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Neurobiological mechanisms underlying sex-related differences in stress-related disorders: Effects of neuroactive steroids on the hippocampus

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ABSTRACT

Men and women differ in their vulnerability to a variety of stress-related illnesses, but the underlying neurobiological mechanisms are not well understood. This is likely due to a comparative dearth of neurobiological studies that assess male and female rodents at the same time, while human neuroimaging studies often don't model sex as a variable of interest. These sex differences are often attributed to the actions of sex hormones, i.e. estrogens, progestogens and androgens. In this review, we summarize the results on sex hormone actions in the hippocampus and seek to bridge the gap between animal models and findings in humans. However, while effects of sex hormones on the hippocampus are largely consistent in animals and humans, methodological differences challenge the comparability of animal and human studies on stress effects. We summarise our current understanding of the neurobiological mechanisms that underlie sex-related differences in behavior and discuss implications for stress-related illnesses.

1. Introduction

It has long been known that men and women differ in the susceptibility and prevalence of a wide-range of stress-related illnesses such as psychiatric disorders, neurological and neurodegenerative disorders. While men show a higher prevalence in neurodevelopmental disorders like autism or ADHD (Faraone, 2015; Schuck et al., 2019), women show a higher prevalence in stress-related disorders like anxiety or depression in adulthood (Albert, 2015; Angst et al., 2002; Barnes et al., 2005; Breslau et al., 1995; Cahill, 2006; Irvine et al., 2012; Kessler et al., 1994; McLean et al., 2011; Olff, 2017; Seeman, 1997) with higher prevalence rates emerging during adolescence. Furthermore, an increased prevalence in stress-related disorders is observed during periods of drastic hormonal changes (puberty, pregnancy, postpartum, menopause) along the female life-span (see Slavich and Sacher, 2019 for review). Accordingly, sex hormones and their interaction with stress hormones seem to play an important role in the development of stress-related disorders. Many of these disorders have been linked to altered structure, function and neurogenic processes within the hippocampus, as well as hippocampus-dependent cognitive functions, all of which have been shown to differ between males and females. Thus, in order to understand the moderating influence of sex and stress hormones on the development of stress-related disorders, it is important to disentangle the effects of these hormones on hippocampal morphology and function. Since the complexity of this topic and a variety of different methodological approaches has led to a multitude of different research findings, this review aims to provide a thorough and timely overview of steroid actions on the hippocampus.

Most importantly, this review seeks to integrate findings from both the animal and human literature on the topic. While animal models allow us to study the neurobiological underpinnings of sex differences in behavior down to the molecular level, it is not possible to model all aspects of human behavior in rodents. This is particularly true for verbal functions, certain socio-emotional functions and fine-motor skills, as they only developed in primates/humans. Furthermore, rodent-models cannot cover stress-related disorders like depression, post-traumatic stress disorder (PTSD) or anxiety disorders in their entirety. While many animal models have been developed to assess stress-related disorders, they have traditionally used male rodents; although this has recently changed, partly due to altered regulations by funding agencies.

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However, the available studies have shown that there are large behavioral, neurochemical, endocrine and neurobiological sex differences in most of these models (Dalla et al., 2005, 2008; Dallak et al., 2008; Palanza, 2001). Accordingly, this review will compare the cellular and molecular findings in animals to neuroimaging findings in humans in order to work out parallels and discrepancies between these approaches. This overview can help to identify which of the factors observed to modulate hippocampal morphology in pre-clinical animal studies are also of behavioral, and possibly clinical relevance in humans.

2. Why sex hormones matter for sex-related disorders: Sex and sex hormone influences on the stress response

Cortisol is chronically elevated in patients with stress-related disorders, such as depression or PTSD (Travis et al., 2016; Szeszko et al., 2018; Keller et al., 2017; Bremner, 2006) and also cortisol reactivity to acute stress appears to be altered. In humans the cortisol awakening response (CAR) has been described as an indicator of the capacity of the HPA-axis to respond to stressors (Langelaan et al., 2006). While some studies show an increased CAR in patients under chronic stress (Wust et al., 2000; Schlotz et al., 2004), other studies demonstrate that the cortisol awakening response is blunted in patient groups with chronically elevated cortisol levels (Wessa et al., 2006; Roberts et al., 2004; Duan et al., 2013). Accordingly, the elevated CAR in participants who report chronic stress represents a healthy adaptation to the expected stress during the upcoming day. However, if the chronic stress continues, this adaptive capacity is lost, resulting in disorders like depression, PTSD or chronic fatigue syndrome. Likewise, it appears that chronic stress/chronically elevated cortisol levels affect acute stress reactivity. While some studies show that participants under chronic stress show an increased cortisol response to acute stress, most studies demonstrate blunted cortisol reactivity in patients under chronic stress (Zorn et al., 2017).

Accordingly, the question arises, whether the increased prevalence of stress-related disorders in females can be linked to sex differences in the endocrinological response to chronic and acute stressors. Indeed, animal studies show that females display increased basal and stress-induced levels of ACTH and corticosterone (CORT) compared with males (Hillerer et al., 2013; Luo et al., 2013; Romeo et al., 2004; Handa et al., 1994; Jezova et al., 1996). In humans however, the CAR, which is usually assessed as area under the curve, is stronger in women compared to men due to a delayed decrease in cortisol (Hollanders et al., 2017; Wust et al., 2000), but does not change along the menstrual cycle (Wolfram et al., 2011). Conversely, men show a higher cortisol response to psychosocial stress (mostly TSST) than women (Pulopulos et al., 2018; Stephens et al., 2016; Reschke-Hernandez et al., 2017; Kogler et al., 2017; Kirschbaum et al., 1992; Khaksari et al., 2005; Herbison et al., 2016; Childs et al., 2010). However, since the cortisol response to stress is attenuated in depressed patients and rates of depression are higher in women, it is possible that a higher proportion of depressed individuals in the female group have contributed to these findings. Indeed a recent study was not only able to show that attenuated cortisol responses in women are related to depressive symptoms, but that in men, the opposite pattern was observed. In men depressive symptoms predicted a higher cortisol response in stressful situations (Zorn et al., 2017; Powers et al., 2016). Accordingly, sex differences in the physiological stress response may be overestimated, if depression symptomology is not accounted for.

Several studies indicate that sex hormones contribute to the stress response difference between men and women. Firstly, sex differences in the stress response appear to emerge around puberty due to a reduction in cortisol elevations in girls (Stroud et al., 2017; Cameron et al., 2017). Some studies also indicate an increased cortisol response in girls compared to boys before puberty (Hollanders et al., 2017). Secondly, the sex difference in the cortisol response appears to be moderated by women's menstrual cycle phase. While women in their follicular phase show reduced cortisol responses, women in their luteal cycle phase showed comparable cortisol reactivity to stress as men (Stephens et al., 2016; Childs et al., 2010; Montero-Lopez et al., 2018; Kirschbaum et al., 1999; Kajantie and Phillips, 2006). Likewise, high estrogen levels in women being associated with the increased basal levels of ACTH and CORT (Altemus et al., 2001; Marinari et al., 1976) and female rodents in proestrus show higher levels of basal and stress-induced CORT compared to other estrus phases (Carey et al., 1995; Figueiredo et al., 2002; Viau and Meaney, 1991). This finding is somewhat unexpected, given the fact that depressive symptoms are more common in the luteal phase of the menstrual cycle (see Sundstrom Poromaa and Gingnell, 2014 for a review). Indeed, premenstrual syndrome is associated with blunted cortisol reactivity to social or physical stress (Roca et al., 2003; Huang et al., 2015) as well as a blunted CAR (Roca et al., 2003) and the finding of increased cortisol response to stress during the luteal cycle phase is controversial, with some studies reporting no difference between cycle phases (Bouma et al., 2009; Abplanalp et al., 1977) and other studies reporting higher cortisol response during the follicular cycle phase (Nakajima et al., 2019; Maki et al., 2015; Hlavacova et al., 2008). Accordingly, sex and sex hormones are important factors to consider in the etiology of stress-related illnesses.

3. The role of the hippocampus in stress-related disorders

In animals, impaired hippocampal neurogenesis has been linked to an increase in anxiety-like and depressive-like behavior and ablation and/or altered neurogenesis has been associated with increased anxiety-related behavior (Kheirbek et al., 2012; Revest et al., 2009; Sah et al., 2012; Boldrini et al., 2012; Boldrini et al., 2009; Santarelli et al., 2003; Dias et al., 2014). Likewise, in human neuroimaging studies, stress-related disorders like major depressive disorder (MDD), bipolar disorder (BD), anxiety disorders and PTSD have reliably been associated with hippocampal volume loss (MDD: Zhao et al. (2008), Taylor et al. (2005), Spalletta et al. (2014), Sivakumar et al. (2015), Schuhmacher et al. (2012), Opel et al. (2014), MacMaster et al. (2014), Kong et al. (2013), Hastings et al. (2004), Gerritsen et al. (2011), Frodl et al. (2002, 2014); see Vythilingam et al., 2004; Schmaal et al., 2017 for review; BD: MacMaster et al. (2014), Redlich et al. (2014), Frazier et al. (2008, 2005), anxiety disorders: Yamasue et al. (2008), Moon et al. (2014), Irle et al. (2010), Coker et al. (2010): (Ahmed-Leitao et al., 2016; Keding and Herringa, 2015; Logue et al., 2018; Woon and Hedges, 2011. In the case of MDD, which has been most extensively studied, reduced hippocampal volumes have also been related to higher symptom severity (Lorenzetti et al., 2009; Jaworska et al., 2014; Axelson et al., 1993); see Dotson et al., 2009 for review), number of depressive episodes (Axelson et al., 1993; Wisse et al., 2015; Han et al., 2014), longer disorder duration (Sheline et al., 1999; McKinnon et al., 2009) and suicide attempts (Colle et al., 2015). These effects appear to be stronger in the left compared to the right hippocampus (Zhao et al., 2008; Sivakumar et al., 2015; MacMaster et al., 2014). Neither in MDD, nor in PTSD, a sex difference in volume reduction was observed (Woon and Hedges, 2011). However, volume reductions in BD appear to be stronger in females (Frazier et al., 2008, 2005), while no volume reduction was observed in female survivors of sexual abuse (Landre et al., 2010). Furthermore, smaller hippocampal volumes were also observed in schizophrenia (Pruessner et al., 2015; Pegues et al., 2003; Irle et al., 2011; Exner et al., 2008) and ADHD (Wang et al., 2018). Along with volume reductions, a reduced activation of the hippocampus during memory tasks and viewing of emotional pictures was observed in female patients with MDD (Milne et al., 2012; Holsen et al., 2011, 2012). Furthermore, women with PTSD displayed reduced hippocampal reactivity to fear compared to men (Felmingham et al., 2010). Accordingly, understanding the factors that lead to this altered hippocampal morphology and functioning is of uttermost importance for understanding the development of stress-related disorders.

4. Hippocampus-dependent cognitive functions and their role for mood and anxiety disorders

The role of the hippocampus in stress-related disorders has been linked to its function. As an important part of the limbic system the hippocampus has been linked to emotional processing in a wide range of tasks (Mackiewicz et al., 2006). Larger, more active hippocampi, particularly in women, have been related to emotion regulation ability (Kong et al., 2014). However, in both animal and human studies, the hippocampus is, above all, seen as a key area in cognition. The hippocampus forms part of a larger network of structures involved in various aspects of learning and memory (Orsini et al., 2015) and hippocampal neurogenesis and dendritic morphology has long been linked with hippocampal-dependent learning and memory (Leuner et al., 2006; Gould et al., 1999; Jessberger et al., 2009; Kee et al., 2007; Shors et al., 2001). Most prominently, the hippocampus has been implicated in spatial processing (navigation) on the one hand (Wegman et al., 2014; Sneider et al., 2018; Ohnishi et al., 2006; Iaria et al., 2008) and episodic memory processing on the other hand (Pletzer et al., 2019; Protopopescu et al., 2008). Specifically, the right hippocampus seems to play an important role in spatial navigation, while the left hippocampus is more involved in verbal memory (Ezzati et al., 2016). Reduced spatial learning and memory are associated with hippocampal impairments in several animal models (Lassalle et al., 2000; Morris et al., 1982) and are also seen in humans with damage to the hippocampus or in psychiatric disorders and AD (Corkin, 2002; Perl, 2010). Accordingly, it is not surprising that several neuropsychiatric disorders associated with hippocampal volume loss, are also characterized by cognitive deficits (McKinnon et al., 2009; Beinhoff et al., 2008; Gutierrez-Lobos et al., 2002; Scheff et al., 2006; Baum and Sex, hormones, 2005). Therefore, spatial and memory tasks are widely used in both animal and human studies to behaviorally assess hippocampal function.

The fact that cognitive training can also affect hippocampal morphology may even be of therapeutic relevance for stress-related disorders. As an example, hippocampal neurogenesis has been shown to be essential for spatial pattern separation and completion (Clelland et al., 2009; Creer et al., 2010; Sahay et al., 2011); although an optimal level is required i.e. too much is not necessarily a good thing (Akers et al., 2014; Jessberger et al., 2007; Scharfman and Myers, 2016) as has also been demonstrated using computational models (Aimone et al., 2009; Butz et al., 2006). On the flipside, hippocampal neurogenesis can be promoted through spatial training, although the effect is dependent on the developmental stage in which the immature neurons are exposed to the training and the sex of the individual (Epp et al., 2007).

5. Sex differences in hippocampus-dependent cognitive functions

As for the prevalence of stress-related disorders that are associated with altered hippocampal morphology, sex differences for hippocampus-dependent functions are well-documented. Men and women differ in various aspects of cognition, social functioning and emotion (Hollanders et al., 2017; Andreano and Cahill, 2009; Halpern, 2000; Hamann and Canli, 2004; Merz and Wolf, 2017). Sex differences in spatial performance exist across a variety of species and tasks, including MWM and spatial perception tasks in rodents. Typically, males outperform females in spatial acquisition, spatial reference and working memory (Galea et al., 1996; Perrot-Sinal et al., 1996; Jonasson, 2005; Dabbs et al., 1998; Kaufman, 2007; Woolley et al., 2010; Endo et al., 1994; Markowska, 1999). In humans, sex differences in spatial performance have also been observed quite robustly and across cultures in spatial navigation and mental rotation tasks (Galea and Kimura, 1993; Saucier et al., 2002; Schoning et al., 2007; Silverman et al., 2000; Voyer and Bryden, 1990; Voyer et al., 1995). *Vice versa*, women outperform men in verbal memory tasks (Capitani et al., 2005; Capitani et al., 1998; de Frias et al., 2006; Gauthier et al., 2009; Hirnstein et al., 2014; Kimura and Seal, 2003; Soleman et al., 2013; Yonker et al., 2003). This advantage in verbal memory is accompanied by a female advantage in other aspects of memory (Pillemer et al., 2003) including the recognition of objects (Bettis and Jacobs, 2012), female faces (Lewin and Herlitz, 2002), locations (Voyer et al., 2007) or even odors (Oberg et al., 2002). Additionally, in both animals and humans, sex differences in cognition have also been linked to differential cognitive strategies in males and females (Galea and Kimura, 1993; Pletzer, 2014; Beiko et al., 2004; Grön et al., 2000; Williams et al., 1990). For example in the Morris water maze, it has been shown that males prefer extra-maze spatial/geometric cues, which are hippocampus-dependent, whereas females tend to rely on visible landmark cues, which are more dependent on the striatum (Cherney et al., 2008; Grissom et al., 2013). A stronger focus on local landmark cues by women has also repeatedly been demonstrated in spatial navigation in humans (see Harris et al., 2019 for review).

Regarding emotion recognition, women appear to particularly outperform men in the recognition of sad and fearful faces (Olderbak et al., 2019). Nevertheless, women appear to show greater expression of emotions (Hamann and Canli, 2004). Interestingly, it appears that in summary, a female advantage is more likely found in those aspects of behavior that cannot be studied in animals, like verbal functions, such that the neurobiological underpinnings of these behaviors are not as well understood as for those showing a male advantage, like spatial functions. Therefore, the molecular mechanisms that differ between males and females are likely to play key roles in the differences that have been observed regarding cognitive processes and the higher incidence of psychiatric disorders in women. In the following sections, we outline some of the molecular mechanisms, focussing on the hippocampus that underpin these sex differences.

6. Preclinical studies on the molecular mechanisms of sex and stress hormone actions in the hippocampus – Studies on neurogenesis and dendritic morphology

Steroid hormones are potent regulators of adult hippocampal neurogenesis and dendritic morphology with its regulation being dependent on sex, age and reproductive experience (see Mahmoud et al., 2016 for review). Estrogens (i.e. 17α/β-estradiol, estrone), progestins (i.e progesterone) and androgens (i.e. testosterone) play an important role in regulating different stages of adult hippocampal neurogenesis i.e. proliferation, differentiation and survival of new neurons during developmental and adult hippocampal neurogenesis in males and females (Bowers et al., 2010; Waddell et al., 2013; Zhang et al., 2008). Similar to sex differences in adult hippocampal neurogenesis, there is a profound amount of data suggesting similar differences with respect to dendritic morphology that may underlie sex-differences in behavior (for review see Koss and Frick, 2017; Scharfman and MacLusky, 2017). The predominant evidence for a role of sex hormones in adult hippocampal neurogenesis comes from exogenous hormone manipulation studies in ovariectomised (OVX) and castrated (GDX) animals. In the following section, we review the available literature about the influence of acute and chronic treatment of estrogens, progestogens and testosterone on adult hippocampal neurogenesis and dendritic morphology in males and females.

6.1. Sex differences in hippocampal neurogenesis

During adolescence, the number of immature neurons in the dentate gyrus declines more rapidly in males and the number of immature neurons is higher in adult females compared to males (Siddiqui and Romeo, 2019). As outlined in a recent review, sex differences in hippocampus-dependent cognitive functions have also been linked to sex differences in hippocampal proliferation during learning (Yagi and Galea, 2019). For example, better spatial acquisition in males is concomitant with increased survival of new neurons during training; however these two factors were not correlated (Chow et al., 2013).

When cell activation within the granule cell layer (GCL) was assessed *via* co-labelling of bromodeoxyuridine (BrdU) and EGR-1 again there was a greater activation of new cells in males than in females; however, performance was positively correlated in females, but not in males and the response to spatial memory retrieval was similar between the sexes (Chow et al., 2013). Moreover, better spatial learning is associated with greater activation of 20d neurons only in females, which may be interpreted such that (1) new neurons are more excitable in females than in males, (2) new neurons mature faster under the influence of estradiol, which regulates cell development/facilitates effects on neural excitability (Lee et al., 2004; Smith and McMahon, 2006) and (3) may depend on an increased perceived task difficulty in females, which increases involvement of the hippocampus (Beylin et al., 2001). Fast acquisition of trace eyeblink conditioning, which is a hippocampal-dependent task, is correlated with greater cell survival (in terms of percentage) in females (Dalla et al., 2009).

6.2. Sex differences in dendritic morphology

Sex differences in hippocampal morphology, vary across the life span and different effects have been reported for different hippocampal subfields (Bartesaghi et al., 2003; Shors et al., 2001). For instance, while young adult males show stronger dendritic branching in CA1 than young adult females, this sex differences disappears during aging (Markham et al., 2005). Since sex differences in dendritic morphology of the adult hippocampus appear to be largely dependent on the estrus cycle in females and other endocrinological factors like stress, these changes across the life span are likely also dependent on hormonal variations (Markham et al., 2005). Accordingly, the following sections will focus on the modulation of dendritic morphology by sex and stress hormones.

6.3. Estrogens

Estrogens, with its most important endogenous specimen 17β-estradiol, are among the most important sexual hormones, enzymatically derived *via* transformation of androgens, which is catalysed by the enzyme aromatase. Synthetic estrogens used in animal studies are mostly 17β-estradiol, estrogen benzoate, estrone or conjugated estrogens like sodium estrogen sulfate or sodium equilin sulfate. Estrogens exert its neuronal and behavioral action *via* the specific estrogen receptors ERα/β, by classical and non-classical mechanisms (see Fuentes and Silveyra, 2019; Galea et al., 2017 for review). The effects of estrogens on hippocampal neurogenesis and dendritic morphology have been investigated by observing natural estrogen fluctuations in female animals (e.g. along the estrous cycle), by surgical intervention (ovariectomy) as well as by pharmacological intervention (exogenous estrogen administration, inhibition of estrogen synthesis). Overall results demonstrate a positive effect of estrogens on hippocampal neurogenesis and dendritic morphology in females. Studies in males are less common, but seem to demonstrate rather little effect, but perhaps an increase in cell survival (Barker and Galea, 2008; Spritzer and Galea, 2007).

6.3.1. Estrogenic effects on hippocampal neurogenesis

Generally it seems that estrogen levels are positively correlated with cell proliferation and negatively correlated with cell death (Pawluski et al., 2009 for review). However, its effects are highly dependent on a variety of factors including temporal dynamics, dose, age, sex and species (Bowers et al., 2010; Barker and Galea, 2008; Chan et al., 2014; Galea, 2008; Galea et al., 2013 for review). The first hint about a possible involvement of sex steroids in regulating adult hippocampal neurogenesis came from observations of Galea and Ormerod. They demonstrated that female meadow voles express decreased levels of cell proliferation during breading season, when estrogen levels are naturally high (Galea and McEwen, 1999; Ormerod and Galea, 2001). In contrast, rats during pro-estrus/phases of high estrogen, have been shown to have increased levels of c-Fos and zif268 activation, cell proliferation, 14d cell survival and neural excitability in the DG (McClure et al., 2013; Rummel et al., 2010; Tanapat et al., 1999; Warren et al., 1995; Yagi et al., 2017). Further corroborating the first findings about a possible involvement of estrogen in regulating hippocampal neurogenesis, lowering estrogen levels *via* removal of ovaries, significantly reduced cell proliferation, which could be rescued by estrogen replacement (Fowler et al., 2008; Perez-Martin et al., 2005) (see Pawluski et al., 2009; Galea, 2008 for review). However, the aforementioned effect of OVX on cell proliferation is dependent on the time elapsed since OVX. In detail, OVX decreases cell proliferation when assessed at 6-7d (Tanapat et al., 1999), but this appears to be a short-lasting consequence as long-term OVX (21/27d) has no effect on cell proliferation in rats and mice (Banasr et al., 2001; Green and Galea, 2008; Lagace et al., 2007; Tanapat et al., 2005). Together, these findings suggest that the female brain may have a compensatory mechanism that restores cell proliferation after longer periods of OVX, i.e. by an increase of extragonadal aromatization (Zhao et al., 2005) and synthesis of estrogen in hippocampal neurons (Fester et al., 2012; Hojo et al., 2008). Indeed, *in vitro* studies demonstrate that hippocampal granule cells in hippocampal dispersion cultures require local estrogen to proliferate, as inhibition of its synthesis with the specific aromatase inhibitor letrozole decreases cell proliferation, whereas application of exogenous estrogen had no effect (Fester et al., 2006).

Similar to OVX, the effects of exogenous estrogen administration are largely treatment duration-, time- and dose-dependent. Thus, acute treatment with estrogen has been shown to have a dose-dependent non-linear effect (Tanapat et al., 2005; Barha et al., 2009), with single injections of low (di-estrus range; 0.3 μg) and high doses (pro-estrus range; 10 μg) restoring cell proliferation in OVX rats, whereas medium/supraphysiological doses (1 μg/50 μg) are ineffective (Tanapat et al., 2005; Barha et al., 2009). The acute effect of estrogen seems to have a rapid within hour effect that is persistent, but only if it occurs within a critical period after OVX. Respectively, acute estrogen replacement in high/pro-estrus doses (10 μg) is able to restore cell proliferation to the level of SHAM controls in young adult rats 1 week after OVX, whereas treatment 28d after OVX was ineffective in this manner (Tanapat et al., 2005). These findings suggest that long-term OVX reduces the cells sensitivity, or ability, to respond to the proliferative effect of acute estrogen treatment after long-term deprivation. Time-dependent effects of acute estrogen treatment are rather transient, occurring rapidly with an increase in cell proliferation followed by a decrease after longer timepoints. In more detail, 17β-estradiol, estradiol benzoate and estrone increase cell proliferation 30 min, 2 h and 4 h post-administration in young adult, adult and middle-aged OVX rats (Ormerod and Galea, 2001; Tanapat et al., 1999; Tanapat et al., 2005; Barha et al., 2009; Barha and Galea, 2011; Ormerod et al., 2003), whereas a decrease in cell proliferation has been observed 48 h after estradiol benzoate administration (Ormerod and Galea, 2001; Ormerod et al., 2003). The observed time-dependent and transient effects of acute estrogen may be a result of stimulating different populations of proliferative cells i.e. cells in a progressive steady state and a replenishing cell population (Nowakowski et al., 2008). In this context, stimulating one population of cells would decrease the rate of division in the other population to keep the amount of proliferating cells constant, which in fact may also explain why longer times of acute estrogen administration do not increase cell proliferation.

Similar to the temporal effects of OVX, chronic estrogen treatment seems to play a minor role in influencing hippocampal cell proliferation in females, as 21d treatment with either release pellets, injections or cyclic regimen of injections every four days for one week post OVX showed no effect on cell proliferation in rats (Chan et al., 2014; Tanapat et al., 2005). However, results may also vary dependent on methodological differences (i.e. continuous exposure *via* pellet *vs.* pulsatile exposure *via* subcutaneous injections), as 15d continuing estrogen

treatment had a positive effect on cell proliferation in female rats, when administered one week after OVX (Barker and Galea, 2008). Another important point to consider when investigating the effects of estrogen on adult hippocampal neurogenesis is the timeline of estrogen administration relative to the examination of cell proliferation and relative to the length of estrogen exposure.

Overall, the effects of estrogen on stages of neurogenesis apart from proliferation i.e. cell survival are significantly less well studied. Regarding the latter, the outcome seems to be largely dependent on whether the proliferative marker (i.e. BrdU) is injected before or after the hormonal treatment. Injecting BrdU prior to estrogen treatment will reveal the effect of estrogen independent of cell proliferation, whereas BrdU injections after hormonal application include the effects of estrogen on proliferation and survival. Thus, the hormone-related environment during which the cells are generated determines the outcome of chronic estrogen on cell survival. In this context, a decreased survival was observed in cells produced prior to treatment with estradiol benzoate (with BrdU injected prior to treatment) (Barker and Galea, 2008; Chan et al., 2014), whereas an increase in cell survival has been shown in populations produced after initiation of 17β-estradiol treatment (with BrdU injected following hormonal treatment) (McClure et al., 2013). This is most likely attributed to the estrogen-induced increase in cell proliferation, as the increase in cell survival is only seen, when respective cells are produced in an estrogen-enriched environment. Other forms of estrogen seem to negatively impact cell survival under chronic conditions, as high estrone for 20d decreases new neuron survival in the DG, revealing that cells that proliferate under estrone do not survive in an estrogen-rich environment (McClure et al., 2013).

Unfortunately, the aforementioned studies do not include males, which limits our understanding of the effect of estrogen treatment mostly to females. However, the few studies performed point towards a sex-dependent effect of estrogen in hippocampal neurogenesis. Thus, acute treatment with high doses of estradiol benzoate (100 μg) in intact neonates (postnatal day (PND) 0) increases cell proliferation in females, with no effect observed in males, despite an increased level of cell proliferation under basal conditions. In contrast, administering the aromatase inhibitor, formestane, or the estrogen receptor antagonist, tamoxifen, significantly decreased the number of new cells in males but not females. Given the fact that the increased rate of proliferation induced by neonatal estradiol persisted until at least 3 weeks of age, there appears to be an organizational effect (Bowers et al., 2010). Although interpreting the results of the latter study needs caution, as it has to be kept in mind that endogenous estrogen synthesis may have influenced the outcome of exogenous estrogen application, the results in neonates are mirrored by those in adult rats revealing that chronic estradiol benzoate treatment had no significant effect on cell proliferation or survival in males (Barker and Galea, 2008; Spritzer and Galea, 2007). In contrast short-term treatment has been shown to increase survival in males after a 3–5 day treatment with estradiol benzoate in voles and mice (Ormerod et al., 2004; Saravia et al., 2007; Zhang et al., 2010), an effect that seems to be limited to the axon extension phase of the cell development as 29d treatment did not affect neurogenesis (Ormerod et al., 2004; Saravia et al., 2007). Therefore, taken as a whole, the general consensus is that neurogenesis in males is not, or only minimally, affected by exogenous estrogen exposure.

The molecular mechanism mediating the effect of estrogen on adult hippocampal neurogenesis may be largely attributed to the action of estrogen receptors (ERs), ERα and ERβ that are located in the CA1/3 region and DG of the hippocampus of males and females (Fowler et al., 2005; Mazzucco et al., 2006; Perez-Martin et al., 2003; Shima et al., 2003; Shughrue et al., 1997) (and see Duarte-Guterman et al., 2015 for review), as activation of ERα/ERβ with the specific agonists propyl pyrazole triol (PPT) and diarylproprionitrile (DPN) increases cell proliferation (Mazzucco et al., 2006), whereas the use of a selective ER antagonist blocks the effect of estrogen in OVX females (Nagy et al., 2006). However, treatment with the above mentioned agonists is not able to restore cell proliferation to levels seen with estrogen, suggesting that modulation of neurogenesis by estrogen occurs not only *via* ERα/β, but also *via* the G-protein coupled estrogen receptor GPER, which is expressed in the DG, CA1,2,3 in male and female rats (Brailoiu et al., 2007). Indeed, treatment with the GPER antagonist G15 or the GPER agonist G1 has been shown to have a proliferative/anti-proliferative effect (Duarte-Guterman et al., 2015). Furthermore, there seems to be a mediation of estrogen effects *via* adrenal hormones, as adrenalectomy (ADX) eliminates the estradiol benzoate induced increase in cell proliferation seen after 48 h of estrogen exposure in OVX rats (Ormerod et al., 2003). Whether these ERα and ERβ-mediated effects are *via* membrane estradiol signalling or transcriptional or a combination of both remains to be fully elucidated. In a recent study using the streptozocin-induced diabetic mouse model, ERα and ERβ agonists were shown to increase the membrane ERα and ERβ protein levels in the hippocampus, but not in the nucleus and subsequently CREB and BDNF levels (Tang et al., 2019). Moreover, sex-differences in the molecular mechanism *via* which estradiol potentiates glutamatergic signalling and within the hippocampus have been observed. While this occurs in both sexes, at both the pre-synapse and post-synapse, it appears to occur through the oppose receptors in males and females (Oberlander and Woolley, 2016). In keeping, the mechanism through which estradiol facilitates long-term potentiation also differs between males and females (Jain et al., 2019).

6.3.2. Estrogenic effects on dendritic morphology

The effects of estrogen on hippocampal dendritic morphology are wide-ranging, not only affecting dendritic density, but also spine type. Thus, whereas males tend to express higher numbers of thin spines, females have been shown to have more mushroom spines, an effect that is even more pronounced during phases of high estrogen (i.e. pro-estrus) compared to phases of lower estrogen (i.e. estrus) (Gonzalez-Burgos et al., 2005; Vierk et al., 2012) (see Sheppard et al., 2019 for review). This is an interesting finding given the fact that thin and mushroom spines differ in their functional characteristics with the latter being more mature/stable spines, with a larger postsynaptic density and increased number of AMPA receptors. In contrast, thin spines are typically more dynamic/transient spines (Ashby et al., 2006; Harris et al., 1992; Holtmaat et al., 2005; Shinohara et al., 2008; Zuo et al., 2005) (see Bourne and Harris, 2007; Kasai et al., 2010 for review). Such differences may also explain differences in behavioral performances between males and females or females during different phases of the estrus cycle.

Estrogen treatment is known for its rapid effect on dendritic spines. Accordingly, dendritic spine density has been shown to fluctuate in CA1 pyramidal cells across the estrus cycle, with highest spine density levels observed during phases of high estrogen i.e. pro-estrus (McEwen and Woolley, 1994; Woolley et al., 1990). In keeping with the changes observed in hippocampal neurogenesis, the density of spines in the CA1 region of the hippocampus gradually decrease after OVX (Gould et al., 1990), an effect that remains stable for up to 40d (Woolley and McEwen, 1993). The reduction can be rescued by exogenous estrogen administration in rats (Gould et al., 1990; Woolley and McEwen, 1993; Jacome et al., 2016; MacLusky et al., 2005) and mice (Mukai et al., 2007; Phan et al., 2012; Tuscher et al., 2016), or after treatment with specific ER agonists. In more detail, *in vivo* studies revealed and increase in the number of dendritic spines in CA1 after the administration of the ERα agonist PPT (Phan et al., 2011) or the GPER agonist G1 (Gabor et al., 2015), whereas the antagonist DPN had the opposite effect (Phan et al., 2011). Similar findings of increased spine density have been reported in the CA1 region of male rats following 17β-estradiol administration in male rats (Jacome et al., 2016). Importantly, the results observed *in vivo* are mirrored by *in vitro* studies using hippocampal sections from female and male rats that were exposed to exogenous estrogen application or application of an ERα agonist (Mukai et al., 2007; Phan et al., 2015; Tsurugizawa et al., 2005). However, the effects

observed *in vivo* and *in vitro* may rather be dependent on local estrogen synthesis in spines than estrogen from the periphery, at least in females, as revealed by studies using the aromatase inhibitor letrozole, which induces a non-steroidogenic, reversible inhibition of the local estrogen synthesis in hippocampal spines. Hence, inhibition of local hippocampal estrogen synthesis leads to a loss of spines in intact and OVX females, as well as in hippocampal cell cultures from female rats (Fester et al., 2012; Brandt et al., 2013; Kretz et al., 2004), with the degree of spine loss being even higher in cycling females (Zhou et al., 2010). The fact that there was no effect observed in males/male cell culture (Fester et al., 2012; Brandt et al., 2013; Kretz et al., 2004; Zhou et al., 2010), suggests a sex-specific difference in sexual steroid-induced synaptogenesis. The observed gender differences after letrozole treatment may be either a result of a dramatic impairment of LTPs in females, which play an important role in spine formation (Yuste and Bonhoeffer, 2001; Yuste and Bonhoeffer, 2004), or may depend on a GnRH-regulatory mechanisms, which may stimulate estrogen synthesis in hippocampal neurons and spine synapse density in a dose-dependent manner in females. Indeed, treatment with the GnRH antagonist antide has been shown to abolish the effect of local estrogen synthesis in female rats (Zhou et al., 2010). Although, the exact mechanisms are unknown, and there are no direct neuronal connections present that could account for the observed phenomenon, there may be an indirect pathway *via* the median eminence.

6.4. Progestogens

The second group of sex hormones are progestogens. In contrast to estrogens, their precursor-stage is not testosterone, but pregnenolone, which is enzymatically converted into progesterone *via* the 3β-hydroxysteroide dehydrogenase (3β-HSD). The most important endogenous progestogen in humans is progesterone (synthetic progestogens are termed progestins). In addition, its metabolite allopregnanolone, which is also produced in hippocampal neurons plays an important role in a variety of processes.

Progestogens act *via* the progesterone membrane receptors PR-A/B expressed throughout reproductive tissue and the brain (see Brinton et al., 2008 for review). Studies on the effects of progesterone on molecular mechanisms in the hippocampus are rare and have yielded inconsistent results. While some studies demonstrate facilitating effects on estrogenic mechanisms, other studies demonstrate counteracting effects on estrogenic mechanisms. The results appear to be dose- and time-dependent, which may account for some of the inconsistencies in the literature.

6.4.1. Progestogenic effects on hippocampal neurogenesis

In addition to estrogens, progestins like progesterone are important regulators that can modulate the effect of estrogen in influencing adult hippocampal neurogenesis in adult females (Tanapat et al., 2005). In this context it seems that progesterone may antagonize the effect of estrogen on cell proliferation, as a single dose of progesterone given 24 h after estrogen administration diminishes the estrogen-induced increase in cell proliferation in female rats (Tanapat et al., 2005; Liu et al., 2010). However, the interaction of progesterone and estrogen to affect neurogenesis differs from acute to chronic administration. Respectively, acute progesterone increases cell proliferation in the SVZ of OVX rats after 1 h (Bali et al., 2012), whereas chronic progesterone plus or minus estrogen for 21d (1/4mg/kg) one week after OVX has no significant effect on cell proliferation in rats, while decreasing the survival of cells that were built prior to hormonal treatment (Chan et al., 2014). Due to a dearth of studies the importance of progesterone in regulating hippocampal cell proliferation or cell survival in males is largely unknown, but some results in rats pointing towards a stimulating effect on cell proliferation, with no effect seen on survival after a 7 day treatment with progesterone (Barha et al., 2011). Despite this, and like the case for estrogens, the results are largely dependent on the species and timepoint of hormonal treatment relative to BrdU administration. Male mice were shown to display increased levels of surviving cells, when progesterone treatment took place 5–7 days post BrdU, whereas no effect was observed 10–12 or 15–17 days post BrdU (Zhang et al., 2010). In summary, the few studies available to date suggest a sex-difference regarding the effect of progesterone on neurogenesis, with progesterone increasing it in males and decreasing it in females, however there is need for more detailed studies to prove this assumption.

6.4.2. Progestogenic effects on dendritic morphology

The effects of progesterone on dendritic morphology in the hippocampus are significantly less well studied compared to estrogen. The few available studies suggest a potential involvement of progesterone with initially potentiating the effect of estrogen on spine formation, while observation of later timepoints rather suggests a downregulation in number (Gould et al., 1990; Woolley and McEwen, 1993).

6.5. Androgens

The third group of sex hormones, known for their regulatory function in adult hippocampal neurogenesis are androgens, which particularly play an important role in males and have mostly been studied in males. The most important androgens are testosterone and dihydrotestosterone (DHT). While testosterone is enzymatically derived from androstenedione *via* 17β-HSD, the pharmacologically more active DHT results from another reductive step out of testosterone *via* the 5α-dehydrogenase; with both acting *via* the androgen receptor AR (for review see Hajszan et al., 2007).

The most frequently used synthetic androgens used in animal studies are testosterone propionate, androsterone and 3α-androstandione. Studies in animals include surgical intervention (gonadectomy) as well as pharmacological intervention (testosterone/DHT administration). Overall androgens appear to facilitate hippocampal neurogenesis and dendritic spine formation in males, with rather no effect in females.

6.5.1. Androgenic effects on hippocampal neurogenesis

Although GDX does not affect cell proliferation in the male DG, it significantly decreases the number of newly generated neurons that survive to maturity (Spritzer and Galea, 2007; Hamson et al., 2013; Ormerod and Galea, 2003; Spritzer et al., 2011). Interestingly, the timing of castration during development may play a role, as the negative effect on cell survival was only observed when GDX takes place in adulthood (Spritzer and Galea, 2007), whereas GDX prior to puberty rather increased survival of new neurons and enhanced differentiation of cells into neurons (Allen et al., 2014). However caution is required when interpreting these results, as they are highly likely to be influenced by methodological differences i.e. species (i.e. rodents *vs*. rhesus macaques) and the timing of neurogenesis measurement (i.e. 37d *vs.* 2y after GDX). There is also conflicting evidence regarding the ability of androgen administration to rescue the GDX-induced deficit in cell survival in male rats, as 30d administration of testosterone or DHT, but only at doses of 0.25 mg/day or higher, was able to rescue cell survival in male rats (Spritzer and Galea, 2007; Hamson et al., 2013), whereas others have shown that testosterone supplementation does not affect survival in GDX males (Spritzer et al., 2011; Buwalda et al., 2010; Carrier and Kabbaj, 2012). Thus, the neurogenesis promoting effect of testosterone may rather be attributed to the necessity of a stable optimal hormone level than high levels of testosterone. Indeed, androgens may also have deleterious effects on hippocampal neurogenesis, as seen after a seven day treatment with finasteride, which lead to a diminished cell proliferation one day post treatment in intact male mice (Romer et al., 2010). Furthermore, the duration of androgen administration is a critical factor in promoting the survival of cells, with short-term treatments (up to 21d) rather decreasing (Spritzer et al., 2011; Carrier and Kabbaj, 2012; Brännvall et al., 2005) and long-term treatments

(30–90d) rather increasing (Spritzer and Galea, 2007; Hamson et al., 2013) the number of new neurons in the DG of GDX rats. The effect of testosterone in females is virtually unknown, with only one study directly comparing males and females showing that testosterone increases proliferation in the SVZ of male rats, with no effect in females (Farinetti et al., 2015).

The molecular mechanism behind the effects of testosterone to mediate neuronal survival are most likely regulated *via* an AR-mediated mechanism, as treatment with high-AR-affinity testosterone metabolite DHT, led to an increase in neurogenesis, while this enhancement was blocked by the AR antagonist flutamide. Moreover, mutations of ARs have been shown to be associated with an inhibition of neurogenesis in male rats (Hamson et al., 2013). Although the expression of ARs has been revealed in the hippocampus of male and female rats, with higher density in males (Xiao and Jordan, 2002), they seem to be absent in the DG of most rodents (see Mahmoud et al., 2016; Galea et al., 2013 for review), suggesting a lack of direct actions of androgens in the DG, but rather a molecular mechanism initiated outside of it. Given the presence of ARs in the CA3 region of the hippocampus and the fact that granule neurons contact thorny excrescences located on CA3 pyramidal neurons, it is likely that ARs in CA3 contribute to the neurogenesis promoting effect of testosterone in the DG. In addition, a retrograde transport survival mechanism that is secreted from CA3 has been suggested (Hatanaka et al., 2009).

6.5.2. Androgenic effects on dendritic morphology

Similar to estrogen, testosterone and its metabolite DHT seem to increase spine density in the CA1 region as revealed in hippocampal slice culture from male rats (Ooishi et al., 2012), with DHT rather increasing the number of large and middle head spines, while testosterone rather increasing the number of small spines, which may have functional consequences as discussed above for estrogen.

6.6. Stress and stress hormones

Although acute and chronic stress are generally known for their negative effect on adult hippocampal neurogenesis, like described for the sex steroids above, this is dependent on the age-, sex-, stressor- and BrdU-timing (Gould et al., 1997; Gould et al., 1998; Pham et al., 2003; Tanapat et al., 2001; Torner et al., 2009; Uno et al., 1989) (and see Abrous et al., 2005; Cameron and Schoenfeld, 2018; Gobinath et al., 2015 for review). In general, there are significant stress-induced sex-differences on diverse phases of hippocampal neurogenesis, which are mainly due to differences in the stress response between males and females, who do not only differ in their stress sensitivity but also with respect to coping mechanism (Dalla et al., 2008; Bowman et al., 2001) and see Goel et al., 2014 for review). Unfortunately, most of the studies available to date only include one sex when assessing the effects of acute or chronic stress exposure on neurogenetic processes like adult hippocampal neurogenesis, dendritic morphology or synaptic plasticity. To examine how stress alters plasticity in the male and female hippocampus and how these changes in neuroplasticity in fact translate to sex-differences in behavior and susceptibility for mood related-disorders like depression and anxiety, there is certain need for studies investigating sex-differences in those processes by direct comparison of males and females. In the following section, we summarise the current literature about the effects of stress during different developmental windows (i.e. prenatal and early life, adolescence and adulthood) on sex-differences in adult hippocampal neurogenesis and dendritic morphology.

6.6.1. Early-life (adolescent) stress and stress hormones – effects on hippocampal neurogenesis

Prenatal stress (PNS), which is usually achieved by exposure of the dam to stressful physiological or psychological events during different stages of pregnancy has been shown to have wide-ranging consequences on offspring brain development and behavior (for review see Weinstock, 2016). Although there is a general lack of studies assessing the effect of PNS on hippocampal neurogenesis, the few available datasets suggest deleterious effects on hippocampal neurogenesis in juvenile, adolescent and adult rodents (Belnoue et al., 2013; Lemaire et al., 2000; Mandyam et al., 2008; Rayen et al., 2015) and pre-pubertal rhesus monkeys (Coe et al., 2003), with effects being more prominent in the ventral hippocampus (Zuena et al., 2008), which has been linked with stress regulation and anxiety (Fanselow and Dong, 2010). Further complicating an analysis of sex-differences of PNS on hippocampal neurogenesis, there are even fewer studies performed in females. However, it appears that males are more susceptible to perturbations induced by PNS than females. In more detail, RS of the dam 3 times per day for 45 min from gestation day (GD) 15–20 and twice per day on GD21 resulted in a markedly reduced hippocampal cell proliferation and a trend towards a decreased survival in male rats (Rayen et al., 2015), when assessed during adulthood (i.e. on postnatal day (PND) 69–76; 3w post BrdU). The results in females are rather controversial, most likely attributed to the use of different PNS paradigms, with some studies showing no effect on cell proliferation (Zuena et al., 2008) and others showing a similar decrease in cell proliferation (Mandyam et al., 2008) as observed in males. Additionally, the limited nesting and bedding material paradigm was shown to cause a rapid increase in neurogenesis as observed by increased proliferation and differentiation in the DG at PND9 in both sexes. However, when assessed at PND150, both the early life stress paradigm was revealed to cause a long-lasting decrease in DG volume as well as long-term survival of developmentally-born neurons in both sexes. Males were also shown to display reduced neuronal survival, without changes in proliferation or differentiation, whereas females did not display such changes. These changes in survival correlated with impaired learning and memory in males, whereas such impairments were less pronounced in females (Naninck et al., 2014). Taken together, these findings suggests that the paradigm is more suited for use in male rodents than females. While not performed in the same study, social instability stress in adolescence has been shown to differentially affect hippocampal neurogenesis, but not spatial memory in males and females. Thus, exposure to the stressor leads to spatial memory impairments in adulthood in males and females. However, male rats initially (PND 33) displayed increased Ki67 immunoreactive cells and a greater survival, as assessed using DCX as a marker (PND 46), whereas females showed a reduction in both proliferation and survival (McCormick et al., 2012; McCormick et al., 2010). Thus, given the fact that any disturbances of developmental neurogenesis may relate to sex-dependent differences in the outcome of psychiatric disease later in life, there is urgent need for studies directly comparing males and females regarding different stages of hippocampal neurogenesis during different developmental windows after PNS in one experimental outline.

While our understanding of the effects of PNS on hippocampal neurogenesis is rather limited, the effects of early life stress (ELS) are well-studied in both males and females. ELS can be achieved by disturbances of the mother-infant-interaction, which includes maternal deprivation/separation or exposure of the dam to high CORT, thus decreasing maternal care, limited bedding or exposure to psychological stressors like predator odor. Although the exact mechanisms are unknown, adverse early life events seem to negatively affect hippocampal neurogenesis due to a persistent rise of HPA axis activity during a very sensitive developmental window (Sapolsky and Meaney, 1986). The outcome of ELS on sex-differences in hippocampal neurogenesis is dependent on various factors that have to be considered when interpreting the results i.e. stress paradigm/species used in the studies and the timepoint of the assessment of hippocampal neurogenesis after ELS exposure. Thus, while early maternal deprivation for 24 h at PND3 increases proliferation in the DG of PND21 male rats, it decreases it in females (Oomen et al., 2009), whereas maternal separation for longer periods (i.e. 2–6 h/day for up to 21 days) or high maternal exogenous

CORT administration (40 mg/kg/day) leads to a decreased cell proliferation in males with no effect in females, when investigated on PND15, PND 22, juvenile age or adulthood (Baek et al., 2011; Baek et al., 2012; Brummelte et al., 2006; Hulshof et al., 2011; Lajud et al., 2012; Mirescu et al., 2004; Oreland et al., 2010; Suri et al., 2013). However, there are other studies in rats and mice revealing an increased level of cell proliferation after similar maternal separation periods or after exposure to limited nesting stress, when examined on PND19, during late postnatal life and young adulthood (Suri et al., 2013; Feng et al., 2014; Naninck et al., 2015). Taken as a whole, these studies indicate that ELS may transiently endow animals with a potential adaptive advantage in a stressful environment, but with long-term deleterious effects across the life span. Moreover, it is likely that the decreased cell proliferation observed in females during this critical period of brain development could be one factor contributing to the increased vulnerability of females to develop psychiatric disorders such as depression in later life. The sex-dependent effects of ELS are not limited to differences in hippocampal cell proliferation, but also include changes in immature neuron production and cell survival. In more detail, maternal separation for 24 h on PND3 increases immature neuron production in male rats, but decreases it in females (Oomen et al., 2009). However, the observed increase in males may be a short-term-restricted adaptive change in response to stress exposure, as it was only observed when immature neuron production was investigated at the time of weaning. In contrast, the number of DCX positive cells in the ventral hippocampus were shown to be significantly diminished after maternal separation when assessed during adulthood, with no effect in females (Oomen et al., 2011; Oomen et al., 2010), suggesting that males express more dynamic, long-lasting changes in hippocampal plasticity in response to ELS. Nevertheless, the effects of ELS on immature neuron production may be largely dependent on the stress protocol and species used, as maternal exposure to high CORT (postpartum day (PPD) 2–23; in rats) or limited nesting and bedding material (PPD2-9; in mice) revealed contrary results, with adult males showing either no effect or an increased density of immature neurons, while in females the opposite picture occurred (Naninck et al., 2014; Gobinath et al., 2016). The effects of ELS on cell survival are rather conflicting and as discussed above, dependent on species, as maternal deprivation, early weaning or limited nesting material diminished the number of BrdU+ and BrdU+/NeuN+ cells in adult male mice, with mostly no effects in females (Naninck et al., 2014; Kikusui et al., 2009; Leslie et al., 2011), whereas maternal separation did significantly affect cell survival in male rats when assessed in adulthood (Hulshof et al., 2011; Mirescu et al., 2004). Overall, it is likely, that the different changes observed after ELS may be an adaptive mechanism to enable the individual to cope with a potential future adversity in life.

PNS and ELS rely on the disturbance of the mother-infant-relationship and stressors during adolescence are mostly effective when a social stress component is used i.e. social isolation stress (Perani and Slattery, 2014; Hillerer et al., 2012). Thus, social isolation for one or three weeks reduces cell proliferation in the rostral hippocampus and reduced the number of immature neurons throughout the hippocampus in adolescent non-human primates (Cinini et al., 2014). Although the latter study did not assess stress-induced sex-differences in hippocampal neurogenesis, studies in rodents suggest, that in contrast to PNS and ELS, which seem to affect males more than females, stress during adolescence induces predominantly deleterious effects in females. Thus, social instability stress (1 h isolation/d and change of cage partner on PND30-45) reduces hippocampal cell proliferation and survival in female rats on PND49 (McCormick et al., 2010), whereas the same stress protocol induced an increase in cell proliferation in males on PND46 and in adulthood (McCormick et al., 2012). Similar sex-dependent effects were observed after chronic restraint stress (RS) (1 h/d from PND30-52), when rats were perfused on PND70 (Barha et al., 2011).

6.6.2. Early-life stress (adolescent) and stress hormones – effects on dendritic morphology

Although less well studied, the available data suggest that acute and/or chronic stress can also affect dendritic morphology and synaptic plasticity of the hippocampus throughout different developmental stages. However, given the overall lack of studies in females regarding this topic, sex-dependent effects are largely unknown, illustrating the need for more research in this field. Similar to the effects of ELS on hippocampal neurogenesis, different stressors during early life have been shown to have deleterious effects on dendritic morphology in different rodent species. Thus, maternal separation or chronic RS results in a diminished dendritic complexity in CA3 pyramidal neurons in mice and rats (Leslie et al., 2011; Galea et al., 1997), with males expressing a reduced number of branching points and dendritic length particularly in apical dendrites, whereas the same effect was more pronounced in basal dendrites in females (Galea et al., 1997).

6.6.3. Stress during adulthood – effect on hippocampal neurogenesis

Given the importance of long-term consequences of acute and chronic stress during adulthood on physiological and mental health, there have been numerous studies dealing with this topic during the last decades. Although these studies have tremendously increased our understanding of stress-induced alterations in hippocampal plasticity in males and females, the various different experimental outlines makes a direct comparison of results virtually impossible. Nevertheless, the following section reviews the available data on sex-dependent effects of acute and chronic stress during adulthood on hippocampal neurogenesis.

The effects of stress on adult hippocampal neurogenesis are largely dependent on the duration of stress exposure as well as the sex of the individual. Although different forms of acute stress may induce one specific picture in males and females, the opposite may occur after chronic stress exposure. Accordingly, acute foot-shock stress (Shors et al., 2007) or predator stress (Falconer and Galea, 2003) was shown to decrease the number of proliferating cells in males and females, whereas chronic exposure to the same paradigms increases the number of BrdU+ cells in females, while not affected proliferation in males (Westenbroek et al., 2004). Although various stress paradigms like acute psychosocial- (social dominance), restraint- or footshock stress did not reveal significant effects of stress on cell proliferation in male rats (Pham et al., 2003; Hanson et al., 2011; Thomas et al., 2007), extended time courses of daily RS, inescapable stress, chronic mild stress (CMS) and social stressors were shown to diminish the rate of proliferation up to 24% (Hillerer et al., 2013; Pham et al., 2003; Shors et al., 2007; Westenbroek et al., 2004; Czeh et al., 2002; Ferragud et al., 2010; Malberg and Duman, 2003) with either no effect on survival (Hillerer et al., 2013; Heine et al., 2004) or a distinct, up to 47% decrease in cell survival (Pham et al., 2003; Lee et al., 2006). While most chronic stress procedures do not appear to effect cell proliferation in female rodents and primates (Hillerer et al., 2013; Uno et al., 1989; Galea et al., 1997; Shors et al., 2007; Westenbroek et al., 2004); there seem to be long-term consequences of chronic stress exposure in females, as cell survival was shown to be either decreased (6/16d post BrdU) (Hillerer et al., 2013; Kuipers et al., 2006) or increased (2w post BrdU) (Westenbroek et al., 2004) after RS/footshock stress in rats.

The observed effects of acute and chronic stress on hippocampal neurogenesis in males and females are predominantly attributed to stress-induced alterations of the HPA axis and the rise in CORT levels. Thus, both acute and chronic exogenous CORT administration have been shown to decrease cell proliferation in both, male and female rodents (mice and rats) (Tanapat et al., 2001; Shors et al., 2007; Falconer and Galea, 2003; Heine et al., 2004; Brummelte and Galea, 2010; Cameron and Gould, 1994; Murray et al., 2008; Yap et al., 2006). However, an increase in CORT is not necessarily associated with changes in cell proliferation as seen after various acute or chronic stress procedures in female rats (Shors et al., 2007; Falconer and Galea, 2003;

Westenbroek et al., 2004).

One disadvantage of all of the studies discussed above is that they do not directly assess and compare the effect of the experimental manipulation on male and female hippocampal neurogenesis in the same study. A few years ago, we were the first group to perform a direct and detailed evaluation of sex-dependent and chronic stress-induced changes in adult hippocampal neurogenesis, revealing significant differences between males and females regarding hippocampal cell proliferation, astroglial and neuronal differentiation, cell survival and stem cell quiescence. In more detail, we revealed that chronic RS (2 h/d for 12 days) induced a significant decrease in hippocampal cell proliferation and an increase in stem cell quiescence (BrdU + /SOX2 + /PCNA–cells) in male rats with no effect on those parameters in females. Interestingly, chronic stress significantly diminished hippocampal cell survival in females, but not males. Further analysis of astroglial and neuronal differentiation patterns revealed that the reduced cell survival was solely attributed to a profound decrease in the number of cells differentiating into neurons (BrdU + /GFAP-/NeuN + cells) (Hillerer et al., 2013), a result that might be of clinical relevance, given the known increased susceptibility for women to suffer from stress-related disorders like major depression and the fact that there seems to be a link between a reduced neurogenesis and depression.

6.6.4. Stress and stress hormones during adulthood – effects on dendritic morphology

Overall, studies in rodents and non-human primates suggest that stress during adulthood is associated with alterations in dendritic atrophy in CA3 pyramidal neurons in males and females (Uno et al., 1989; Galea et al., 1997; Magarinos and McEwen, 1995). By directly comparing male and female rats in one experimental outline, Shors et al. were able to show that there are not only basal sex differences in hippocampal dendritic morphology, but moreover that phases of acute stress differentially affect males and females with regard to dendritic spine density in the hippocampus. In more detail, females during proestrus had a greater density of spines in the CA1 region of the hippocampus, when compared to males. Interestingly, spine density was affected in opposite directions after exposure to acute intermittent footshock stress, with males showing an increased density of spines, while females expressing reduced levels of spines in the CA1 region of the hippocampus (Shors et al., 2001), suggesting that males and females response to stress is opponent with respect to neural anatomy in the hippocampus, when exposed to the same stressful event. A similar effect was observed in cycling and masculinized females. Here they were able to show that cycling females exposed to acute RS tended to possess fewer spines on apical and basal dendrites in the CA1 area of the hippocampus, whereas the masculinized females possessed significantly more spines after the stressor (Dalla et al., 2009). Although there are some studies suggesting a negative effect of acute stress on dendritic morphology in males (Chen et al., 2008; Sebastian et al., 2013), the bulk of available data suggest that the neuroendocrine background of males may be rather associated with an increase in dendritic complexity after exposure to acute high levels of stress hormones. Thus, a rapid increase in CA1 and CA3 pyramidal spines was also observed *in vitro* when hippocampal slice cultures from males were exposed to high doses of acute CORT (100, 500 or 1000 nM) or stressful high concentrations of DEX (100 nM) (Komatsuzaki et al., 2005; Yoshiya et al., 2013); an effect that was particularly observed within thin and mushroom spines, but not stubby or filopodium spines (Komatsuzaki et al., 2005). In contrast, chronic exposure to stress hormones induces dendritic atrophy in both sexes. Chronic DEX (0,2mg/kg for 5d) or CORT (10 mg/kg for 21d) administration or exposure to repeated stress (social defeat) were all shown to decrease the number of spines, the number of branching points, reduces the surface area and length of apical and basolateral CA1/3 dendrites in male rats (Kole et al., 2004; McKittrick et al., 2000; Silva-Gomez et al., 2013; Woolley et al., 1990), which was even more pronounced in the ventral than the dorsal hippocampus (Silva-Gomez et al., 2013). Although the effects of stress on hippocampal dendritic morphology occur rapidly, typically within hours, they can be reversible, as they were shown to be abolished 10 days after the cessation of stress and after a 1 month recovery period (Conrad et al., 1999; Sousa et al., 2000).

In summary it seems that chronic stress during adulthood alters hippocampal functioning in a sex-dependent manner with shorter-term alterations in males and long-term consequences in females.

7. Neuroimaging studies on the effects of sex and stress hormones in the human hippocampus

In the following we will present an overview of neuroimaging studies on the human hippocampus, assessing structural aspects (grey matter volumes, grey matter density, microstructural integrity) on the one hand and brain activation (BOLD-response) on the other hand. It is important to point out, that – unlike animal studies – human neuroimaging studies usually capture the whole brain and have thus identified sex differences and hormonal influences on a wide range of areas and brain network properties that are not captured by this review. After summarizing results on sex differences in these aspects, we will focus primarily on the effects of steroid actions on hippocampal volumes and brain activation.

With the emergence of studies investigating short-lived intra-individual changes in gray matter volumes, the question arises, how these changes are to be interpreted. It is yet unclear, whether an increase in grey matter volumes in a certain brain area represents an increase in cell bodies, i.e. neurogenesis, an increase in synaptic spines, i.e. synaptogenesis or an increase in the size of cell bodies, i.e. cell swelling. In animal studies, sex hormone influences have been demonstrated on either of these processes (Barker and Galea, 2008; Fester et al., 2012; Rutkowsky et al., 2011). While the functional implications of an increased number of cells or spines are apparent, it has only recently been demonstrated that even cell swelling has an impact on brain function by influencing the excitability of neurons (Chiang et al., 2019). The BOLD-signal on the other hand has been linked to glutamate signalling (Attwell et al., 2010). In this section, we summarize the small number of studies investigating sex hormone influences on hippocampal volumes and brain activation.

7.1. Sex differences in hippocampal volumes in healthy individuals

The brains of men and women differ in several aspects. Female brains are overall smaller, but show a larger proportion of gray matter than males (Cosgrove et al., 2007). Of greater interest to sex differences in behavior however, are regional gray matter volumes, i.e. sex differences in the size of brain areas proportional to overall brain size. A recent meta-analysis of whole-brain voxel-based morphometry (VBM) analyses revealed larger inferior and middle frontal areas, planum temporale and thalami in women, but larger amygdalae, hippocampi and parahippocamapl gyri, as well as larger cerebelli in men (Ruigrok et al., 2014). However, sex differences in the size of the human hippocampus are disputed as it appears that in younger populations, up until early adolescence hippocampi are larger in girls than in boys (Tan et al., 2016; Gur et al., 2002). This suggests a strong remodelling of male and female hippocampi during puberty due to its activation via sex hormones (Cosgrove et al., 2007). Indeed, some studies report a stronger puberty-related increase in hippocampal volumes in boys compared to girls (Suzuki et al., 2005; Bramen et al., 2011). However, without controlling for pubertal stage, non-significant sex-differences in age-related trajectories (Neufang et al., 2009; Dennison et al., 2013) and stronger age-related increases in girls (Giedd et al., 1997; Giedd et al., 1996) have also been reported. Studies extracting hippocampal volumes directly, rather than testing for differences at the whole-brain level often also report larger hippocampal volumes in women after puberty (Filipek et al., 1994; Garcia-Falgueras et al., 2006;

Satterthwaite et al., 2014), although sometimes only in certain hippocampal subfields (Persson et al., 2014; Maller et al., 2006; Riggins et al., 2018; Meyer et al., 2017). However, a recent meta-analysis arrives at the conclusion that irrespective of age, hippocampal volumes do not differ between males and females after correcting for total brain size (Gur et al., 2002; Babson et al., 2017; Perlaki et al., 2014; McHugh et al., 2007; Jancke et al., 2015; Bhatia et al., 1993). In contrast, a large-scale, world-wide, study including almost 16.000 subjects reported slightly larger volumes in males compared to females (Guadalupe et al., 2017).

A variety of methodological issues need to be considered when comparing male and female hippocampi at different age groups: (i) Whole-brain analyses rely on normalization techniques on the one hand and smoothing kernels on the other hand. Normalization fits both male and female individual brains to a standard template. However, given the pronounced differences between male and female brain morphology, it is unclear whether normalization works equally well for all brain structures in men and women. As a subcortical structure, the hippocampus lies in close proximity to the amygdala, the basal ganglia, but also to the parahippocampal gyrus. Unlike for the hippocampus, studies of various methodology consistently show that all these structures are larger in men compared to women, even after correcting for total brain size (Pulopulos et al., 2018; Stephens et al., 2016; Reschke-Hernandez et al., 2017; Kogler et al., 2017; Kirschbaum et al., 1992; Khaksari et al., 2005; Herbison et al., 2016; Childs et al., 2010; Powers et al., 2016; Stroud et al., 2017; Cameron et al., 2017). In whole-brain studies, larger volumes for men compared to women are usually found in large subcortical clusters including the basal ganglia and amygdala and extending to the parahippocampus and cerebellum (Pletzer et al., 2010; Pletzer, 2019). If these clusters also include the hippocampus, it is possible that normalization and smoothing techniques transfer some of the differences in the basal ganglia and amygdala to the hippocampus. In line with this argument, we recently found sex differences favouring men in the hippocampi at the whole brain level, while in the same sample extracted hippocampal volumes did not differ between men and women (Pletzer, 2019). (ii) Studies extracting hippocampal volumes vary greatly in methodology. While some rely on normalization, others work on individual brain morphology. Furthermore, some assess regional hippocampal volume differences by calculating relative hippocampal volumes *via* division of absolute volumes by total brain size (Satterthwaite et al., 2014), while others correct for total brain size *via* covariate analyses. Since, compared to cortical gyri, the hippocampus is rather small relative to total brain size, these methods may give markedly different estimates for regional hippocampal volumes. Especially with regard to developmental trajectories these different statistical procedures may arrive at different results, if cortical areas develop at a different rate than the hippocampus. (iii) Female hippocampal volumes vary with changes in hormonal status, e.g. along the menstrual cycle (see below), due to current or previous hormonal contraceptive use (Pletzer et al., 2010; Pletzer, 2019; Pletzer et al., 2015), due to current or previous pregnancies (Hoekzema et al., 2017) and due to menopause and hormone replacement therapy (see below). Differences in hippocampal volumes between males and females are hard to interpret, if these factors are not adequately controlled for.

7.2. Sex differences in hippocampal activation in healthy individuals

Regarding cognitive processing, sex differences in hippocampal activation appear to be task- and strategy dependent. During spatial navigation and spatial memory, stronger right hippocampal activation was observed in men, while hippocampal activation in women was more left-lateralized (Persson et al., 2013; Frings et al., 2006). Accordingly, a more verbal strategy has been suggested for women, while a more spatial strategy has been suggested for men. However, it has repeatedly demonstrated that women utilize landmark-information in the environment more than men (Harris et al., 2019; Lawton, 2001; Lawton et al., 1996; Lawton, 1994), which may also contribute to sex differences in hippocampal/parahippocampal activation (Sneider et al., 2011).

Vice versa, women show stronger activation of the hippocampus in verbal memory tasks (Jacobs et al., 2016). Women also show stronger hippocampal activation (and limbic activation in general) during working memory tasks (Hill et al., 2014). Accordingly, women recruit the (left) hippocampus more strongly during memory tasks, while men recruit the (right) hippocampus more during spatial tasks.

Regarding emotion processing, women show stronger activation for negatively valenced words, faces and memories compared to men (Young et al., 2013; Victor et al., 2017; Hofer et al., 2007). Stronger activation for emotional words was found in the left hippocampus, while stronger activation for emotional pictures was found in the right hippocampus (Bellace et al., 2013). A *meta*-analysis of 56 neuroimaging using emotion-eliciting stimuli revealed distinct brain networks for men and women, confirming stronger hippocampal activation in women compared to men (Filkowski et al., 2017). Results regarding sex differences during fear conditioning are inconsistent, with some studies demonstrating stronger hippocampal activation to conditioned stimuli in women (Merz et al., 2010; Benson et al., 2014), other studies report no sex differences in the hippocampus (Merz et al., 2013; Lebron-Milad et al., 2012). In line with the increased BOLD-response during verbal and emotional tasks, women show stronger glutamate concentrations in the hippocampus (Hadel et al., 2013).

Flexibility of dynamic functional connectivity of the hippocampus was lower in women compared to men (Nini et al., 2017). Women show stronger resting state functional connectivity between the amygdala and the hippocampus (Kogler et al., 2016). Increased connectivity between amygdala and hippocampus during emotion processing was related to decreased dysphoric mood in women (Mareckova et al., 2016).

7.3. Estrogens

Estrogen-dependent modulation of hippocampal volumes and activation has mostly been studied in women. Evidence comes from menstrual cycle studies focusing on the pre-ovulatory estradiol peak, studies on post-menopausal or post-partum loss of estradiol and estrogen replacement therapy during menopause, as well as a limited number of studies using an estrogen administration protocol in pre-menopausal women. Studies discussing changes in male-to-female transsexuals will not be discussed here, since they receive both, estrogen and anti-androgen treatment, complicating the interpretation of results (Seiger et al., 2016; Kim and Jeong, 2014).

7.3.1. Estrogenic effects on hippocampal volumes

With one exception (den Heijer et al., 2003), the studies performed to date demonstrate a positive effect of estrogens on hippocampal volumes and differential effects on brain activation during cognitive *vs.* emotional processing. Along the menstrual cycle, hippocampal grey matter volumes increase during the pre-ovulatory estradiol peak compared to other cycle phases (Protopopescu et al., 2008; Barth et al., 2016; Lisofsky et al., 2015), an effect that has recently been linked to estradiol (Pletzer et al., 2018). Hippocampal gray matter volumes decrease during menopause (Goto et al., 2011), but increase with estrogen only treatment in both peri-/postmenopausal women (Yue et al., 2007; Pintzka and Haberg, 2015; Lord et al., 2010; Lord et al., 2008; Hu et al., 2006; Eberling et al., 2003) (see Maki and Dumas, 2009 for a review) and pre-menopausal women (Albert et al., 2017). Furthermore, long-term use of combined oral contraceptives containing the potent estrogen ethinylestradiol is associated with larger hippocampal GM volumes (Pletzer et al., 2015; Pletzer et al., 2019). Also in males, genotypes associated with higher estradiol levels, showed larger hippocampal gray matter volumes (Bayer et al., 2013), and females with Turner syndrome, who typically show reduced estradiol levels, had smaller hippocampi (Kesler et al., 2004). Furthermore, the fact that

up until menopause the age related decline in hippocampal volumes is steeper in men than in women (Raz et al., 2004; Nordin et al., 2017; Malykhin et al., 2017; Li et al., 2014; Golomb et al., 1993) (for review see Murphy et al., 1996) has been attributed to the neuroprotective effects of estradiol (see Pruessner et al., 2008 for a review). In a recent study, circulating estradiol levels were not related to hippocampal volumes in either men or women (Pletzer, 2019), suggesting that changes in estradiol levels are more relevant to hippocampal morphology than absolute levels. However a positive association between left hippocampal volumes and serum estradiol levels was observed in female patients with prolactinomas (Yao et al., 2017).

7.3.2. Estrogenic effects on hippocampal activation

Furthermore, hippocampal activation increases during the pre-ovulatory cycle phase during cognitive tasks (Pletzer et al., 2019; Wei et al., 2018) as well as to food stimuli (Frank et al., 2010), while the BOLD-response to negatively valenced emotional stimuli seems to decrease during this high-estradiol cycle phase (Jacobs et al., 2015; Goldstein et al., 2005; Goldstein et al., 2010; Bayer et al., 2014). The latter finding has been interpreted as a hormonal capacity to regulate stress circuitry (Jacobs et al., 2015). During menopause, estrogen therapy users showed stronger hippocampal activation and better performance during a variety of memory tasks (Maki and Resnick, 2000; Maki et al., 2011; Braden et al., 2017; Berent-Spillson et al., 2010; Shafir et al., 2012) (see Maki and Dumas, 2009 for a review). Likewise, estrogen administration in pre-menopausal women increased hippocampal activation during a recognition memory tasks (Bayer et al., 2018). Furthermore, estrogen receptor agonists increased hippocampal brain activation in schizophrenic patients during an emotion recognition task (Ji et al., 2016), as well during a probabilistic learning task (Kindler et al., 2015), while aromatase inhibitors decreased hippocampal brain activation and memory performance in breast cancer patients (Bayer et al., 2015; Apple et al., 2017). Postmenopausal women show reduced hippocampal activation compared to age-matched pre-menopausal women in a verbal memory task (Jacobs et al., 2016). However, during a working memory task, when the hippocampus was deactivated, post-menopausal women showed less hippocampal activation than age-matched pre-menopausal women (Shafir et al., 2012; Jacobs et al., 2017).

Finally, some studies have also evaluated the effects of estrogen modulation on hippocampal connectivity, particularly on the connectivity between the hippocampus and pre-frontal cortex. Post-menopausal women, who showed decreased working memory performance, demonstrated increased fronto-hippocampal connectivity compared to age-matched pre-menopausal controls (Jacobs et al., 2017). Results regarding the effects of estrogen-blockade therapy (tamoxifen) on fronto-hippocampal connectivity in breast-cancer survivors are mixed. One study reports increased fronto-hippocampal connectivity after tamoxifen treatment to be related to more cognitive deficits (Apple et al., 2018), while another study reports decreased fronto-hippocampal connectivity during tamoxifen treatment to be related with working memory deficits (Chen et al., 2017). Along the menstrual cycle fronto-hippocampal connectivity changes in a task-dependent manner during the pre-ovulatory phase, but these changes intensify during the luteal phase (Pletzer et al., accepted). Postpartum women, who experience a rapid loss of estradiol, showed a decrease in hippocampal connectivity to the ACC, which was related to decreased memory performance (Shin et al., 2018; Shin et al., 2018). Likewise, hippocampal connectivity to the ACC was decreased in the resting state after treatment with a gonadotropin releasing hormone agonist, resulting in reduced estradiol levels (Fisher et al., 2017). These changes in hippocampal-ACC connectivity were related to depressed mood (Fisher et al., 2017).

7.4. Progestogens

Compared to studies focussing on estrogen-dependent effects on the hippocampus, studies regarding progesterone are rare and yield less consistent results. The reason for this lack of studies may be that in natural designs, progesterone never varies alone, but always in combination with estradiol. Likewise, many hormone replacement therapy regimens, as well as hormonal contraceptives contain progestins in combination with estrogens.

Along the menstrual cycle, both structural and functional studies indicate that progesterone increases during the luteal cycle phase reverse the estradiol-dependent effects during the pre-ovulatory cycle phase (Pletzer et al., 2019; Protopopescu et al., 2008; Barth et al., 2016; Pletzer et al., 2018). Our most recent study indeed demonstrates a significant estradiol-progesterone interaction in the modulation of hippocampal brain activation during cognitive tasks (Pletzer et al., 2019), suggesting positive effects of estradiol only in the absence of progesterone. However, focussing on arousal circuitry, increased hippocampal activation was observed during the luteal cycle phase (Andreano and Cahill, 2010), suggesting that like estradiol, progesterone has opposite effects on hippocampal activation in cognitive and emotional tasks. In a meta-analysis of neuroimaging studies until 2013, Lisofsky and colleagues found larger luteal compared to early follicular hippocampal activations in the left hemisphere, but larger follicular compared to luteal activations in the right hemisphere (Lisofsky et al., 2015). Our own study found a decrease in hippocampal activation after ovulation only in the left, but not in the right hemisphere (Pletzer et al., 2019). Thus, studies suggest differential effects of progesterone on the left and right hippocampus. Combining these seemingly contradicting finding, it is important to note, that the majority of studies included in the Lisofsky meta-analysis focused on emotional stimuli or response inhibition, while our own study focused on cognitive tasks.

As outlined above, menstrual cycle dependent changes in fronto-hippocampal connectivity intensify during the luteal cycle phase, suggesting a role of progesterone, rather than estradiol, in that respect (Pletzer et al., 2019). During the resting state, progesterone increases fronto-hippocampal connectivity along the menstrual cycle (Arelin et al., 2015).

Similarly, studies focusing on peri-menopausal hormone replacement therapy yield less consistent results than the above reported estrogen replacement therapy studies, when using combined hormone replacement therapy, i.e. HRT containing an estrogen + a progestin (Coker et al., 2010; Hu et al., 2006; Resnick et al., 2009). In fact the majority of these studies demonstrate a reduction in hippocampal volumes in combined HRT users (Coker et al., 2010; Resnick et al., 2009). Studies of progesterone only administration demonstrate larger hippocampal brain activation during face processing (van Wingen et al., 2007) and verbal processing (Berent-Spillson et al., 2015). However, while face recognition performance was reduced, verbal memory performance was improved following progesterone administration.

7.5. Androgens

In an effort to explain the presumed sex differences in hippocampal volumes and activation, studies on the testosterone-dependent modulation of hippocampal volumes and activation have focused on either testosterone increases during puberty, circulating testosterone levels or testosterone administration, and clinical conditions of androgen excess (e.g. congenital adrenal hyperplasia - CAH) or androgen deficiency (e.g. Klinefelter syndrome). The vast majority of these studies report larger hippocampal volumes and activation in higher testosterone stages.

7.5.1. Androgenic effects on hippocampal volume

During puberty, testosterone increases were predictive of increases in hippocampal volumes in both males and females (Neufang et al., 2009; Wierenga et al., 2018). In fact, these studies show that

testosterone was a better predictor of hippocampal volumes than pubertal stage or age (Neufang et al., 2009; Wierenga et al., 2018; Herting et al., 2014). Circulating testosterone levels were positively related to hippocampal volumes in young adult women (Pletzer, 2019) and elderly men (Lee et al., 2017), while no association was observed in young adult men (Pletzer, 2019) (Panizzon et al., 2012). However, patients with Klinefelter syndrome (XXY caryotype), who typically show lower circulating testosterone levels, also have lower hippocampal volumes compared to controls (Skakkebaek et al., 2014). Treatment with oxandrolone, a synthetic hormone analog of testosterone, increased hippocampal volumes in Klinefelter patients (Foland-Ross et al., 2019). However, CAH seems to be more strongly associated with larger amygdalae than hippocampi (see Mueller, 2013 for a review).

7.5.2. Androgenic effects on hippocampal activation

In keeping, cerebral blood flow in the hippocampus was related to circulating testosterone levels in elderly men (Moffat and Resnick, 2007). Testosterone administration in healthy young women during their early follicular phase increased hippocampal activation and performance during a navigation task (Pintzka et al., 2016), the recognition of male, but not female faces (van Wingen et al., 2008). A recent meta-analysis focusing on affective stimuli, identified positive effects of both exogenous testosterone administration (to women only) and circulating endogenous testosterone levels on brain activation in bilateral amygdala/parahippocampal regions including the hippocampus (Heany et al., 2016). Specifically, since negative associations of endogenous testosterone levels to parahippocampal/amygdala activations were also observed, this meta-analysis identified the right cornu ammonis (CA) hippocampus as the area, in which activations were positively related to testosterone levels (Sundstrom Poromaa and Gingnell, 2014). Patients with Klinefelter syndrome show reduced hippocampal activation during a word generation task (Steinman et al., 2009) while patients with familial male-precocious puberty (FMPP), which is characterized by early excess testosterone secretion, show increased hippocampal activation to fearful faces (Mueller et al., 2009).

Focussing on hippocampal connectivity, the structural covariance between the hippocampus and the anterior cingulate cortex (ACC) was positively related to testosterone levels in boys, and this covariance in turn related negatively to executive functions (Nguyen et al., 2017).

7.6. Effects of stress and stress hormones on hippocampal volumes and brain activation

Regarding cortisol effects on the hippocampus, an important distinction has to be made between chronically elevated cortisol levels (e.g. chronic stress) and the short-lived cortisol response to an acute stressor. Cortisol is chronically elevated in patients with Cushing's syndrome (Crapo, 1979) and in patients with stress-related disorders, such as MDD (Travis et al., 2016; Szeszko et al., 2018; Keller et al., 2017; Bremner, 2006). Furthermore, patients with chronic pain, rheumatoid arthroitis, or multiple sclerosis receive hydrocortisone treatments over prolonged time periods (Gold et al., 2010; Coluccia et al., 2008). Studies focusing on chronic stress usually assess diurnal cortisol, e.g. from 24 h urine or repeated salivary sampling, or hair cortisol. Some studies have also assessed the cortisol awakening response (CAR). However, while some studies show an increased CAR in patients under chronic stress (Wust et al., 2000; Schlotz et al., 2004), other studies demonstrate that the cortisol awakening response is blunted in patient groups with chronically elevated cortisol levels (Wessa et al., 2006; Roberts et al., 2004; Duan et al., 2013). The CAR has been described as an indicator of the HPA-axis' capacity to respond to stressors (Langelaan et al., 2006). Accordingly, the elevated CAR in participants who report chronic stress represents a healthy adaptation to the expected stress during the upcoming day. However, if the chronic stress continues, this adaptive capacity is lost, resulting in disorders like depression, PTSD or chronic fatigue syndrome. Likewise, it appears that chronic stress/chronically elevated cortisol levels affect acute stress reactivity. While some studies show that participants experiencing chronic stress show an increased cortisol response to acute stress, most studies demonstrate blunted cortisol reactivity in patients under chronic stress (Zorn et al., 2017).

7.6.1. Stress effects on gray matter volumes

Chronically elevated cortisol levels have been linked to reduced hippocampal volumes in a variety of studies including different patient groups and healthy subjects of different sex and ages (Travis et al., 2016; Babson et al., 2017; Wolf et al., 2002; Watanabe et al., 2017; Vachon-Presseau et al., 2013; Sudheimer et al., 2014; Starkman et al., 2003; Jin et al., 2016; Davis et al., 2017; Chen et al., 2016; Burkhardt et al., 2015; Brown et al., 2004) and have been linked to declarative memory deficits (Coluccia et al., 2008; Starkman et al., 2003). Likewise, increased diurnal cortisol levels are related to reduced hippocampal activation (Cunningham-Bussel et al., 2009). While it was originally assumed that high cortisol causes the hippocampal volume reduction, newer studies discuss the hippocampus as an important mediator in stress reactivity. Accordingly, participants with smaller hippocampi show reduced cortisol awakening response (Valli et al., 2016; Seo et al., 2019; Pruessner et al., 2007; Dedovic et al., 2010; Buchanan et al., 2004) and reduced stress reactivity of the HPA-axis (Frodl et al., 2014; Valli et al., 2016; Pruessner et al., 2007; Knoops et al., 2010). Likewise, hippocampal damage abolishes the cortisol response to psychosocial stress (Buchanan et al., 2009). Accordingly, smaller hippocampal volume has been discussed as a vulnerability factor for developing stress related disorders like MDD (Dedovic et al., 2010), PTSD (Szeszko et al., 2018) or psychosis (Valli et al., 2016; Collip et al., 2013). Also in patients with head injuries or patients receiving hydrocortisone treatment, smaller hippocampi were related to more depressive symptoms (Gold et al., 2010; Jorge et al., 2007).

Recent results indicate that effects of MDD on the hippocampus are probably explained by childhood adversities (Opel et al., 2014), since differences between MDD patients and controls disappeared if childhood maltreatment was controlled for. Multiple studies indeed show that childhood adversities, ranging from low birth weight or social status to severe maltreatment or abuse, are associated with chronically-elevated cortisol levels (Sheridan et al., 2013; Frodl and O'Keane, 2013; Engert et al., 2010; Dahmen et al., 2018; Bremner, 2005), but lower hippocampal volumes (Dahmen et al., 2018; Samplin et al., 2013; Frodl et al., 2017; Everaerd et al., 2012; Calem et al., 2017). While there seem to be no sex differences in MDD effects on hippocampal volumes, effects of childhood adversities are consistently stronger in males (Samplin et al., 2013; Everaerd et al., 2012; Calem et al., 2017; Helpman et al., 2017). Following the idea that smaller hippocampal volumes are not so much a result of chronically elevated cortisol levels, but represent a vulnerability factor for HPA-axis dysregulation due to severe stress, the fact that pre-adolescent girls have larger hippocampi and a larger cortisol response than boys may contribute to this finding (Whittle et al., 2011). Both factors may protect girls up until adolescence against the adverse effects of childhood maltreatment. In contrast, the smaller increase in hippocampal volumes in girls compared to boys during puberty may represent a vulnerability factor explaining the increasing prevalence rates of stress-related disorders in girls during adolescence (Kessler, 2003).

Relatedly it has been discussed that the age-related decline in hippocampal volumes is related to accumulated effects of glucocorticoids over the life time on the one hand (see Pruessner et al., 2008 for a review) and the fact that cortisol levels increase with age on the other hand (Seeman et al., 1997; Lupien et al., 1998). Indeed hippocampal atrophy was stronger in elderly participants with higher cortisol levels (Valli et al., 2016). However, a series of studies failed to show an associated between age-related volume decline in the hippocampus and increased cortisol levels (Brown et al., 2004; Stomby et al., 2016; Cox

et al., 2017; Cox et al., 2015). It is thus again possible, that smaller hippocampal volumes represent a risk factor for cortisol effects during aging.

However, even short term elevations in cortisol due to hydrocortisone treatment have been associated with a reduction in hippocampal volumes within the same participant (Tessner et al., 2007; Brown et al., 2015). A recent study suggests that both high and low levels of stress-induced cortisol release are associated with smaller hippocampi, suggesting an inverse u-shaped relationship between hippocampal volumes and the cortisol response to stress (Admon et al., 2017).

7.6.2. Stress effects on hippocampal activation

Naturally, while most studies on chronic stress have focused on hippocampal volumes, studies on acute stress have focused on hippocampal brain activation. Short-term elevations in cortisol are induced either by pharmacological treatment (hydrocortisone) or using psychophysiological stress paradigms. Those paradigms include the Trier social stress test (TSST), which is mostly performed outside the scanner, the Montreal imaging stress task (MIST), which can be performed inside the scanner and the cold pressure stress test (CPT), which may or may not include a social evaluative component (see Noack et al., 2019 for a review of stress paradigms in the scanner). Importantly, a common finding in studies using the TSST or MIST is that only a certain proportion of participants respond to the task with elevated cortisol, while up to 50% do not show elevated cortisol levels and are classified as non-responders. It is possible that chronic stress, as discussed before, contributes to the non-responders blunted cortisol response to stress. This is relevant since associations between cortisol or subjective stress ratings and brain activation or memory performance are (mostly) only observed in group of responders, but not among non-responders (Khalili-Mahani et al., 2010; Dedovic et al., 2009). These studies have assessed (i) brain activity during acutely elevated cortisol either at rest or in some paradigm, or (ii) brain activity in some emotional or cognitive paradigm following acutely elevated cortisol.

Regarding brain activity during acute stress, studies found hippocampal deactivation, which was correlated to the cortisol response (Dedovic et al., 2009; Brown et al., 2013; Klaassen et al., 2013; Kukolja et al., 2011; Liu et al., 2012; Lovallo et al., 2010; Mareckova et al., 2017; Pruessner et al., 2008). A minimum in hippocampal activation was observed after about 30 min of cortisol exposure (Lovallo et al., 2010). Accordingly, even stressors applied before entering the scanner are effective during scanning. This fact has been used to study the effects of cortisol elevation on memory retrieval. Patients who received a hydrocortisone injection or performed the TSST prior to scanning, showed reduced hippocampal activation during a memory retrieval task (Khalili-Mahani et al., 2010; Wolf, 2009; Kukolja et al., 2008). Relatedly, during acutely elevated cortisol, the hippocampus showed stronger connectivity to the default mode network, which usually deactivates during cognitive tasks (Thomason et al., 2013). This reduced hippocampal activation resulted in impaired retrieval performance for contents learned prior to cortisol exposure (Khalili-Mahani et al., 2010; Wolf, 2009; Kukolja et al., 2008). Interestingly, also during the encoding phase, elevated cortisol results in reduced hippocampal activation (Weerda et al., 2010; Vogel et al., 2015; Vogel et al., 2018; van Stegeren et al., 2010; Oei et al., 2007; Merz et al., 2018; Henckens et al., 2009). However, elevated cortisol during learning results in better recall of the learned materials (Wolf, 2009). Recent studies show that this reduced hippocampal activation during memory tasks is accompanied by increased striatal involvement, suggesting a strategy shift from hippocampus dependent declarative strategies to more procedural striatum-dependent strategies during stress (Vogel et al., 2015; Totterman et al., 1989; Schwabe and Wolf, 2012; Schwabe et al., 2013). This shift in learning strategy may explain why acute stress enhances memory performance when applied during encoding, but decreases memory performance when applied during retrieval. In the latter case, cortisol seems to block access to previously formed hippocampus dependent memories, while in the former case cortisol seems to support a strategy of memory formation that is more easily accessible during retrieval.

Note, however, that a series of studies, specifically focussing on emotional material, have also reported a cortisol-dependent increase in hippocampal activation during the encoding phase (van Stegeren, 2009; Bos et al., 2014). These studies suggest that enhanced memory after stress during encoding is related to enhanced hippocampal activation, potentially mediated also *via* stronger involvement of the amygdala (de Voogd et al., 2017). It is thus possible that hippocampal activation in response to cortisol during encoding follows an inverted u-shaped function, with low and high cortisol causing increased hippocampal activation, while moderate cortisol elevations reduce hippocampal activation.

It is important to point out that – with the exception of MDD samples, which are primarily female – the majority of studies reviewed in this paragraph have been performed on male subjects and that information regarding sex differences or the impact of sex hormones on stress effects on hippocampal activation is limited. While a number of studies have identified sex differences in the cortisol response to psychosocial stress, only few studies have explicitly focused on sex differences in stress effects on the brain. Such studies are however, of uttermost importance to understand sex differences in stress related disorders.

Given the attenuated cortisol response in women, and the fact that reduced hippocampal activation is observed in response to elevated cortisol, one could expect stronger hippocampal activation during psychosocial stress in women. As outlined above, even when no specific stressor is applied, hippocampal activation during verbal and emotional tasks is higher in women compared to men (see above). Assuming that an MRI scan induces a mild stress reaction in scanner naïve participants, it is possible that these sex differences are in part attributable to sex differences in the cortisol response. Data regarding sex differences in hippocampal activation during psychosocial stressors are however limited and inconsistent. While some studies report higher activation in men (Kogler et al., 2017; Seo et al., 2011), others report higher activation in women (Kogler et al., 2015; Abercrombie et al., 2011), particularly women during their luteal cycle phase (Chung et al., 2016; Chung et al., 2016). Furthermore, in women stronger hippocampal activation was related to increased subjective stress ratings (Kogler et al., 2015; Chung et al., 2016). Following the rationale, that hippocampal deactivation during acute stress relates to enhanced memory performance when administered during memory encoding or consolidation, but impaired memory performance when administered during retrieval, it can be predicted that these effects should be abolished in women, due to their reduced cortisol response. While indeed the memory enhancing effects of acute stress during encoding were observed more strongly in men compared to women, the situation is less consistent with regards to memory retrieval (Merz and Wolf, 2017). While there is some evidence to stronger retrieval deficits in men (Hidalgo et al., 2015; Bentz et al., 2013), most studies also observe retrieval deficits in women, but focus on memory for emotional material or fear conditioning (Merz and Wolf, 2017; Quas et al., 2018). Results are mixed suggesting a role of emotional valence (Merz and Wolf, 2017; Quas et al., 2018), but also – most importantly – women's hormonal status (Maki et al., 2015).

8. Effects of sex and stress hormones on the hippocampus: Comparing animal and human studies

In summary, even though animal and human studies show some differences regarding sex differences in the stress response, there are striking parallels regarding the effects of sex hormones on hippocampal morphology and activity (summarised in Table 1). with the consensus from both animal and human studies, is that sex differences in

Table 1
Summary of the effects of sex (a)/stress (b) hormones on hippocampal plasticity/morphology and behavior (cognition/mood). M = MALE, F = FEMALE, OVX = ovariectomy, GDX = gonadectomy, T = Testosterone, DHT = Dihydrotestosterone, E = Estrogen, P = Progestogen, ER = estrogen receptor, PR = progesterone receptor, ERT = estrogen replacement therepy, HRT = combined hormone replacement therapy, OC = combined oral contraception; WM = working memory.

a)		Hippocampus				Behavior			
		Neurogenesis (NG)	Dendritic Morphology	Gray matter (GM)	Activation (ACT)	Cognition		Mood	
	Sex	Animal studies		Human studies		Animal studies	Human studies	Animal studies	Human studies
ESTROGENS ...		*... INCREASE NG IN FEMALES; NO EFFECT IN MALES*	*... INCREASE DM IN FEMALES; NO EFFECT IN MALES*	*... INCREASE GM IN FEMALES*	*.... INCREASE ACT. DURING COGNITION ... DECREASE ACT. DURING EMOTION*	*... SEEM TO IMPROVE COGNITION; CYCLE DATA INCONSISTENT*	*... SEEMS TO IMPROVE COGNITION; CYCLE DATA INCONSISTENT*	*... SEEM TO BE ANXIOLYTIC AND ANTIDEPRESSIVE*	*... SEEM TO BE ANTIDEPRESSIVE*
high systemic E /E increase	F	↑ Cell proliferation ↑ Cell survival 14d	↑ mushroom spines ↑ density in CA1	Pre-ovulatory: ↑	↑ during cognition ↓ during arousal	↓ spatial performance (proestrous) ↑ object memory (proestrous) ↓ following OVX	?	↓ anxiety ↑ extinction recall	
	M			Genetic high E: ↑					
Exogenous E/ ER agonist	F	acute: ↑ cell survival ↑ cell prolif. 1w post OVX ↔ cell prolif. 4w post OVX Chronic: ↑ cell proliferation 15d ↔ cell proliferation 21d	↑ density in CA1	ERT: ↑ OC: ↑	ERT: ↑ during cognition Agonists: ↑ during cognition	acute 17β-estradiol ↑ memory acute estrone: ↓ memory	ERT: ↑ memory OC: ↑ memory	systemic ↓ anxiety ↓depression local ↓ anxiety	ERT: ↓depression
	M	Acute: ↑ cell survival ↔ cell proliferation Chronic: ↔ cell survival ↔ cell proliferation	AcuteL ↑ density in CA1						
low systemic E /E withdrawal	F	OVX Short term: ↓ cell proliferation OVX Long term: ↔ cell proliferation	OVX: ↓ density in CA1 up to 40d after OVX	Turner: ↓ Menopause: ↓	Menopause: ↓ during memory	OVX: ↓	Menopause: ↓ memory	postpartum: ↑ depression OVX: ↑ depression	Postpartum/ Menopause/ Premenstrual: ↑ depression
ER antagonist/ Aromatase inhibitors	F	ER antagonists: ↔ Synthesis inhibition: ↑	↓ density in CA1		↓ during memory		↓ memory	↔ depression	
	M	↓ cell proliferation	↔ density In CA1						
PROGESTOGENS ...		*... DECREASE NG IN F ... INCREASE NG IN M*	*... INITIALLY POTENTIATE THE EFFECT OF E ON DM; DOWNREGULATE AT LATER TIMEPOINTS*	*.... PROBABLY DECREASE GM IN FEMALES*	*.... DECREASE ACT. DURING COGNITION ... INCREASE ACT. DURING EMOTION*	*... SEEM TO COUNTERACT THE EFFECTS OF OESTROGENS*	*RESULTS INCONSISTENT*	*... SEEM TO BE ANXIOLYTIC AND ANTIDEPRESSIVE*	*... SEEM TO BE ANXIOLYTIC*
High systemic P /P increase	F			↓	↓ during cognition ↑ during arousal		?		
Exogenous P/ PR agonist	F	Acute: ↓ cell prolif. 24h post E ↑ cell prolif. 1h post Ponly Chronic: ↔ cell proliferation 21d ↓ cell survival 21d		Combined HRT: ↓	P only: ↑	↑	?	↓ anxiety ↑ extinction recall ↓ depression	↓ anxiety
	M	↑ cell proliferation ↔ cell survival						↓ depression	
ANDROGENS ...		*... INCREASE NG IN THE LONG TERM IN M; SHORT-TERM EFFECTS AND EFFECTS IN F. UNCLEAR*	*... INCREASE DM IN MALES; EFFECT IN FEMALES UNKNOWN*	*... INCREASE GM IN MALES AND FEMALES*	*... INCREASE ACT. IN MALES AND FEMALES*	*... INCREASE SPATIAL COGNITION IN MALES*	*... PROBABLY IMPROVE COGNITION AT OPTIMAL LEVELS*	*... ACT ANXIOLYTIC AND ANTIDEPRESSIVE*	*... PROBABLY ACT ANTIDEPRESSIVE AT OPTIMAL LEVELS*
Systemic high T/T increase	F			Puberty: ↑ Circulating T: ↑	↑ during arousal		?		
	M			Puberty: ↑ Circulating T: ↑ in older men ↔ in young men	Circulating T: ↑ in older men FMPP: ↑ during face proc.		?		↑ depression
Exogenous T/DHT	F	↔ cell proliferation in the SVZ			↑ during cognition ↑ during arousal			↓ anxiety	↓depression
	M	Short-term: ↓ cell survival ↔ cell proliferation Long Term: ↑ cell survival ↑ cell proliferation	↑ density in CA1 ↑ small spines (T) ↑ large/middle head spines (DHT)	↑		↑ spatial WM		↓ anxiety ↓depression	↓depression
Systemic low T/T loss	M	GDX: ↓ cell survival ↔ cell proliferation		Klinefelter: ↓	Klinefelter: ↓ during word gen.	↓ spatial WM	Aging: ↓ memory	↑ anxiety ↑ depression	↑ depression
Blockade of DHT synthesis	M	↓ cell proliferation 7d							

(*continued on next page*)

Table 1 (*continued*)

b)		*Pre-/peri-adolescent stress*			***Post-adolescent stress***			
		Neurogenesis (NG)	**Dendritic Morphology (DM)**	**Gray matter (GM)**	**Neurogenesis (NG)**	**Dendritic Morphology**	**Gray matter (GM)**	**Activation (ACT)**
Sex		*Animal studies*		*Human studies*	*Animal studies*		*Human studies*	
NOTE: LACK OF STUDIES DIRECTLY COMPARING M AND F		*... MOSTLY DECREASE NG IN MALES; RESULTS IN FEMALES INCONSISTENT*	*... DECREASE DM IN FEMALES ... ACUTELY INCREASE DM IN MALES ... CHRONICALLY DECREASE DM IN MALES*		*... MOSTLY DECREASE NG IN FEMALES; RESULTS IN MALES INCONSISTENT*	*... MOSTLY DECREASE DM IN FEMALES; RESULTS IN MALES INCONSISTENT*	*... DECREASE GM*	*... DECREASE ACT. DURING COGNITION ... INCREASE ACT. DURING EMOTION*
F	**Prenatal stress / High maternal CORT**	↓/↔ cell proliferation (depends on PNS model) ↔ cell prolif. PND15/22 juvenile age and adulthood ↓ immature neurons			Acute Physical: ↓cell proliferation Chronic Physical: ↑cell proliferation ↓/↑ cell survival 6,16d/2w post BrdU ↔ stem cell quiesc. ↓ neuronal differentiation Chronic Social: ↔ cell proliferation	Acute: ↓ nb. of apical and basal dendrites in CA1 ↓density in CA1		
	Early Life Stress	Acute: ↓ cell prolif. PND21 ↓ immature neurons PND21 ↔ immature neurons adult Chronic: ↔ cell prolif. PND15/22 juvenile and adult ↔ cell survival	Chronic: ↓ dendritic length and branching points in CA3 (basal dendrites)	Chronic: ↔				
	Adolescence	Chronic: ↓ cell prolif. PND49, adult		Chronic: ↓				Acute: ↓ during encoding of cognitive material ↑ during encoding of emotional material ↓ during retrieval Chronic: ↓
M	**Prenatal stress / High maternal CORT**	↓ cell prolif. PND 69-76 ↓ cell prolif. PND15/22, juvenile and adulthood ↓ cell survival PND 69-76 (after pregn. RS) ↑ immature neuron prod.			Acute Physical: ↓ cell proliferation Acute Social: ↔ cell proliferation Chronic Physical: ↔ cell proliferation ↔/↓ cell survival ↑ stem cell quiesc. ↔ neuronal differentiation Chronic Social: ↓ cell proliferation	Acute: ↑ density in CA1 ↑ thin and mushroom spines in CA1/3 Chtronic: ↓ dendritic length and branching points in CA1/3 ↓ density in CA1/3	Acute: ↓ Chronic: ↓	
	Early Life Stress	Acute: ↑ cell prolif. on PND21 ↑ immature neurons PND21 ↓ immature neuron prod. in adulthood Chronic: ↓cell prolif. PND15/22, juvenile and adult ↑ cell prolif. PND19, adult ↓/↔ cell survival	Chronic: ↓ dendritic length and branching points in CA3 (apical dendrites)	Chronic: ↓				
	Adolescence	Chronic: ↑ cell prolif. PND46		Chronic: ↔				

hippocampal structure and function occur across the lifespan and depend on hormonal modulation and its interactions with stress hormones (stressful events).

8.1. Estrogens

Both preclinical animal and human neuroimaging studies demonstrate positive effects of estrogen on the hippocampus. The estrogen-dependent increase in neurogenesis and cell survival may play a role in the observations of increased hippocampal gray matter in humans. Likewise the increase in hippocampal spine density observed in animal study, may play a role in findings of increased hippocampal activation in humans. The consistencies regarding the effects of estrogen are most pronounced in females, possibly in part because females have been more extensively assessed in both animal and human studies. While preclinical studies suggest rather no effect of estrogen in females, some human studies show positive effects of estrogen on the hippocampus also in males.

8.2. Progestogens

Similarly, both animal and human studies appear to struggle with disentangling the effects of gestagens on the hippocampus. In both designs, gestagens have hardly been studied in isolation, but rather in combination with estrogens. It appears that some effects of estrogen are even increased due to gestagens, while gestagens counteract the effects of estrogen in other situations. Accordingly, a better understanding of gestagen effects on the hippocampus should be the focus of future studies, particularly to understand the precise dose- and time-dependent mechanisms that may lead to a facilitation or counteraction of estrogen effects. Thereby, it will be important to also take into account the differences in hormonal fluctuations along the very short estrous cycle in animals and the much longer menstrual cycle in humans.

8.3. Androgens

Regarding androgens, an important difference between preclinical and human studies is that preclinical studies have studied androgens mostly in males, while several human studies have studied testosterone effects in females, who usually have low testosterone levels. Human studies in males usually use a correlational design, while animal studies allow for a more causative approach. Furthermore, animal studies have also taken into account the effects of the physiologically more active androgen DHT, while human studies have focussed more strongly on testosterone. A striking parallel between these studies is that most of them report positive effects of androgens on the hippocampus in terms of morphology and activity. While those effects appear to be partially restricted to males in animal studies, human studies also report effects in females – sometimes even exclusively in females. However, these differences may be due to the differences in experimental design between studies.

8.4. Stress and stress hormones

Stress effects on the hippocampus are complex and appear to depend on the timing of stress exposure, as well as the duration of stress exposure. While there are striking consistencies between animal and human studies regarding the effects of estrogens and androgens, some discrepancies emerge regarding stress effects (see Table 1). These discrepancies are likely due to differences in study design. For ethical reasons, effects of stress on pre-pubescent girls and boys have not been studied systematically in humans. While chronic stress can be systematically modelled in animal studies, studies in humans concern mostly clinical populations. Furthermore, animal and human studies differ in the way, acute stress is induced and measured with more immediate approaches in humans, but more delayed measurement of the stress effects in animals. Furthermore, human studies focus more strongly on

cortisol increases and subjective stress ratings in their evaluation of the stress response, the latter of which are not available in animal studies. Accordingly, a potential focus of prospective studies in animals could be the more direct pharmacological induction of stress *via* corticosteroid elevation, while human studies could extend their analyses to the group of endocrinological non-responders.

Despite these methodological differences, some parallels can be observed. In both animal and human studies chronically elevated cortisol levels appear to negatively affect hippocampal morphology. While preclinical studies make a pretty convincing case for these effects to be more severe in males if they appear pre-puberty, but more severe in females if they appear during or after puberty, this dissociation is less clear in humans. However, there is some indication that also in humans, childhood adversities show more severe effects in males, while the prevalence in stress-related disorders rises during adolescence in females. Acute elevations of cortisol have shown mostly negative effects on the hippocampus in animal and human studies, with the exception that hippocampal activation during processing of emotional material appears to be elevated in humans during stress exposure. While animal studies prominently report differential effects of stress on the hippocampus of males and females, only few studies have focused on sex differences in stress-effects on the hippocampus in humans. However, direct comparisons between males and females are rare in all species. While the problem in animal research is that studies mostly focus on only one sex, the problem in human studies is that many studies employ mixed-sex samples without modelling sex as a variable of interest.

9. Effects of sex steroids on the hippocampus – behavioral implications

After summarizing the effects of sex steroids on hippocampal morphology and activity, the question arises regarding the behavioral implications of these results. As outlined in the introduction the hippocampus has been linked to spatial abilities and memory, as well as mood disorders like anxiety and depression. In order to provide an idea regarding the behavioral implications of the above-mentioned findings, the following sections shall provide a short overview of sex hormone actions on hippocampus-dependent cognitive functions as well as mood symptoms. However, this summary is by no means exhaustive, since there is a much larger number of behavioral than neurobiological studies. Also, the results of behavioral studies appear to be less consistent, since – especially in humans – behavior is influenced by a multitude of social, biological and psychological factors that are harder to control experimentally.

Regarding hippocampal-dependent cognitive functions, the question arises whether hormones that increase aspects of hippocampal morphology, also lead to improved performance in spatial cognition and memory tasks. Likewise, since many stress-related disorders, particularly mood and anxiety disorders are associated with a reduction in hippocampal volumes and activation, the question arises, whether such hormones can also result in a reduction of depressive symptoms and anxiety. While there are some indications supporting this assumption, it is important to point out that particularly in the human literature, many studies regarding sex hormone actions on cognition report null or opposite findings (see Sundstrom Poromaa and Gingnell, 2014 for review). This problematic may largely arise from methodological issues in both experimental design and hormone assessment. Accordingly, the following paragraphs will focus less on correlational approaches and summarize mostly those studies that implicate a causative role of sex hormones in cognitive functions and mood.

9.1. Estrogens

9.1.1. Estrogenic effects on hippocampus-dependent cognitive functions

Cognitive performance is correlated with the fluctuation in ovarian hormones levels across the oestrous cycle in humans and rodents. In keeping, administration of 17β-estradiol has been shown to have positive effects on cognition, whereas estrone has negative effects on cognition (Barha et al., 2009; Lymer et al., 2017). These effects appear to be mediated *via* rapid actions of ERs, which are important for memory consolidation (Frick, 2015). Moreover, changes in learning performance across the oestrus cycle may be related to changes in neurogenesis (Hampson, 1990; Warren and Juraska, 1997). Thus, hippocampus-dependent tasks are negatively affected during reproductive phases with high estrogen at pro-oestrous: females in pro-oestrous perform worse in spatial tasks, such as the MWM, compared to oestrous females (Warren and Juraska, 1997; Frye, 1995). These findings may be related to the higher level of stress reactivity that occurs during pro-oestrous (Viau and Meaney, 1991; Conrad et al., 2004). In contrast, pro-oestrous has been shown to be associated with increased object memory (Cordeira et al., 2018) showing that the effects of estrus cycle are complex and perhaps task dependent. This may be in part related to some studies only distinguishing between pro-oestrous/oestrous and di-estrus/met-estrus. Indeed, it has been shown that OVX leads to a decrease in cognitive function in young adult humans and rodents in a variety of tasks and oestrogen replacement can reverse these negative effects in a species, dose and temporal manner (Duarte-Guterman et al., 2015) (see Galea et al., 2013 for a review). In humans, effects of estradiol variations along the menstrual cycle on cognition are less clear, with some studies demonstrating positive effects, other studies demonstrating negative effects (see Sundstrom Poromaa and Gingnell, 2014 for review). A recent study suggests positive effects in participants with low baseline dopamine, but negative effects in participants with high baseline dopamine (Jacobs and D'Esposito, 2011). Exogenous estradiol administration to ageing females may decrease the risk of AD, as well as AD-associated cognitive decline (Hogervorst et al., 2005; Hogervorst et al., 2000; Maki, 2013). Likewise, rapid hormone loss during menopause in aging women has been associated with cognitive decline and ERT has been discussed to reverse these effects in a time-sensitive manner (Galea et al., 2017; Duarte-Guterman et al., 2015; Hamson et al., 2016 for review).

9.1.2. Estrogenic effects on mood and anxiety:

Rodents typically show decreased anxiety-related behavior during pro-estrus when estrogen levels are high and exogenous administration of estrogen has anxiolytic and antidepressant-like effects in females (Walf and Frye, 2007; Walf and Frye, 2007; Walf and Frye, 2009). Moreover, OVX induces depressive-like symptoms in female rodents and this outcome can be prevented through estrogen replacement (Bekku and Yoshimura, 2005) with similar findings observed following hormone withdrawal after hormone-stimulated pregnancy (Green and Galea, 2008; Craft et al., 2010; Galea et al., 2001; Suda et al., 2008). Additionally, lower estradiol levels have been associated with an increased prevalence of such disorders in humans (Baum and Sex, hormones, 2005; Rosario et al., 2011; Wieck, 2011). In humans, estrogen therapy is used to treat post-partum depression (Moses-Kolko et al., 2009), as well as mood symptoms during menopause (Toffol et al., 2015). Furthermore, oral contraceptives containing the potent estrogen ethinyl-estradiol are used in the treatment of pre-menstrual dysphoric symptoms (for review see Lete and Lapuente, 2016). These effects may be mediated *via* ER-dependent hippocampal actions, since bilateral injection of 17β-estradiol into the dorsal hippocampus has been shown to be anxiolytic (Walf and Frye, 2006; Walf et al., 2006; Frye and Rhodes, 2002). However, altered hippocampal neurogenesis is not necessarily predictive for the behavioral outcome, as inhibition of estrogen synthesis *via* chronic letrozole treatment increases the number of immature neurons in the DG without affecting depressive-like behavior in middle-aged female mice (Chaiton et al., 2019).

9.2. Progestogens

9.2.1. Progestogenic effects on hippocampus-dependent cognitive functions

Progestogens, like estrogens, have repeatedly been linked to cognitive functioning with the consensus showing that progesterone improves memory; both object and spatial (see Frick and Kim, 2018 for review). As stated above, OVX leads to spatial memory impairment and this can be reversed by estrogen in combination with progesterone (Harburger et al., 2009; Frye et al., 2007). Interestingly, as with its effects on hippocampal morphology, these effects appear to be age-dependent as the positive effects are lost in aged rats (Bimonte-Nelson et al., 2004).

9.2.2. Progestogenic effects on mood and anxiety

Progesterone has also been implicated in anxiety- and depressive-like behavior in rodents. Thus, it has been shown that exogeneous progesterone administration in female rats facilitates extinction recall to a similar degree as estrogen (Milad et al., 2009). Similar findings have been described for allopregnanolone, the metabolite of progesterone, which also displays anxiolytic properties in a variety of tests, especially following OVX (Milad et al., 2009; Pibiri et al., 2008; Toufexis et al., 2004; Sovijit et al., 2019). Also in humans, the anxiolytic properties of progestogens and the metabolite allopregnanolone have been extensively studied (Le Melledo and Baker, 2004). There are also reports supporting a role for progesterone in depressive-like behavior. Thus, exogenous progesterone administration to progesterone knockout mice resulted in an antidepressant-like effect in the forced swim test independent of sex (Frye, 2011). However, it is clear that more studies are warranted to further assess the role of progestins on behavior.

9.3. Androgens

9.3.1. Androgenic effects on hippocampus-dependent cognitive functions

Androgens have also been shown to influence spatial memory, but only when given for a limited duration. In more detail, short-term testosterone supplementation can influence early (7d), but not late (15d), spatial memory whereas testosterone-induced increase in hippocampal neurogenesis occurs after 30d showing it to be unrelated to its behavioral effect (Spritzer and Galea, 2007). The aforementioned findings appear to be mediated through an AR-dependent mechanism within the CA1 since flutamide has been shown to impair MWM acquisition (Edinger and Frye, 2007; Naghdi et al., 2001). While OVX leads to a decline in cognitive function in women, the loss of androgens may contribute to cognitive decline in older men with AD, since AD has been associated with reduced brain and serum levels of testosterone (Rosario et al., 2011; Moffat et al., 2004); even before diagnosis of AD (Moffat et al., 2004). In keeping, castration reduces accuracy in spatial working memory, whereas testosterone administration improves spatial working memory in rodents (Gibbs and Johnson, 2008; Spritzer et al., 2008). In humans, positive effects of testosterone on spatial cognition and memory have been discussed, but results remain inconsistent with some studies demonstrating effects only in females, other studies demonstrating effects only in males and some studies suggesting an inverse u-shaped relationship of testosterone to cognition (Celec et al., 2015).

9.3.2. Androgenic effects on mood and anxiety:

In contrast, there is evidence purporting to a correlation in age-related testosterone decline and major depressive disorder (McIntyre et al., 2006; Shores et al., 2009; Shores et al., 2005; Shores et al., 2004) and testosterone replacement therapy can reverse depressive symptoms in hypogonadal men (Shores et al., 2009; Zarrouf et al., 2009). Moreover, exogenous testosterone administration results in anxiolytic effects in male mice (Aikey et al., 2002), as well as reversing the anxiogenic and pro-depressant-like effects of castration (Carrier and Kabbaj, 2012; Wainwright et al., 2016; Carrier and Kabbaj, 2012). These effects can be blocked by flutamide suggesting that the actions of testosterone are mediated *via* ARs (Fernandez-Guasti and Martinez-Mota, 2005; Hodosy et al., 2012). In human men, both high and low testosterone levels appear to increase depression rates, while testosterone administration seems to be effective in the treatment of depressive symptoms (Amanatkar et al., 2014). While less studied, there is also evidence that androgen administration may have similar effects in females (Carrier and Kabbaj, 2012; Carrier and Kabbaj, 2012; Buddenberg et al., 2009; Frye and Walf, 2009). Finally, there is clinical evidence as well that testosterone may be effective to reverse depression in premenopausal women and woman with treatment-resistant depression (Goldstat et al., 2003; Miller et al., 2009).

10. Conclusions and outlook

In the present review, we have summarised the role of sex- and stress-hormones on hippocampal morphology and functioning in both preclinical and clinical studies. These studies reveal a strong agreement between animal and human studies regarding the influences of sex hormones on hippocampal morphology and functioning. Indeed, pre-clinical neurogenesis findings closely resemble those observed regarding hormonal influences on human neuroimaging results regarding grey matter suggesting the former may, at least in part, underlie the latter. Likewise, pre-clinical results regarding dendritic complexity may point to a mechanism underlying the human functional imaging results. While estrogens and androgens appear to exert positive effects on the hippocampus, the effects of gestagens are less well understood and require further investigation. Stress hormones appear to exert negative effects on the hippocampus depending on sex and timing of the stressor. While findings on behavioral implications are less consistent, these hormonal influences on the hippocampus are, at least partially, also reflected in cognitive and emotional changes due to sex and stress-hormone actions. Nevertheless, studies directly linking hormonal influences on the hippocampus to associated behavioral changes are scarce Importantly, the majority of studies have been performed in only one sex, rending sex/gender differences difficult. Accordingly, the effects of estrogen are well studied in females, but not males, while the effects of androgens are well studied in males, but not females. Regarding stress effects on the hippocampus, most studies have been performed in either males or females, with few direct comparisons between the sexes. While the results clearly indicate sex differences in stress effects on the hippocampus, more studies are required to gain further insight into the interactive effects between sex and stress hormones. Due to the opposite effects of estradiol and glucocorticoids on the hippocampus, a protective effect of estradiol against stress effects on the hippocampus has repeatedly been discussed and was recently reviewed (Ycaza Herrera and Mather, 2015). A similar effect of testosterone has also been proposed, but has not been studied extensively (for review see Toufexis et al., 2014). In both cases, timing of estrogen/androgen exposure appears to be critical, since stress also down-regulates the HPG-axis (for review see Ycaza Herrera and Mather, 2015; Toufexis et al., 2014). Importantly, a comparison of stress and sex hormone interactions on hippocampal morphology between clinical and pre-clinical studies depends on the comparability of stress-models between animals and humans. The fact that sex differences in the stress response differ between animal and human models questions their said comparability. One contributing factor may be that rodents and humans differ in respect to the glucocorticoid that mainly carries the stress response (corticosterone in rodents, cortisol in humans). However, the striking parallels observed across species regarding sex hormone actions on the hippocampus, suggest that the discrepancies in stress effects are – at least partly – of a methodological nature. Accordingly, the further development of comparable translational stress and behavioral paradigms that can be used in both animal and human research is an important step towards a comprehensive understanding of potentially

protective effects of estrogens and androgens against stress-effects on the brain. Such an understanding is essential for developing sex-specific treatment options against stress-related disorders.

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Appendix A. Supplementary material

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