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**Abstract:**

Gonadal steroids not only regulate physiological functions such as reproduction, maintenance of secondary sexual characteristics, and various metabolic processes (fat, muscle, and bone mass) but also play a major role on brain functions, including on motivation, emotion, and social interactions. Neuroimaging, in combination with endocrinologic manipulations, starts to unveil the neural influences of gonadal steroid hormones on brain activity related to reward processing and social cognition. These studies have clinical implications 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.

**Keywords:** Andropause; Estradiol; Estrogen; fMRI; Gonadal steroid hormones; Menopause; Menstrual cycle; Progesterone; Reward; Testosterone

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**Biographical Sketch**

**Jean-Claude Dreher**, is a research director at the Cognitive Neuroscience Center, CNRS (Lyon). He leads the neuroeconomics research group focusing on decision-making in humans and on reward processing. He studied mathematics, psychopathology, and cognitive neuroscience in Paris and did his postdoctoral research at NIH, Bethesda (the United States), where he conducted research on the neural substrate of the reward system and on cognitive control processes. The goals of his researches are to understand the functional organization of the prefrontal cortex in humans, the functions that the reward dopaminergic system exerts on cognition and motivation, and the neural mechanisms underlying dysfunctions of these two systems (prefrontal cortex and reward system). In parallel, he studies how individual variations in hormones and genes involved in dopamine transmission influence reward processing and decision-making. This latter axis of research helps to understand the neurobiological foundations of the impact of gonadal steroid hormones and of genetically influenced variations in dopamine transmission on predisposition to neuropsychiatric disorders and on vulnerability to drug abuse.

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a0010

# Neuroimaging Evidences of Gonadal Steroid Hormone Influences on Reward Processing and Social Decision-Making in Humans

**J-C Dreher**, Centre de Neurosciences Cognitives, Bron, France



## Glossary

dt0010 **Gonad** The organ that makes gametes, the germ cells used for fertilization. The gonads in males are the testes or testicles and the gonads in females are the ovaries.

dt0015 **Gonadal hormones** Also called sex steroids or sex hormones, are hormones produced in the gonads, including estrogen and testosterone. Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades.

dt0020 **Neurosteroids** Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system and modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. The nonsteroid hormones luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing hormone are usually not regarded as sex hormones, although they play major sex-related roles.

dt0025 **Sexual dimorphism** The systematic difference in form or function between individuals of a different sex in the same species. Body features that are affected by sexual dimorphism include color of skin or coat (fur, feathers), size, the presence of body parts, and behaviors.

dt0030 **Steroid hormones** Steroid hormones are divided in five major classes: testosterone (androgen), estradiol (estrogen), progesterone (progestin), cortisol/corticosterone (glucocorticoid), and aldosterone (mineralocorticoids). Testosterone and its more potent metabolite dihydrotestosterone (DHT), progesterone, and estradiol are classified as sex steroids, whereas cortisol/corticosterone and aldosterone are referred to as corticosteroids.

dt0035 **The hypothalamic–pituitary–gonadal axis (also HPG axis)** Refers to the effects of the hypothalamus, pituitary gland, and gonads as if these individual endocrine glands were a single entity. The HPG axis controls development, reproduction, and aging.

s0015 ## Key Points

u0010 - Estrogen and progesterone not only influence ovulation and reproductive behavior but also affect cognitive functions, affective state, mood, and vulnerability to drugs of abuse.

u0015 - The reward system is sensitive to circulating gonadal steroid hormones in humans as demonstrated by neuroimaging experiments.

u0020 - Estradiol and progesterone modulate social cognition, as tested by various economics games (effects of menstrual cycle, pharmacological manipulations, and effects of hormone replacement therapy).

u0025 - Testosterone modulates reward processing and social decision-making in both men and women.

p0040 Sex steroids regulate important physiological functions, such as reproduction, maintenance of secondary sexual characteristics, response to stress, neuronal function, and various metabolic processes (body hair, fat, muscle, and bone mass). Sex hormone production is sexually dimorphic and involves differences not only in hormonal action but also in regulation and temporal patterns of production. Gonadal steroids have numerous effects on the brain throughout the life span, beginning during gestation and continuing on into senescence. The actions of gonadal steroid hormones produce organizational, long-lasting, structural changes leading to sexual dimorphisms. The influences of these hormones on neuronal activity can occur even if brain structures are devoid of specific nuclear receptors because gonadal steroids can act on the brain through several genomic and nongenomic pathways, having broad functional consequences for modulating cognitive, reward, and social processes.

## The Hypothalamic–Pituitary–Gonadal Axis

s0020

p0045 Gonadal steroid hormones, which are secreted by the ovary and testis, exert their effects on distal locations in the body. At the heart of this system is the hypothalamic–pituitary–gonadal (HPG) axis, a feedback loop controlling the secretion of gonadal steroid hormones (Cameron, 2004). The main functions of the Au4 HPG axis are to regulate reproduction and life cycle and also to affect sexual dimorphism and behavior (**Figure 1**). The gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and causes the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In women, under FSH and LH influences, the ovaries secrete estradiol and, after ovulation, progesterone. In turn, the increasing gonadal steroid hormonal level into the blood system feedbacks to both the hypothalamus and the anterior pituitary, causing FSH and LH to stop being released. In males, LH increases the production of testosterone by Leydig cells in the testes. Testosterone, in turn, suppresses GnRH activity via a negative feedback mechanism. The HPG axis has been highly conserved throughout the evolution. Testosterone and estradiol are derived from closely related ancient steroids. The central nervous system acts as both a source and a target of gonadal steroids, which pass through the blood brain barrier. The influences of sex steroids are exerted in the brain through widespread



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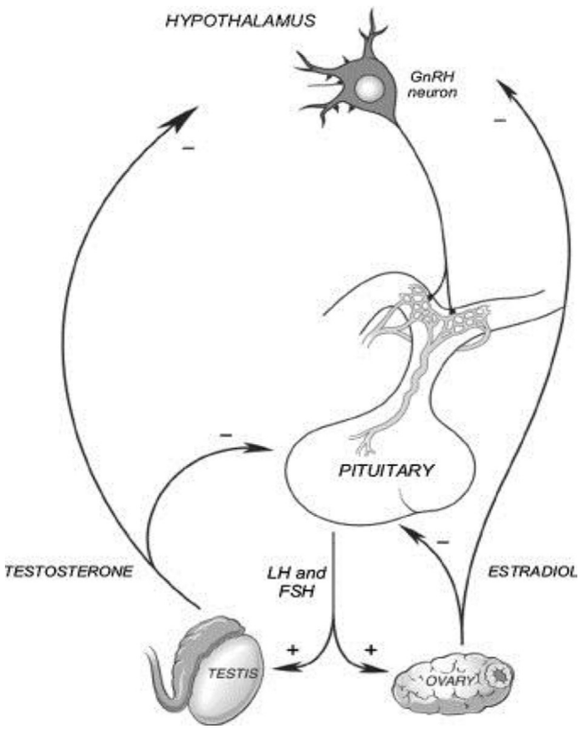



Au1 f0010 Au2 **Figure 1** The hypothalamic–pituitary–gonadal axis. Interactions between the hypothalamus, pituitary gland, and gonads (females: ovaries; males: testes). Interrelationships between hormones are depicted as stimulatory (+) or inhibitory (−). Adapted from Cameron, J. L (2004). Interrelationships between hormones, behavior, and affect during adolescence: Understanding hormonal, physical, and brain changes occurring in association with pubertal activation of the reproductive axis. Introduction to part III. *Annals of the New York Academy of Sciences*, *1021*, 110–123, with permission.

modulation of both neocortical areas and evolutionary ancient brain regions, such as the basal ganglia and amygdala.

s0025

## Toward a Functional Characterization of Gonadal Steroid Hormones on the Brain

p0050 Recent functional neuroimaging studies in humans indicate that the brain is highly sensitive to circulating gonadal steroid hormones in a number of cognitive domains. This line of research has broadened the classical view of gonadal steroid actions, primarily considered in the regulation of reproduction, and extended their roles to the modulation of cognitive and socio-emotional processes. Indeed, gonadal steroids not only regulate the menstrual cycle, pregnancy, and maternal behavior. They also play a major role in reward and emotion processing, arousal, social cognition, and motivation. Similarly, testosterone modulates brain response related to reward processing and social decision-making in both men and women. Although indirect correlational evidence between hormonal levels and brain activity has been widely reported, the results are often inconsistent. For this reason, here, we will focus on more direct evidence coming from the menstrual cycle neuroimaging literature and from fMRI studies using controlled external administration of sex steroids.

s0030

## Estradiol and Progesterone Influences on Brain Activity in Women

p0055 In women, estrogen and progesterone not only influence ovulation and reproductive behavior but also affect cognitive functions, affective state, and vulnerability to drugs of abuse. The levels of estradiol and progesterone fluctuate throughout 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 to 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. There is evidence that the menstrual cycle effects extend beyond those merely related to reproduction. The menstrual cycle phases influence spatial and verbal cognitive abilities, attention, mood, and vulnerability to drugs of abuse. In an early working memory study of healthy women, regional cerebral blood flow was attenuated in the dorsolateral prefrontal cortex, inferior parietal lobule, and posterior inferior temporal cortex during GnRH agonist-induced hypogonadism, whereas the characteristic pattern of cortical activation reemerged during both estradiol and progesterone add-back.

s0035

## Menstrual Cycle Influence on the Reward System

p0060 The modulatory influence of estradiol and progesterone on the reward system during the menstrual cycle concerns a number of reward-related domains, such as sexual stimuli, preferences in male virile traits, food intake, subjective response to addictive drugs, and anticipation and experience of monetary reward (Caldú & Dreher, 2007, 2009). Studies of neural activity during the menstrual cycle have compared activation across menstrual phases within subjects. In the domain of sexual stimuli, although early fMRI studies reported decreased cerebral activation in women compared with men upon visual erotic stimulation, in the amygdala in particular, subsequent investigations demonstrated that the anterior cingulate cortex, insula, and orbitofrontal cortex response increased with higher estrogen levels during the follicular phase. In these regions, women around ovulation showed similar brain activation upon erotic stimulation as men. Also, a combined estrogen and androgen therapy in ovariectomized women increased cerebral responsiveness for erotic stimuli, particularly in limbic regions.

p0065 In the domain of food reward, it has been shown that hedonic intake of palatable food is increased by administration of gonadal steroids, suggesting direct effects on reward seeking. Food intake is decreased during the late follicular phase and increased in the luteal phase of the menstrual cycle. Brain activity in response to visual food stimuli engaged numerous corticolimbic brain regions in the follicular phase while viewing pictures of high-calorie and low-calorie foods, whereas

only high-calorie stimuli were effective in the luteal phase. Activation of the nucleus accumbens, amygdala, and hippocampus in response to the high-calorie food was significantly increased in the late follicular phase compared with the luteal phase. These results demonstrate that brain responses to visual food cues are particularly responsive in the follicular phase.

p0070 A number of studies have investigated menstrual cycle's influence on women's social preferences. Women 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. On the other hand, during the midluteal phase, women display higher attraction for apparent health and self-resemblance. A woman preference for testosterone markers on male faces may be influenced by her estrogen/progesterone ratio, although this effect may be mediated by progesterone rather than estrogen levels. Interestingly, similar effects have been reported for voice pitch, male odor, and male social behavioral displays. Women evaluating pictures of male faces (some masculinized and others feminized) have been shown to engage a set of brain regions during the follicular phase that respond more to the masculinized than to the feminized faces. These cyclical changes in male traits preferences may be interpreted as signaling social dominance (i.e., enhancing one's status and control of resources over conspecifics) and 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. 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), women show stronger preferences for features that might be beneficial at this time, such as social and material support.

p0075 Ovarian hormones also modulate neural monetary reward function in humans, with increased follicular phase activation (compared with the luteal phase) of the orbitofrontal cortex and amygdala during reward anticipation and of the midbrain, striatum, and frontopolar cortex at the time of reward delivery (**Figures 2** and **3**) (Dreher et al., 2007). These data demonstrated for the first time that reactivity of the reward system is heightened in women during the midfollicular phase of the menstrual cycle, when estrogen is unopposed by progesterone. The increased activity of specific components of the reward system during the follicular phase may modulate basic behavioral functions of reward, such as approach behavior during reward anticipation and consummatory and hedonic behavior at the time of reward delivery. These effects could be due to gonadal hormone influences on the dopaminergic system, since they potentiate dopamine release.

## s0040 Hormone Therapy Modulates the Reward System at Menopause

p0080 The role of gonadal steroid levels on the reward domain is not only demonstrated by studies comparing phases of the menstrual cycle. Women with menopause, who show drastic drop of estradiol levels, have recently been studied after either hormone therapy (HT) or placebo. A recent fMRI study using fMRI and a counterbalanced, double-blind, randomized, and crossover placebo-controlled design administrating HT (sequential 17β-estradiol plus oral progesterone) showed that administration of HT increases the response of the reward system in early postmenopausal women (Thomas et al., in press). More specifically, HT relative to placebo increased the response of the striatum and ventromedial prefrontal cortex, two areas that have been shown to be, respectively, involved during reward anticipation and at the time of reward delivery (**Figures 4** and **5**). These neuroimaging results indicate that HT increases reactivity of the reward system in early menopausal women to a younger adulthood level. Although controversial studies reported that HT may prevent the deleterious effects of aging on cognition, and reduces the risks of dementia, including Alzheimer's disease, mild cognitive impairment, and mood-related disorders, others have found that initiation of HT more than a few years after menopause is associated with an unchanged or increased risk of dementia and age-associated cognitive decline. The age when the treatment was initiated has been proposed to be one important factor explaining part of the discrepant observations regarding a neuroprotective effect of HT. According to the 'critical time window period' hypothesis, HT effectively decreases cognitive decline in aging women when it is initiated around the time of menopause, but this

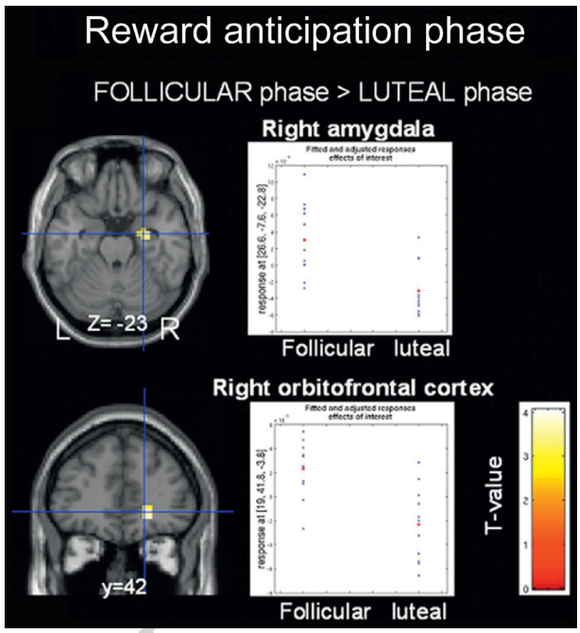
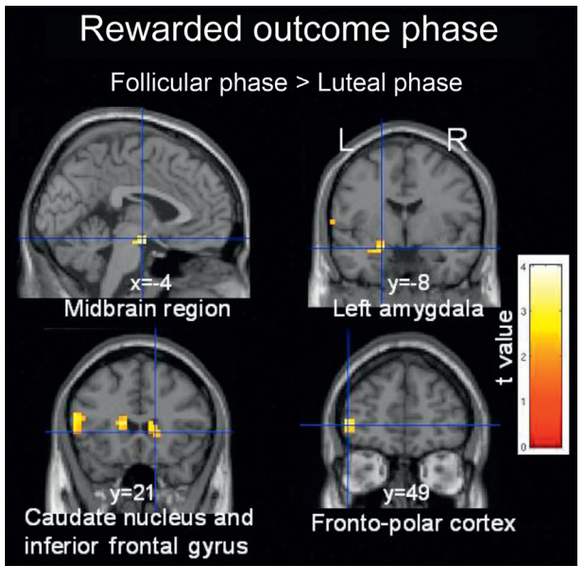



**Figure 2** Cross menstrual cycle phase differences in BOLD response during reward anticipation. During reward anticipation, higher BOLD responses were observed in follicular phase than in luteal phase in the right amygdala and orbitofrontal cortex. To the right of each map is shown distributions of BOLD signal response for each woman. Reproduced from Dreher, J- C, Schmidt, P. J., Kohn, P., Furman, D., Rubinow, D., & Berman, K. F. (2007). Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences of United States of America*, *104*(7), 2465–2470. f0015




f0020 **Figure 3** Cross menstrual cycle phase differences in BOLD response at the time of reward delivery. Cross menstrual cycle phase differences in BOLD response at the time of reward outcome. Greater BOLD response during follicular phase than during luteal phase in the midbrain, left amygdala, heads of the caudate nuclei, left inferior frontal gyrus, and left frontopolar cortex. Reproduced from Dreher, J- C, Schmidt, P. J., Kohn, P., Furman, D., Rubinow, D., & Berman, K. F. (2007). Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences of United States of America*, *104*(7), 2465–2470.

beneficial effect is not observed when HT is administered decades later. Although the 'critical time window period' cannot be tested with neuroimaging, the findings reported earlier establish a neurobiological foundation for understanding the neurofunctional impact of early HT initiation on reward processing at the beginning of menopause.

p0085 Finally, the roles of estradiol and progesterone are not limited to the reward domain. For example, increased amygdala activity during the late follicular phase (higher estradiol levels) compared to the early follicular phase (lower estradiol levels) has been reported during passive viewing of negative stimuli and increased activity in the medial orbitofrontal cortex during the luteal phase (higher estradiol levels) compared with the follicular phase (relatively lower estradiol levels). The opposite was true for the lateral orbitofrontal cortex, suggesting that sensory and evaluative neural functions are suppressed in the days prior to menstruation. Moreover, recollection-based recognition memory for negative items has been reported to decrease from early follicular to luteal phase. The superior memory for emotionally arousing events was associated with higher activity in the anterior hippocampus during early follicular compared to luteal phase.

## s0045 Neuroimaging Evidence of the Influences of Testosterone on Brain Activity

### s0050 Testosterone Influences on the Reward System

p0090 The testes secrete several male gonadal steroid hormones, including testosterone, dihydrotestosterone, and androstenedione. The female ovaries also secrete testosterone in mammals, although to a lesser extent. Besides its androgenic and anabolic effects, testosterone exerts influence on brain development and functions. fMRI has been used to explore the effects of gonadal steroid hormones on processing different types of rewarding stimuli. In an early PET study carried out in hypogonadal and eugonadal control men passively viewing sexual stimuli, the orbitofrontal cortex, the insula, and the claustrum showed higher responses in untreated patients compared with controls and when they were compared with themselves after receiving hormone replacement therapy. The testosterone dependency of the orbitofrontal cortex activation suggests that testosterone may increase the motivational salience of sexual stimuli.

p0095 In healthy young men, processing of visual sexual stimuli has been found to elicit activation in the reward system, such as the orbitofrontal cortex, the striatum, and the amygdala. In an fMRI study comparing monetary (secondary rewards) and erotic stimuli (primary rewards) in healthy young heterosexual men, a common brain network composed of the striatum, the anterior cingulate cortex, the midbrain, and the anterior insula was engaged for both types of rewards (Sescousse, Redouté, & Dreher, 2010). Moreover, an anteroposterior dissociation was observed 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 secondary rewards and evolutionary more ancient orbitofrontal region representing primary rewards (Figure 6). Moreover, the amygdala was more activated for erotic rewards than for monetary gains (Figure 7).

p0100 Little is known about the effects of testosterone administration on the reward system in healthy men because most of the neuroimaging studies published so far which administrated testosterone have been performed in women. In women receiving a single sublingual administration of testosterone, increased ventral striatum activation was observed during monetary reward anticipation, but this effect was specific to individuals with low intrinsic appetitive motivation. In men, indirect evidence attests for a neuromodulatory influence of testosterone on the reward system and on drug of abuse. For example, anabolic–androgenic steroids, which are known to partly act as testosterone agonists, can become a drug of abuse in some individuals.

### s0055 Effects of Testosterone on Social Cognition in Men and Women

p0105 Testosterone plays a key role during social interactions. Although folk theories proposed that testosterone leads to increased aggression, dominance, and antisocial behavior, a recent hypothesis is that testosterone, in both men and women, is primarily involved in obtaining or maintaining a high social status in challenging social interactions. According to this 'challenge hypothesis,' testosterone does not increase aggression per se but rather modulates the perception of emotional social challenges to which an animal is confronted (Archer, 2006; Wingfield, Hegner, Dufty, & Ball, 1990). Maintaining a high-status position requires an increased sensitivity to challenging social threats and aversive events. For example, in wild male baboons, the highest-ranking (alpha) males experience higher testosterone and glucocorticoid levels than other

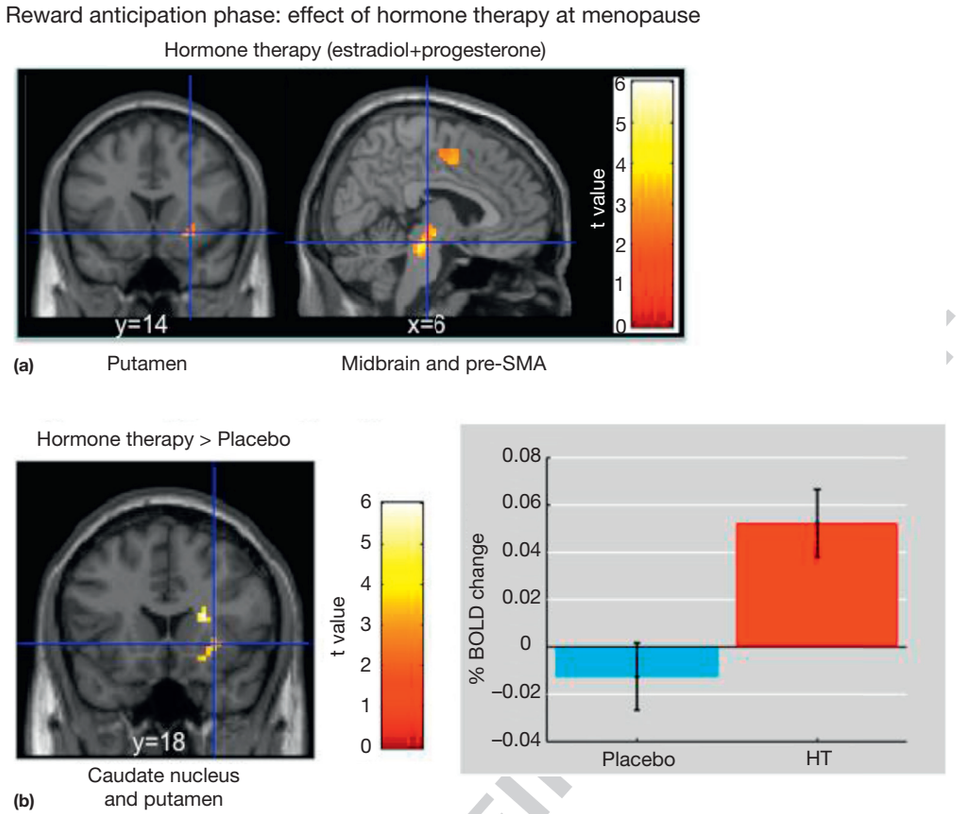
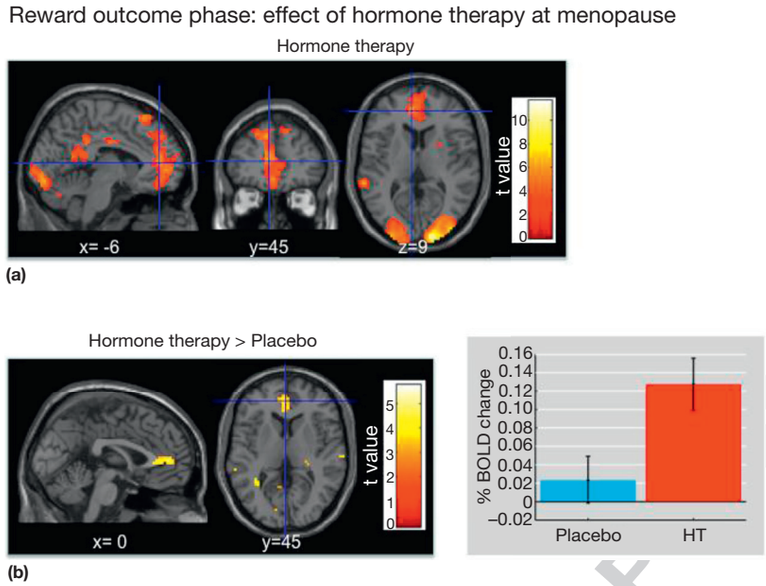



**Figure 4** Significant changes in BOLD response after hormone therapy (HT) and significant difference between HT and placebo in striatal activity during reward anticipation. (a) Significant changes in putamen and midbrain BOLD responses during reward anticipation relative to sure knowledge of no-reward delivery after HT. (b) Between treatment differences (HT > Placebo) in putamen and caudate nucleus activity during anticipation of potentially rewarded slot machines. The color bar indicates *t* values. The graph shows the average percent signal change in a 10 mm radius sphere centered on the peak of putamen activity during reward anticipation. Reproduced from Thomas, J., Metereau, E., Déchaud, H., Pugeat, M., & Dreher, J. C. (in press). Sequential 17β-estradiol plus oral progesterone increase the response of the reward system in early menopausal women: A double blind placebo-controlled fMRI study. *Psychoneuroendocrinology*. f0025

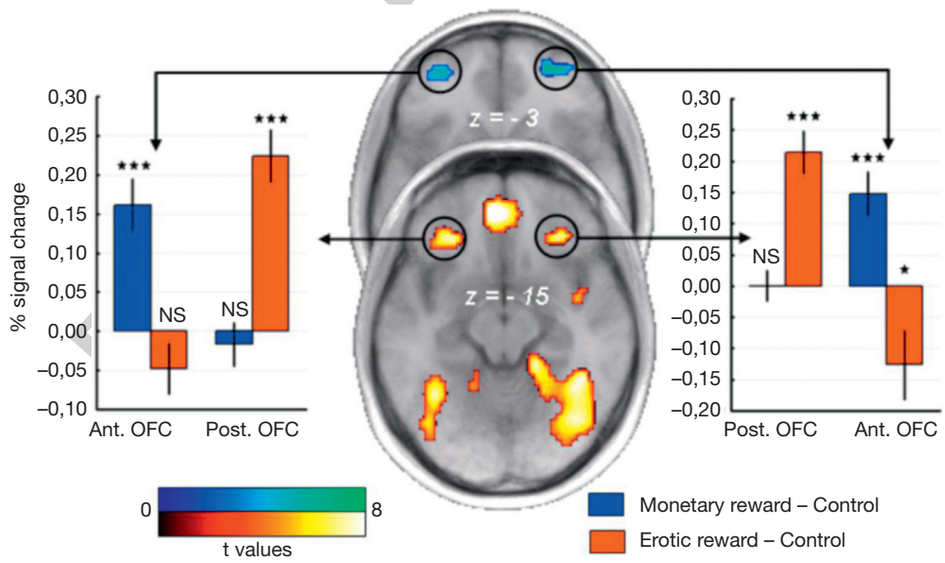
males, potentially due to energetically costly activities, such as maintenance of dominance rank through agonistic encounters and mate guarding of fertile females ('consortships' in primates) (Gesquiere et al., 2011). Some social challenges can lead to reactive aggression, but aggressive behavior is not always adaptive in every situation. In the absence of these challenges or perceived threats to dominance, however, competitive or aggressive behavior may have detrimental effects on reputation and social standing. In such circumstances, dominance and high-status seeking may be better served by displaying prosocial behavior, for example, when males are required to care for offspring. It is thus possible that sexual arousal and challenges raise testosterone levels in young men and that this could, in turn, facilitate direct competitive behavior, including aggression. In contrast, prosocial behavior may be associated with rapid decrease in the levels of testosterone. The challenge hypothesis further proposes that rapid changes in neural sensitivity to testosterone could be observed as a consequence of adaptive challenge. A recent study suggested that such dynamic steroid mechanism exists, at least in male zebra finches, since rapid fluctuations of local forebrain testosterone levels depend upon exposure to a female conspecific (Remage-Healey, Maidment, & Schlinger, 2008).

A number of recent behavioral studies using tools from behavioral economics investigated the role of testosterone during social decision-making. For example, a behavioral study investigating the effect of testosterone administration on trust and reciprocity in women used a double-blind randomized control design (Boksem et al., 2013). This study reported decreased trust but increased generosity when repaying trust, supporting the challenge hypothesis that testosterone mediates different types of status-seeking behavior, increasing competitive, potentially aggressive, behavior with social challenges and promoting prosocial behavior in the absence of these threats, therefore serving high status and good reputation. p0110

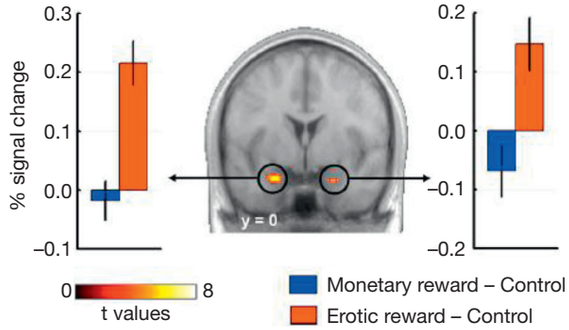
A number of combined pharmacological and behavioral studies also investigated how testosterone influences behavior in the ultimatum game. In this game, one player (the 'proposer') makes an offer to a second player (the 'responder') on how to share a certain sum of money. The word 'ultimatum' reflects the nonnegotiability of the offer, so the only options for the responder are to accept it or to reject it. If the responder agrees, the sum is divided as proposed. If there is no agreement, none of the players receive 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 p0115




f0030 **Figure 5** Significant changes in BOLD response after hormone therapy (HT) and significant difference between HT and placebo in ventromedial prefrontal cortex activity at the time of rewarded outcome. (a) Significant changes in ventromedial prefrontal cortex (vmPFC) and posterior cingulate cortex BOLD responses at the time of reward delivery after HT. (B) Between treatment differences (HT > Placebo) in vmPFC activity at the time or rewarded outcome. The color bar indicates *t* values. The graph shows the average percent signal change in a 10 mm radius sphere centered on the peak of vmPFC activity. Reproduced from Thomas, J., Metereau, E., Déchaud, H., Pugeat, M., & Dreher, J. C. (in press). Sequential 17β-estradiol plus oral progesterone increase the response of the reward system in early menopausal women: A double blind placebo-controlled fMRI study. *Psychoneuroendocrinology*.




f0035 **Figure 6** Functional posteroanterior dissociation in the orbitofrontal cortex depending on reward type. Brain regions responding specifically to monetary reward outcomes are displayed in blue-green, and those responding specifically to erotic reward outcomes are displayed in red-yellow. Plots of mean percent signal change, which are not independent of the whole-brain analysis, are shown only to illustrate the double dissociation between monetary/erotic rewards and anterior (Ant.)/posterior (Post.) OFC. Activations are overlaid on an average anatomical scan of all subjects ($p < 0.05$ FWE whole-brain corrected). Error bars indicate SEM. Reproduced from Sescousse, G., Redouté, J., & Dreher, J.C. (2010). The architecture of reward value coding in the orbitofrontal cortex. *Journal of Neuroscience, 30*(39), 13095–13104.




f0040 **Figure 7** Specific response of amygdala to erotic rewards in healthy young heterosexual males. Specific response of amygdala to erotic rewards. Activations are overlaid on an average anatomical scan of all subjects ($p < 0.05$ FWE whole-brain corrected). Left and right plots of mean percent signal change, which are not independent of the whole-brain analysis, are shown only to illustrate the specificity of amygdala response. Error bars indicate SEM. Reproduced from Sescousse, G., Redouté, J., & Dreher, J.C. (2010). The architecture of reward value coding in the orbitofrontal cortex. *Journal of Neuroscience*, *30*(39), 13095–13104.

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.

p0120 Men with higher levels of testosterone have been reported to reject more low offers than men with lower levels of testosterone. This effect of interindividual testosterone level was associated with reduced activity in the medial orbitofrontal cortex, a region engaged in impulse control. Furthermore, low second to fourth digit ratio, which has been suggested as a marker of high prenatal testosterone exposure, is associated with 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. One possible explanation of this effect is that low offers are interpreted by responders as a challenge and the acceptance of the offers as harmful for their reputation. When facing 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. Perhaps confirming this interpretation, the only combined pharmacological and fMRI study published so far in men showed that testosterone administration plays a key role in modulating threat-related neural circuitry, increasing reactivity of the amygdala, hypothalamus, and periaqueductal gray to angry facial expressions (Goetz et al., 2014). In women, fMRI studies investigating the effect of sublingual testosterone administration (often 0.5 mg) reported faster responses to angry faces and enhanced activation of the amygdala and orbitofrontal cortex when looking at facial expressions, enhanced amygdala response to facial threat, and reduced connectivity between the amygdala and the orbitofrontal cortex. These results suggest that the effect of testosterone on aggressive behavior could be mediated by its fear-reducing properties and its relation to selective attention to threat.

p0125 In women having the role of the proposer in the ultimatum game, sublingual administration of a single dose of testosterone causes a substantial increase in fair offers (Eisenegger, Naef, Snozzi, Heinrichs, & Fehr, 2010), thereby reducing bargaining conflicts and increasing the efficiency of social interactions. However, subjects who believed that they received testosterone, regardless of whether they actually received it or not, behaved more unfairly than those who believed that they were treated with placebo. Thus, the folk hypothesis seems to generate a strong negative association between subjects' beliefs and the fairness of their offers, even though testosterone administration actually causes a substantial increase in the frequency of prosocial behavior (fair offers). These findings can be interpreted within the hypothesis of the social challenge effect of testosterone.

p0130 To conclude, the studies reviewed earlier indicate that evolutionary ancient gonadal steroid hormones have important functions in modulating human brain systems engaged in motivational and socioemotional behavior. There are multiple evolutionary reasons why gonadal steroid hormones affect cognition and brain functioning during lifetime. For instance, hormonal modulation of reward processing and social interactions abilities may confer some advantages for procreation and selection of genetically best-fitted partners. Similarly, testosterone modulation of the perception of emotional social challenges can produce adaptive behavior, triggering reactive aggression or prosocial behavior, depending upon the situation.



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*See also:* **Systems**: Reward (00059); **Clinical**: Emotion and Stress (00121); **Social**: How the Brain Feels the Hurt of Heartbreak (00144); Social Rewards (00145); Prosocial Motivation (00146); Neurochemical Processes in Hedonics (00147); **Anatomy & Physiology**: Sex differences (00196); **Cognitive**: Neuropsychopharmacology of cognitive flexibility (00253); Reward Processing (00255); Economic Decision Making (00262).

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