Sex steroid hormones and Cognition

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Apart from their obvious role in the regulation of reproductive functions, sex steroid hormones also appear to influence cognition. Estrogens, androgens and progestins can have several effects on the central nervous system. Their receptors have been found in the amygdala, hippocampus, basal forebrain, cerebellum, locus ceruleus, raphe nuclei, glial cells, pituitary, hypothalamus and central gray matter (Stomati *et al.*, 1998). This thesis will especially focus on the effects of sex steroid hormones on spatial cognition and working memory. First, the general properties of estrogen, testosterone and progesterone are discussed. Subsequently their actions on spatial cognition and working memory are explored, taking evidence from both humans and animals into account. The neural substrates through which sex steroid hormones could affect cognition and possible evolutionary explanations are also discussed.

1. Sex steroid hormones and their receptors

Steroid hormones include glucocorticoids, mineralocorticoids, androgens, estrogens and progestins. The latter three are counted as sex steroid hormones. They are synthesized from cholesterol and contain four carbon rings. Their high lipid solubility allows them to pass through cell membranes (Bear *et al.*, 2007). However, as steroid hormones are hydrophobic, they require binding proteins such as albumin and SHBG (sex hormone binding globulin) for transportation through the blood stream (Dohanich, 2002). Only free hormones, i.e. not bound to these transporter proteins, can exert a biological effect. Steroid hormones mostly work via cytoplasmatic receptors. Once the hormone binds to its receptor, the complex enters the nucleus and interacts with specific nucleotide sequences to alter gene expression. Time frames mentioned in this context are at least 30 minutes (Hodgson *et al.*, 2008), 45 minutes (Toran-Allerand, 2004), or minutes to hours (Dohanich, 2002).

1.1. Estrogens

There are various types of estrogens: estradiol (E2) binds the estrogen receptor with greatest affinity and is the main form of estrogen in premenopausal women. Estradiol is converted from testosterone by aromatase. The most abundant form of estrogen in pregnant women is estriol (E3). Both estradiol and estriol are produced in the ovaries. After menopause, ovarian production of estrogen seizes and the production shifts to adipose tissue and the less potent

estrone (E1) as predominant form (Galea *et al.*, 2008). The human body produces two isoforms of estradiol: bioactive 17β-estradiol and 17α-estradiol, previously thought to be inactive. 17β-estradiol is a neural growth and trophic factor in mammalian brains of all ages. It influences neurogenesis, neuronal differentiation and neuronal survival of targets cells throughout life (Toran-Allerand, 2004). 17β-estradiol is involved in hippocampal-dependent learning and capable of enhancing LTP, a possible mechanism by which it can facilitate memory (Foy *et al.*, 2008).

Estrogens can operate via genomic and non-genomic pathways. ERα and ERβ are the 'classic' intranuclear estrogen receptors, producing genomic effects. In the absence of estrogen, ERα and ERβ are bound to chaperone molecules. When estrogen binds, the estrogen-receptor complex forms homodimers or heterodimers which can adhere to genes containing ERE sequences and alter their transcription (Dohanich, 2002; Foy *et al.*, 2008). ERα mediates most of estrogen's transcriptional activities in the brain. The role of ERβ has not been fully clarified yet (Toran-Allerand, 2004).

Less is known about the non-genomic effects of estrogen. Korol (2004) hypothesizes that estrogen exerts non-genomic effects through cytoplasmatic signalling pathways following membrane or extracellular receptor activation. Rapid non-genomic responses can occur via second messenger cascades initiated by signalling complexes at cell membranes (Henderson, 2008; Wehling & Lösel, 2006). A putative membrane-bound estrogen receptor, baptized ER-X by Toran-Allerand (2004), supposedly shows some homology with ERα. ER-X has 17α-estradiol, produced by the adrenal glands, as preferred ligand. The cloning of the associated gene is in progress. ER-X might act through changing membrane excitability (Dohanich, 2002). Estrogen may also regulate the balance of neurotransmitters such as GABA, glutamate, acetylcholine (Korol, 2004), serotonin and noradrenalin (Henderson, 2008). For instance, 17β-estradiol can act rapidly by altering AMPA and NMDA responses (Foy *et al.*, 2008).

Estrogen also seems to have profound effects on the cellular level. It has been called 'nature's own psychoprotectant' (Fink *et al.*, 1996). In his extensive review, Dohanich (2002) lists several neuroprotective actions of estrogen. Among these are estrogen's function as antioxidant, protection against exitotoxic levels of amino acids, ERα-mediated decrease of apoptosis and increased synthesis of glucose transporters, which enhances cell survival in times of hypoglycaemia. Moreover, estrogen is associated with the prevention of Alzheimer's

disease. Estrogen can protect neurons against the accumulation of β-amyloid characteristic of this disease, even if these neurons lack functional ERs. The neuroprotective effects of estrogen must therefore occur via non-ER mediated pathways (Woolley, 1999). The amyloid precursor protein (APP) is normally cleaved by β- and γ-secretase, thereby producing insoluble β-amyloid. Cleavage by α-secretase produces soluble sβAPP. 17β-estradiol decreases the amount of β-amyloid in vitro (Xu *et al.*, 1998), probably by upregulating α-secretase. However, results from clinical trials often show no alleviation of Alzheimer symptoms in postmenopausal women receiving hormone replacement therapy (Henderson, 2008).

1.2. Androgens

The Leydig cells of the testes are the main site of androgen production, but adrenal glands also produce a small amount. Testosterone (T) is the most abundant androgen. Female concentrations of testosterone are roughly 10% of those found in males (Bear *et al.*, 2007). Dihydrotestosterone (DHT or stanolone) is a metabolite of testosterone, produced by the enzyme 5α-reductase. In contrast to testosterone, DHT cannot be aromatized. DHT and testosterone bind to the same androgen receptor, but DHT does so with greater receptor affinity. Testosterone and DHT primarily bind to SHBG, while only one third of estrogen binds to SHBG. Normally 60% of testosterone is bound to SHBG and 38% is bound to albumin, leaving only 2% free to be biologically active (Billington, 1998). Testosterone often rises to far greater levels than estrogen when hormones are administered in the same amounts (Hodgson *et al.*, 2008). It should be kept in mind that testosterone administration will also lead to elevated estradiol levels due to aromatase activity. A part of the androgen metabolism is shown in figure 1.

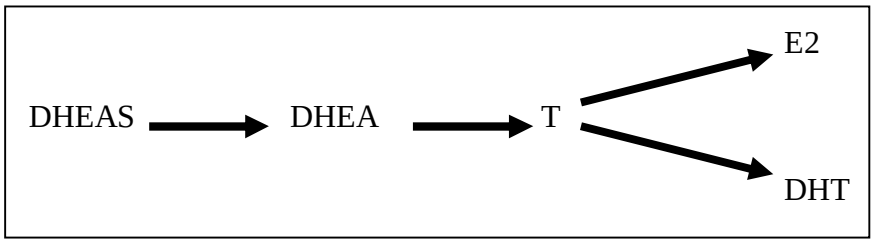

Figure 1. Testosterone metabolism. Conversion from T to E2 is done by the enzyme aromatase, conversion from T to DHT is done by the enzyme 5α-reductase.

1.3. Progesterone

Progesterones (progestins), like estrogens, are ovarian hormones and are essential to sustain pregnancy (Lupo & Niewoehner, 1998). Progesterone often augments the actions of estrogen

in reproduction, and probably plays a comparable modulatory role in cognition (Dohanich, 2002). However, the effects of progesterone on cognition have received far less attention than estrogen and testosterone, and results are often contradictory.

2. Spatial cognition

To assess the effects of sex steroid hormones on cognition, spatial memory is often tested. Spatial tasks often reveal gender differences in humans as well as in animals. A well-known test for human spatial abilities is the Mental Rotation Test, on which robust gender differences are found in favour of males. In the literature, the role of sex steroid hormones in the developing brain of humans is often seen as a fixed fact. Their role in the maintenance of cognitive sex differences on the other hand is viewed as not yet firmly established (Janowsky *et al.*, 1994; Ulubaev *et al.*, 2009). Some factors that can affect cognition are listed in figure 2.

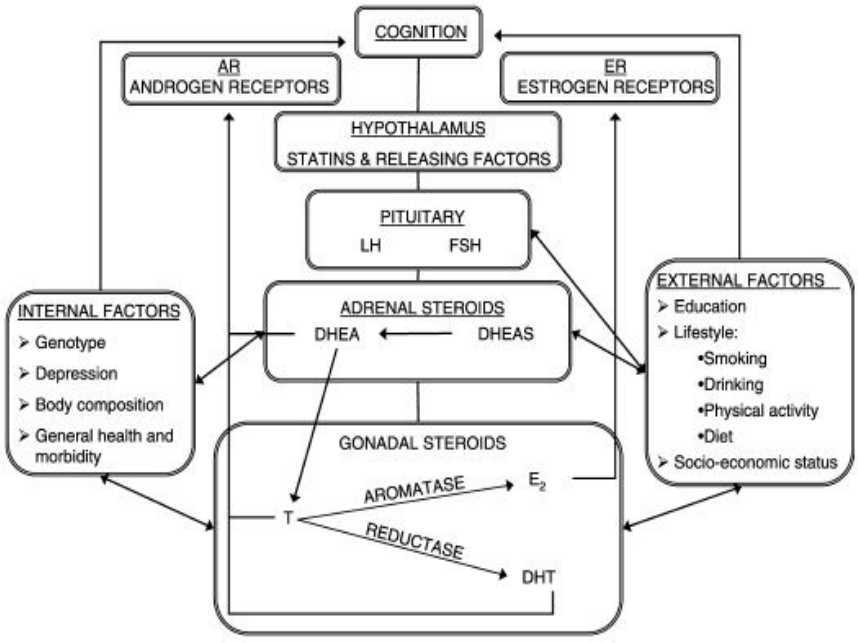

Figure 2. The HPA axis and possible external and external factors influencing cognitive function. Adapted from Ulubaev *et al.* (2009).

Spatial memory in rodents is often tested with the Morris Water Maze, and can only be accomplished with an intact hippocampus (Galea *et al.*, 2000). Both spatial reference memory and spatial working memory can be tested with this task. Working memory is a form of short term memory, which stores information only for the time that it remains useful. Typically, this is only during a single test session, for example because the location of the platform is changed every trial. Reference memory is a form of long term memory, which stores general principles of how the task must be solved (Dohanich, 2002). It continues to be useful across

trials over long periods. To determine the role of sex steroid hormones in spatial tasks like the Morris water maze, animals are generally gonadectomised prior to testing.

2.1.1. Endogenous hormone fluctuations in humans

The effects of estrogen on spatial cognition are well-studied, but results tend to be inconsistent. One study in humans tried to correlate estrogen levels during the menstrual cycle with performance on the Mental Rotation Test. The point in menstrual cycle was deduced by hormone measurements (Hausmann *et al.*, 2000). During the human menstrual cycle, estrogen produced by the ripening follicle dominates the follicular phase, peaks at ovulation and declines during the luteal phase. In the latter phase, there is a rise of progesterone produced by the corpus luteum (Lupo & Niewoehner, 1998). Women in the menstrual phase (characterised by low estrogen and low progesterone) scored better than women in the midluteal phase (characterised by high estrogen and high progesterone). Progesterone did not correlate with spatial performance (Hausmann *et al.*, 2000).

2.1.2 Exogenous hormone elevations in humans

Janowsky *et al.* (1994) found a significant improvement of spatial cognition but no other cognitive domains when testosterone levels were increased to 150% above baseline in old men. In contrast, Wolf *et al.* (2000) found no activational effects of supraphysiological levels of testosterone on spatial abilities of elderly men. Even though tests were conducted five days after a single T injection, testosterone levels in the blood were still high. However, testosterone levels in this study were approximately 500% above baseline and 3 times as high as control group of young men. The fact that both studies find different results despite sharing the same research question is not very surprising, taking into account the differences in set-up. These include the latency of measurement after testosterone administration (while wearing a T patch or 5 days later), method of administration (3 months of chronic T or a single injection), latency between first and second test (5 days versus 3 months), the amount of testosterone that was administered (15 mg or 250 mg), and whether they found elevated or reduced estrogen levels. Cherrier *et al.* (2002) found no meaningful changes on measures of spatial memory in young men receiving testosterone, testosterone in combination with progesterone or progesterone alone. Wolf *et al.* (2000) suggest that the beneficial effects of testosterone might only arise with prolonged treatment. A curvilinear relationship, with an optimum testosterone range, has often been proposed (Cherrier *et al.*, 2002; Janowsky *et al.*, 1994; Ulubaev *et al.*, 2009; Wolf *et al.*, 2000). According to Janowsky *et al.* (1994), the

adverse effects of super-optimal testosterone levels are caused by the fact that a large proportion of it is aromatized. The resulting elevated estradiol levels are responsible for the decline in spatial abilities. The effect of testosterone on spatial ability is mediated by its direct effects on androgen receptors in the brain (Cherrier *et al.*, 2005). A curvilinear relationship has been proposed for the other sex steroid hormones as well (Ulubaev *et al.*, 2009).

2.1.3. Testosterone to estrogen ratio

Hausmann *et al.* (2000) found that the testosterone to estrogen ratio plays an important role: testosterone had a strong positive influence, estradiol had a negative influence. Steroids seem to have a cumulative effect on performance. However, Cherrier *et al.* (2005) found that spatial memory improved in older men when testosterone levels were elevated, regardless of estradiol levels. Participants were administered testosterone alone or testosterone and an aromatase blocker, and tested with a route test. This spatial navigation task probably has very different task demands than the Mental rotation test used in most other studies mentioned here. Therefore, sex steroids might have different effects if tasks have different task demands and employ different brain structures, even if they all test spatial memory.

2.2.1. Endogenous fluctuations in animals

To investigate the role of ovarian hormones in spatial cognition, studies have made use of the natural fluctuation during the estrous cycle. The estrous cycle of the rat lasts four or five days and is divided in estrus, diestrus and proestrus phases. The proestrus phase is characterized by high levels of estrogen and progesterone. During estrus, both estrogen and progesterone levels are low. In diestrus, estrogen levels are low whereas progesterone levels are high. As the rodent estrous cycle is relatively short and hormone levels change rapidly, it can be hard to test all rats while they are in a certain phase of the cycle (Galea *et al.*, 2000; Korol, 2004). This could be a reason why some studies find an effect of the estrous cycle on spatial cognition and some do not. In a study using the Morris water maze, significant differences in performance were found between males and estrous females, but not between males and females in diestrus (Frye, 1995). Generally, female rats tend to show less retention in a Morris water maze task than males (Korol, 2004).

The role of estrogen and progesterone on performance was investigated in pregnant rats. During pregnangy, estradiol levels are very low in first two trimesters (comparable to diestrus and estrus), with an increase during the third trimester (comparable to proestrus). Estradiol

levels are quite stable over time during pregnancy, in contrast to levels during estrous cycle. Progesterone levels are high throughout all trimesters of pregnancy, but drop in the last three days when estradiol levels rise (Galea *et al.*, 2000). Rats in the first and second trimester of pregnancy performed better than non-pregnant females, in terms of both latency and travelled distance. During the third trimester, pregnant rats performed worse than non-pregnant females. These results were found in both the reference and the working memory task. This led the researchers to conclude that estradiol inhibits spatial learning. High circulating estrogen levels during pregnancy have also been linked to maternal amnesia. This occurs during late pregnancy and the early postpartum period. The effects on first-time mothers are significantly more severe than for subsequent pregnancies (Galea *et al.*, 2008). Galea *et al.* (2000) suggest progesterone probably has a facilitatory role on performance, but from the same results Dohanich (2002) draws the conclusion that the ratio of estrogen to progesterone might be an important factor. Better spatial performance is associated with low estradiol and high progesterone levels, impaired performance with high levels of estradiol and low levels of progesterone.

Another paradigm used to test spatial memory in rats is the spatial NOR (novel object recognition) task, where rats have to identify which of two objects have been placed in a novel location. In this task, male rats had better spatial recognition than females. As females in estrus perform better than females in other phases of the estrous cycle, this effect is probably mediated by levels of sex steroids. Elevations of both estrogen and progesterone seemed to be detrimental to spatial memory (Sutcliffe *et al.*, 2007).

2.2.2. Exogenous hormone levels in animals

Ovariectomized female rats receiving estrogen displayed impaired performance on the Morris water maze. However, females that were administered progesterone as well as estrogen performed comparable to the control group, despite receiving the same amount of estrogen as the group treated with estradiol alone. In this study, progesterone seemed to be able to reverse the impairments caused by high levels of estrogen (Snihur *et al.*, 2008). Gonadectomised female mice treated with estradiol failed to learn the task, suggesting their reference memory was impaired (Fugger *et al.*, 1998).

Hodgson *et al.* (2008) conducted research on spatial memory in songbirds. Great tits were fed larvae injected with testosterone or estradiol. Both hormones led to improvement in spatial

memory, and performances declined after treatment ended. No short term effects (5-30 minutes) were found. The hippocampus of great tits turns out to contain androgen receptors, and estrogen receptors ERα and ERβ.

2.2.3. Gender differences in development

A widespread misconception is that male and female brains are the same except for influences of currently circulating sex steroid hormones. While these are responsible for a substantial proportion of gender differences, they cannot explain everything. Many sex differences in adult neural structures stem from differential sex hormone influences during development (Cahill, 2006). Therefore, investigating the roles of sex steroid hormones during development is important to gain a complete picture.

In a study that tested spatial ability with the Morris water maze, male and female mice were injected with estradiol or vehicle during the neonatal period and in the days prior to testing. First, mice treated with vehicle as neonates were examined, to see the effects of high levels of estradiol during adulthood. Females receiving estradiol as adults performed significantly worse than females treated with vehicle, and males treated with either estradiol or vehicle. Males were not significantly impaired by the pre-test estradiol injections (Imwalle *et al.*, 2006). Similarly, another study with ERα knockout mice and their wild-type littermates showed that only wild-type females (with properly functioning ERα) seemed to be affected by estradiol injections. Performances of wild-type males were similar for the estradiol-treated and vehicle-treated group (Fugger *et al.*, 1998). These results show that males and females seem to have a different reaction to high levels of activational estradiol, with females being more affected by high concentrations than males.

In mice given estradiol as adults, developmental influences of estradiol or vehicle on adult response could be investigated. Females receiving estradiol both neonatally and as adults performed significantly better than females treated with vehicle neonatally and estradiol as adults. In contrast, males receiving estradiol at those two points in time performed worse than males that were treated with estradiol as adults only. Imwalle *et al.* (2006) propose that exposure to estradiol during development can counteract the deleterious effects of acute estradiol administration on adult spatial learning. Although it sounds paradoxical, estrogen is needed to masculinise the brain. During normal development, males but not females are exposed to estrogen via aromatisation of testosterone. Activation of ERα during development

defeminises the response to acute estradiol injections (Fugger *et al.*, 1998). Differential responses to adult estradiol in males and females can then be explained by endogenous estrogen levels during development. The fact that males treated with estradiol twice perform worse is probably due to the already high endogenous levels of estrogen to masculinise the brain. Along the same lines of reasoning, knocking out the aromatase gene was predicted to impair performance in males more than in females. However, only in female mice a small effect was found (Imwalle *et al.*, 2006). It is unclear how these results should be interpreted. Aromatase knockout mice possibly have compensatory mechanisms in place to counterbalance the lack of estradiol, for instance by increasing the synthesis of other forms of estrogen.

2.2.4. Other factors that can influence performance

The effects of estrogen on cognition depend on many variables, including stress, type and duration of hormone treatment, dosage, during which phase of learning hormones were administered (Korol, 2004), choice of task, gender, and age (Dohanich, 2002). Forced swimming and the novel environment of the Morris water maze are likely to be very stressful for rats. This stress might impair performance. Interaction effects between estradiol and corticosterone are often predicted in the literature. However, in a study where adult female rats had undergone bilateral ovariectomy and adrenalectomy, estradiol impaired spatial skills independently of corticosterone (Snihur *et al.*, 2008). Another factor that should be reckoned with, is that stress differentially affects males and females (Korol, 2004). Also, females with high levels of estrogen and progesterone show more thigmotaxic behaviour in the Morris water maze. If measuring was started after these females left the periphery and actively started searching for the platform, they were as fast as controls. In this study, impaired performance was caused by the fact that females initially tend to show inadequate thigmotaxic strategies before adopting more adequate strategies to solve the task (Korol, 2004).

In a plus maze, high levels of estrogen have been shown to bias female rats towards place learning (allocentric strategies), which depend on extramaze cues and involves the hippocampus. Low levels of estradiol on the other hand promote response learning (egocentric strategies), which involve the striatum and its connections. These differences in use of strategy were also seen during the estrous cycle, with rats in proestrus using allocentric cues and rats in estrous using egocentric cues. During diestrus, when hormone levels are intermediate, there was no bias for either strategy (Korol, 2004). Estrogen supposedly biases

animals towards using their hippocampus, whether or not it is advantageous to do so. Yet, these results seem to be inconsistent with the believe that finding the platform in the Morris water maze depends on allocentric strategies and an intact hippocampus. If high levels of estrogen promote allocentric strategies, performance on the Morris water maze should be facilitated in stead of impaired. Daniel and Lee (2004) indicate that the hippocampus is essential for the development of cognitive maps, but it is not necessary for and might even interfere with landmark learning. In their study that made use of the Morris water maze, rats could use a floating landmark that had a static position relative to the hidden escape platform as well as extramaze cues. Ovariectomized rats undergoing estrogen replacement did not make use of the landmark, whereas ovariectomized controls did. Estrogen is proposed to bias animals against using landmarks to solve a task, and promote the use of cognitive maps.

Whether sex steroids affect cognition might depend on during which phase of learning they are administered. High levels of estrogen might only influence retention or only acquisition (Galea *et al.*, 2008). When estrogen was administered after acquisition, performance in the Morris water maze was enhanced in stead of impaired (Korol, 2004), indicating that estrogen mainly impairs acquisition. Frye (1995) agrees, saying estrogen only affects acquisition. Meanwhile, Imwalle *et al.* (2006) suggests that estradiol has the most profound effect on retention. More research is needed to draw a final conclusion.

Dohanich (2002) suggests that improved performance in various tests may also be the result of changes in nonmnemonic variables that are related to learning and memory only indirectly, but can have a profound effect on test outcomes. These variables include but are not limited to mood, food intake, motivation and are listed in figure 3. Many studies control for these nonmnemonic variables, for example by pretraining sessions, measuring swim speed and checking whether impairments persist if the platform is visible. However, not all studies control for all variables, making it harder to rule these out. Hence, worse performance when levels of certain sex steroids are high is not necessarily a sign of impaired memory. A myriad of other factors could underlie the longer latencies and larger swimming distances that are generally found in animals with high levels of estrogen.

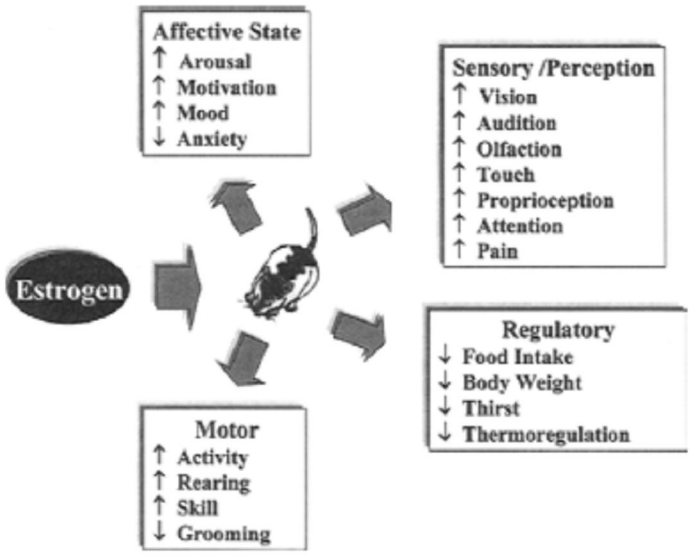

Figure 3. The effects of estrogen on functions that might affect memory performance indirectly through their nonmnemonic actions. Adapted from Dohanich (2002).

3.1. Effects on working memory in humans

Working memory makes use of the PFC and hippocampus (Galea *et al.*, 2008). The PFC contains many sex hormone receptors, especially estrogen (Cahill, 2006). Janowsky *et al.* (2000) have investigated the influence of sex steroid hormones in a non-spatial working memory task in humans. They found that older men receiving testosterone supplementation performed significantly better on this task, while no such improvement was seen in older women receiving estrogen supplementation. They suggest that better working memory in older men is related to a higher testosterone to estrogen ratio. Better frontal lobe mediated working memory is related to higher testosterone and lower estradiol levels.

3.2. Effects on working memory in animals

High levels of endogenous and exogenous estrogen usually improve performance on tasks that depend on working memory. Rats receiving estradiol treatment showed fewer errors during acquisition and better retention over long and short retention periods (Dohanich, 2002). Another study found that high doses of estradiol impair working memory, whereas low doses enhance working memory (Galea *et al.*, 2008). This again points towards an optimal range and a curvilinear relationship.

Sutcliffe *et al.* (2007) used the novel object recognition (NOR) task to test working memory in rats. They found that females are significantly better in the standard NOR task and have

longer retention periods. However, performance on the task was not correlated with the estrous cycle, so estrogen might not mediate these effects.

4. Neural structures involved

The hippocampus is a neural structure that is involved in both spatial memory and working memory. It contains ERα, ERβ (Sutcliffe *et al.*, 2007), and androgen receptors (AR) (Galea *et al.*, 2008). The hippocampus is capable of adult neurogenesis, via progenitor cells in the dentate gyrus. Many newly formed cells die within two weeks, but steroid hormones can enhance their survival. Hippocampal neurogenesis is differentially altered in males and females due to differences in circulating levels of steroid hormones. Estrogens can rapidly influence cell proliferation, and prevent cell death and enhance cell survival in the dentate gyrus. Both ERα and ERβ are involved (Pawluski *et al.*, 2009). Age plays a significant role in estradiol's effects on neurogenesis. Older female rats respond to chronic, but not to acute estradiol treatment. Different forms of estrogen might have other effects on neural plasticity and behaviour. Androgens can upregulate neurogenesis in the dentate gyrus of adult male rats, and do so independently of estradiol (Galea *et al.*, 2008). In the study of Galea *et al.* (2000) where female rats in the first two trimesters of pregnancy outcompeted non-pregnant females, hippocampal volumes were also measured. However, these did not significantly vary between pregnant and non-pregnant rats. The possibility remains that there are differences on the cellular level, such as synapse density and number of spines. Sutcliffe *et al.* (2007) remark that high estrogen leads to poorer spatial ability but more dendritic spines.

Nevertheless neurogenesis, cell proliferation and enhanced cell survival do not necessarily improve memory. As seen in previous sections, high levels of estrogen often impair spatial memory. Young neurons are highly excitable and can therefore change the signal to noise ratio. A large increase in the amount of young neurons can disrupt the balance and impair memory performance (Galea *et al.*, 2008; Pawluski *et al.*, 2009). On the other hand, preventing neurogenesis also has a negative effect on memory. There probably is an ultimate level of neurogenesis, above or below which learning and memory are impaired. Once again, a curvilinear relationship can be proposed (Pawluski *et al.*, 2009). Hippocampal changes induced by sex steroid hormones are the neurobiological pathways through which spatial ability is affected. The fact that a curvilinear relationship is also found for estrogen / testosterone and memory, might mean that estrogen and testosterone exert their action via neurogenesis in the hippocampus. Estrogen and testosterone are probably related to

neurogenesis in a linear fashion: more testosterone or estrogen means more neurogenesis. As neurogenesis is curvilinearly related to performance on memory tasks, testosterone and estrogen also have a curvilinear relation to memory performance.

5. Evolutionary explanations

In a review of Sherry & Hampson (1997), sex differences in spatial abilities are put in an evolutionary perspective. They propose that there is sexual selection pressure for spatial ability in males, but not in females. Males tend to have larger ranges than females, and this results in sex differences in mobility. For males, having a bigger territory often leads to more food and more chance of encountering females. In females, spatial ability is selected against because survival rate and reproduction rate increase if mobility rate decreases. While this sounds plausible, the correlation between spatial ability and mobility of the organism still remain to be tested. As Dohanich (2002) points out: these evolutionary scenarios are post-hoc explanations, and a lot of data is needed to support these assumptions.

6. Discussion

Many reviewers have been reluctant to acknowledge the activational effects of sex steroid hormones on spatial cognition, but there seems to be enough evidence to conclude a small effect exists. At least in human males, testosterone supplementation seems to have a beneficial effect on spatial cognition. Estrogen on the other hand seems to have a detrimental effect, in humans as well as in animals. Reports on the role of progesterone remain scarce and inconclusive. In some studies it enhances spatial memory, whereas it seems to impair in others. More research is needed on the effects of progesterone in combination with estrogen and the effects of progesterone alone. Progesterone could very well modulate the effects of estrogen. The effects on non-spatial working memory are less clear.

There are several arguments in favour of a correlation between sex steroid hormones and spatial cognition. For example, reported effects were found under different circumstances. Effects have been found when hormone levels were exogenously elevated and during the endogenous hormonal fluctuation of the estrous and menstrual cycle. Sex steroids affect spatial cognition in both humans and animals. Additionally, it appears that sex steroid hormones act via changing neural substrates such as the hippocampus. The occurrence of certain changes in the hippocampus seemed to covariate with levels of sex steroid hormones.

However, the role sex steroid hormones play in influencing cognition might be only minor. Dohanich (2002) states that the effects of estrogen are moderate in magnitude and the behavioural significance remains to be determined. Effects found, if significant, tend to be weak. This could explain some of the contradictory results. The influence of estrogen could be limited to certain phases of learning, for example only retention could be affected, or only acquisition. Nonmnemonic factors could have a major effect on study outcomes, accounting for at least some of the effects found. Impaired performance could also be caused by the use of inappropriate strategies. High levels of estrogen and progesterone are correlated with thigmotaxic behaviour. Care should be taken to refrain from generalization, as results often only arise in specific circumstances.

Apparently not the absolute hormone quantities, but hormone ratios seem to be important factors in altering cognition. Also, testosterone and estrogen have optimal levels or ranges, above and below which performance is impaired. Curvilinear relationships have therefore often been proposed. To gain more insight, it would be helpful to quantify the results by measuring exact levels of free circulating hormones in addition to cognitive testing. In animal research, neurogenesis in certain brain structures should be measured. Effect of estrogen on hippocampal neurogenesis might be very time-dependent. More consistent results would take the research in this field a step further.

Sex steroid hormones may act on aspects of cognition and parts of the brain that are not obviously sexually dimorphic (Janowsky *et al.*, 1994). Similar performances do not imply that the same neural mechanisms are involved. Cahill (2006) proposes that sex differences in neural structures might compensate for sex differences that arise due to hormonal influences. Investigating the effects of testosterone in females and estrogen in males could shed a different light on the subject.

The main function of sex steroid hormones is of course the regulation of reproduction, and influencing cognition might be a mere by-product. At first sight, there is no obvious reason why sex steroid hormones should affect cognition. Nonetheless, evolutionary benefits of testosterone enhancing and estrogen impairing spatial cognition have been suggested. To conclude: moderate effects seem to exist, but their significance could be debated. Many factors influence spatial cognition and non-spatial working memory, and sex steroid hormone levels are just one of them.

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