroid hormones may also underlie variations similar to those observed regarding other types of motivated behavior.

14.3.2 Dissociating the roles of estrogen and progesterone on reward processing

In our fMRI study mentioned above [13], we scanned women twice, once during the midfollicular phase and once during the luteal phase. However, because both estradiol and progesterone are simultaneously present during the luteal phase, it was not possible to pinpoint the specific effects of estradiol and progesterone on the reward system. This led us to investigate the influence of estradiol and progesterone independently, using fMRI during reward processing in conjunction with an incisive hormonal manipulation paradigm that pharmacologically induces temporary hypogonadism and replaces estrogen and progesterone separately [140]. The temporary hypogonadism was induced by the gonadotropin-releasing harmone (GnRH) agonist Leuprolide Acetate or Lupron. Lupron is used

clinically when suppression and/or control of gonadal steroid secretion is the goal, such as in infertility in women and prostate cancer in men. After the second to fourth week of lupron administration, there is a down-regulation of GnRH receptors and an inhibition of pituitary release of gonadotropins, resulting in postmenopausal levels of endogenous gonadal steroid hormones. Young, healthy, regularly-menstruating women, who received no hormonal medication within the preceding 6 months, were scanned during three pharmacologically-controlled hormonal conditions spanning 6 months: ovarian suppression induced by the GnRH agonist, depot leuprolide acetate (Lupron), Lupron plus estradiol replacement, and Lupron plus progesterone replacement. Estradiol and progesterone were administered in a double-blind cross-over design, allowing us to disentangle their respective effects on the activation of the reward system. On each occasion, event-related 3T fMRI scans were performed during presentation of images of slot machines that varied reward probability. Our findings show that different components of the reward system are differentially modulated by temporary menopause induced by Lupron, estradiol replacement, and progesterone replacement. More specifically, during reward anticipation, the ventral striatum activity was more robust in the progesterone replacement condition as compared to the ovarian suppression, while the right amygdalo-hippocampal complex was more robustly activated in the estradiol replacement condition as compared to the ovarian suppression condition. This result is consistent with our previous menstrual cycle findings showing increased amygdalo-hippocampal activity during reward anticipation in the follicular phase, when estradiol is unopposed by progesterone. Taken together, these data demonstrate that different components of the reward system were modulated by temporary hypogonadism, estradiol alone, and progesterone alone.

As mentioned previously, estrogen is also present in males, although in lower quantities than in females, and its effects on males brain and behavior have not been so extensively studied. Recent findings in mice demonstrated that estrogen receptors mediate the facilitatory effects of female cues on male risk taking. Exposure of wild-type male mice to the odor of a novel female mouse enhanced risk taking and reduced avoidance to cat odor. Mice knocked out for either the α or the β estrogen receptors failed to display such a behavior [141]. Since sex-related cues have a parallel effect on decision making and risk taking in human males, who make poorer and riskier decisions in the presence of females or their cues [99,142,143], these results suggest that estrogen receptors may also modulate these behaviors in humans [141].

Dopaminergic dysfunction in aging

Healthy aging is associated with a number of neuroanatomical and neurobiological alterations that result in progressive decline in several cognitive functions dependent upon prefrontal cortex and/or hippocampus, such as working memory and verbal memory, as well as episodic memory, task switching, and processing speed [144–149]. The dopaminergic system is also subject to change during aging. In the striatum, a number of studies have shown an age-related decline of D_2-like receptors, which could be related to a decline in motor and cognitive abilities such as speed of processing and episodic memory [150]. Additionally, Kaasinen and colleagues have shown an extra-striatal decrease of D_2 and D_3 receptors, most pronounced in the prefrontal cortex and anterior cingulate cortex compared to temporal and thalamic regions [151]. However, very little is known about the functional consequences on brain activity of the age-related dopamine decline, because most of the studies on dopamine neurons and receptors have been done post-mortem.

To address this question, we have recently used a multimodal neuroimaging approach, combining 6-[(18)F]FluoroDOPA PET and event-related 3T fMRI in the same subjects. We showed that healthy aging induces functional alterations in the reward system [152]. More precisely, we directly demonstrated a link between midbrain dopamine synthesis and reward-related prefrontal activity in humans, showed that healthy aging induces functional alterations in the reward system (Fig. 14.3), and identified an age-related change in the direction of the relationship (from a positive to a negative correlation) between midbrain dopamine synthesis and prefrontal activity (Fig. 14.4). Our findings provide an important characterization of the interactions between midbrain dopamine function and the reward system in healthy young humans and older subjects, and identify the changes in this regulatory circuit that accompany aging. These results indicate an age-dependent dopaminergic tuning mechanism for cortical reward processing [152].

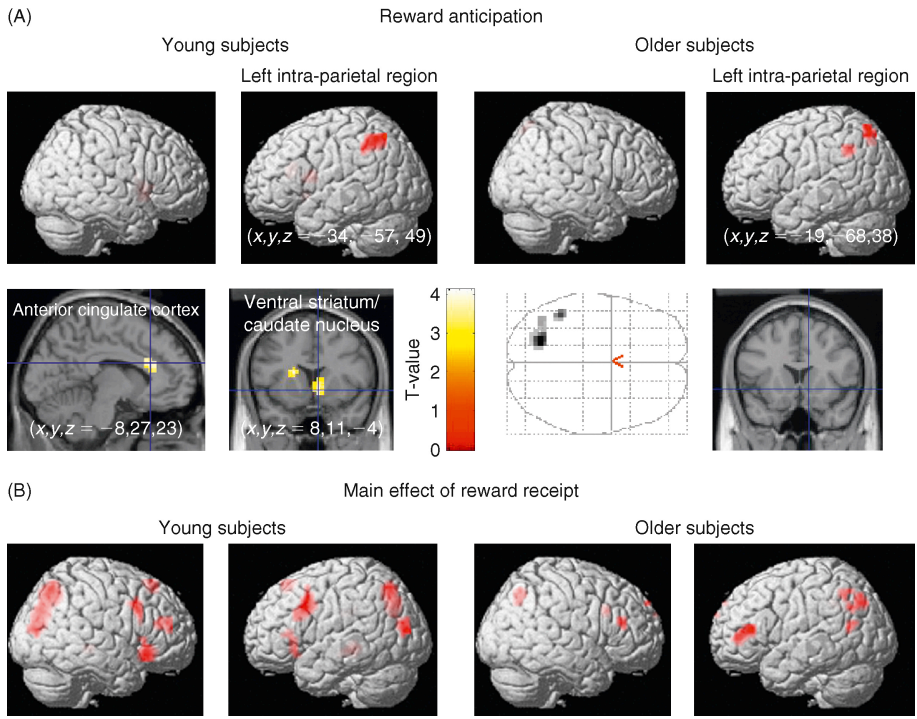

Figure 14.3 Specific brain activation in young and older subjects during reward anticipation and at the time of reward delivery. (A) *Left*. Main effect of anticipating reward in young subjects during the delay period, showing activation in the left intra-parietal cortex, ventral striatum, caudate nucleus, and anterior cingulate cortex. *Right*. Main effect of anticipating reward in older subjects during the delay period, showing activation in the left intra-parietal cortex only. The glass brain and the coronal slice indicate that no ventral striatum activity was observed in older subjects. (B) *Left*. Main effect of reward receipt in young subjects at the time of the rewarded outcome, showing activation in a large bilateral prefronto-parietal network. *Right*. Main effect of reward receipt in older subjects at the time of the rewarded outcome, showing bilateral prefronto-parietal activation [152].

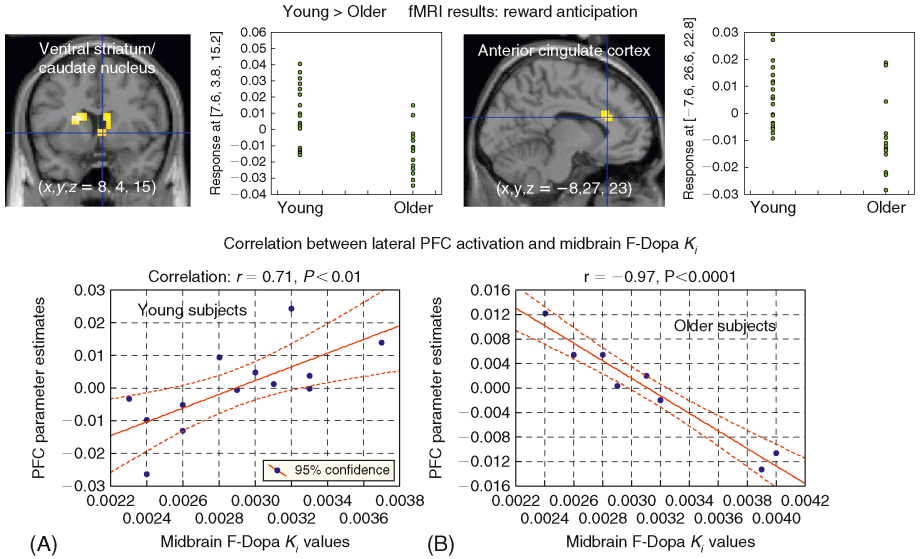

Figure 14.4 *Top*. Between-group comparison during reward anticipation, showing higher ventral striatum and anterior cingulate cortex activation in young subjects. The graphs show parameter estimates in these two brain regions in young and old subjects. *Bottom*. Relationship between midbrain dopamine uptake (K_i) and lateral prefrontal blood oxygen level-dependent (BOLD) signal in young and old adults during reward anticipation. Significant positive correlation of midbrain K_i with BOLD change during reward anticipation in young subjects (x,y,z = 42, 46, 19; Spearman's r = 0.71, $P < 0.01$; regression line with 95% confidence bands) (A) and significant negative correlation of midbrain K_i with BOLD change in older subjects (x,y,z = −23, 30, 15; r = −0.97, $P < 0.0001$) (B). A similar relationship was also observed at the time of reward delivery [152]. See Plate 18 of Color Plate section.

Hormonal replacement therapy (HRT) in aging men and women

Aging is accompanied by gonadal steroid function decline in both men and women, and there is now growing evidence that testosterone and estrogen decline play a role in these aging-related cognitive alterations. It has been proposed that estrogen therapy can reduce or delay the symptoms of Alzheimer's disease and age-related cognitive decline [153–162]. Similar effects have also been reported for testosterone [163–165], although its effects have been less studied. Some studies have reported a beneficial effect of hormone therapy on cognitive decline in women with menopause [166,167]. Current data point toward the existence of a critical window within which estrogen treatment can exert a beneficial effect on the brain [168,169]. Variables such as the time and age at which estrogen is administered and the pattern of administration may predict the clinical outcome [162]. In this sense, for estradiol to exert beneficial effects, it must be administered close to menopause onset and following a pattern of administration that mimics the natural hormonal cycle [162,168,169].

A few studies have started to investigate the influence of HRT in postmenopausal women on different cognitive functions, such as verbal and visuo-spatial abilities, but, to the best of our knowledge, no study to date has investigated decision making or reward

processing. For example, HRT-related effects in postmenopausal women who received hormone therapy either with estrogen alone, an estrogen–progestagen combination, or without HRT, showed that estrogen therapy in postmenopausal women can affect visuospatial abilities by modulating the functional brain organization [170].

In healthy aged men, moderate exogenous testosterone supplementation improves verbal and spatial memory, while low or large supplementations do not affect cognition [187]. A few neuroimaging studies indicate that HRT enhances brain activity during tasks that examine memory function. For example, women on HRT were found to have better performance on a verbal memory test and greater changes in regional cerebral blood flow during verbal and nonverbal memory tests [188]. Also, men and women on HRT report improvement of their mood and motivation.

14.4 Actions of gonadal steroid hormones in the brain

The actions of gonadal steroid hormones on sex steroid-sensitive brain structures, and the cognitive functions tied to them, have been traditionally divided into organizational and activational [171]. Organizational actions involve the modulation of neuronal development and neuronal circuit formation of a permanent nature [36], leading to sexual dimorphisms. On the other hand, activational effects are considered to be transient and reversible [171]. Although it has long been assumed that organizational effects were restricted to the perinatal period, there is now evidence that permanent neural maturation can occur in adulthood [171,172]. The mechanisms by which gonadal steroid hormones cause sexual dimorphisms in the brain and the consequent differences in cognitive abilities begin to be unveiled. For instance, the rat's hippocampus and the monkey's neocortex transiently express high levels of androgen and estrogen receptors during the first weeks of life [173,174]. Also, the aromatase enzyme that converts testosterone to estradiol has been found in the hippocampus and neocortex during the perinatal period [175,176]. It is possible that early in development androgens are converted to estradiol, which can act on local estrogen receptors and potentially lead to the sexually dimorphic development of brain morphology, neurochemistry, and neurophysiology [4].

Due to ethical (e.g., impossibility to manipulate hormone levels in human fetuses or infants) and methodological (e.g., absence of the technology that permits microscopic analysis of neural organization in living people) limitations, it is difficult to test the organizational hypothesis in humans. However, there is evidence in favor of organizing effects of gonadal steroid hormones coming from subjects exposed to atypical hormone environments during early development, from studies correlating measures of hormone concentrations during hypothetical critical periods and cognitive performance later in life, and from the study of female members of opposite-sex twin pairs. Current data suggest that organizational effects also occur in some aspects of human development, although to a more modest degree than is observed in other species [4].

Unlike sexual behavior, which requires the activating effects of gonadal steroid hormones to be expressed, sexual dimorphisms in cognition do not require these activating effects [177]. However, fluctuations in the levels of circulating gonadal steroid hormones can transiently modify cognitive functioning, as well as the structure and function of the related brain regions. For example, women with reduced estrogen levels due to ovariectomy perform less well on verbal memory tasks than women who begin HRT at the time of the surgery [178]. Indeed, experimental work shows that estrogen can promote neuronal growth processes that result in increased number of dendritic spines, axonal sprouts,

and synaptic contacts [158,179,180]. Moreover, the transient nature of these changes is demonstrated by the fact that they are rapidly formed and broken down during natural cyclic variations in estrogen and progesterone in female rats [181].

Many effects of gonadal steroid hormones on human behavior and cognition are probably mediated by their classic actions on the genome. According to the classical model, the effects of gonadal steroid hormones on the brain involve the activation of intracellular receptors that bind to DNA and regulate gene expression. These receptors have been found in several brain regions like the hippocampus, amygdala, cerebral cortex, midbrain, and brainstem [20,36]. The activation of these receptors increases binding of the steroid-receptor complex to steroid receptor binding sites—known as hormones response elements—in the regulatory regions of the target genes, which in turn leads to an alteration of the types and amounts of the mRNA transcripts in the neurons and the consequent change in the production of enzymatic, structural, and receptor proteins [1,36]. For example, estradiol alters the expression of several different enzymes, affecting levels of activity in catecholamine, serotonin, and acetylcholine pathways [4]. These genomic effects are slow, since it takes time for the gonadal steroid hormone to diffuse across the plasma membrane, bind to receptors, and induce the transcriptional changes underlying protein synthesis [36]. However, it is well known that gonadal steroid hormones may produce rapid effects on neuronal excitability [20,36]. For example, estradiol has been found to rapidly excite neurons in the cerebellum, the amygdala, and the CA1 pyramidal neurons of the hippocampus [182–185] by a mechanism that does not seem to involve intracellular estrogen receptors, since these are not found in the responding neurons. Also, estradiol directly potentiates dopamine release in the rat nucleus accumbens [186]. The rapidity of these effects makes it unlikely that they are mediated by a genomic mechanism [21]. The most plausible explanation is that these effects are mediated by membrane receptors or even by novel types of receptors [20,21].

14.5 Conclusions

There is now compelling evidence that gonadal steroid hormones, through cellular and molecular mechanisms of action in the brain, influence behavioral and physiological processes that go beyond their traditional role in the regulation of hypothalamic activity and reproduction. These actions begin during gestation and may produce organizational, long-lasting, structural changes leading to sexual dimorphisms. Later in life, gonadal steroid hormones continue to exert activating, transient effects on specific brain regions. They influence the activity of neurons in brain regions important for cognitive processes, such as the hippocampus and the striatum, even if these structures are practically devoid of specific nuclear receptors. The effects of gonadal steroid hormones in these brain regions may be explained by the powerful trans-synaptic influence on other cells of a small number of neurons containing receptors, or by the action on non-nuclear receptors and second messengers activation [20]. By modulating the neuronal activity of these structures, gonadal steroid hormones influence important cognitive functions and behaviors such as memory, learning, reward processing, and decision making.

Yet one important remaining question is to know why gonadal steroid hormones affect cognition and brain functioning during lifetime. What is the benefit of displaying a better cognitive performance in some functions during periods of life in which estrogen is higher? Unlike women living in modern societies, who go through many cycles of estrogen and progesterone through their lifetimes, it is believed that pregnancy and motherhood was the most common life state of our female ancestors. Thus, it has been suggested that variations in estrogen and progesterone during pregnancy and lactation and their

effects on several cognitive functions have been selected because they improved adaptative behaviors during these epochs. For instance, a better memory function may help nest building and location, pup recognition and retrieval, and foraging for food [4]. In parallel, variations in reward processing and decision-making abilities may also confer some advantages for procreation and selection of genetically best-fitted partners [13,128,133].

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