



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

Katharina M. Hillerer^{a,*,1}, David A. Slattery^{b,1}, Belinda Pletzer^{c,d,1}

^a Department of Obstetrics and Gynaecology, Salzburger Landeskrankenhaus (SALK), Paracelsus Medical University (PMU), Clinical Research Center Salzburg (CRCS), Salzburg, Austria

^b Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University, Frankfurt, Germany

^c Department of Psychology, University of Salzburg, Salzburg, Austria

^d Centre for Cognitive Neuroscience, University of Salzburg, Salzburg, Austria

ARTICLE INFO

Keywords:

Stress
Sex differences
Cognition
Translational

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.

* Corresponding author at: Department of Obstetrics and Gynaecology, Paracelsus Medical University (PMU), Müllner Hauptstrasse 48, 5020 Salzburg, Austria.
E-mail address: k.hillierer@salk.at (K.M. Hillerer).

¹ All authors contributed equally.

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 symptomatology 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 utmost 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. 17 α / 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 (Bartessaghi 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 17 β -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 17 β -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 ER α / 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 breeding 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 (Banar 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 extra-hippocampal 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 μ g) and high doses (pro-estrus range; 10 μ g) restoring cell proliferation in OVX rats, whereas medium/supraphysiological doses (1 μ g/50 μ g) 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 μ g) 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, 17 β -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 17 β -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 μ g) 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), ER α and ER β 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 ER α /ER β with the specific agonists propyl pyrazole triol (PPT) and diarylpropionitrile (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 ER α / 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 ER α and ER β -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, ER α and ER β agonists were shown to increase the membrane ER α and ER β 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 opposite 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 ER α 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 17 β -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 ER α 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 -hydroxysteroid 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 -androstane. 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; Orelund 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 foot-shock 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; Rutkowski 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 parahippocampal 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-Spillion 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 (Arelín 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-Spillion 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 arthritis, 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-Bussell 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 (Weerden 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 = Progesterone, ER = estrogen receptor, PR = progesterone receptor, ERT = estrogen replacement therapy, HRT = combined hormone replacement therapy, OC = combined oral contraception; WM = working memory.

a)	Sex	Hippocampus				Behavior			
		Neurogenesis (NG)	Dendritic Morphology	Gray matter (GM)	Activation (ACT)	Cognition		Mood	
		Animal studies	Human studies	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
<i>high systemic E /E increase</i>	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: ↑					
<i>Exogenous E/ ER agonist</i>	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						
<i>low systemic E /E withdrawal</i>	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
<i>ER antagonist/ Aromatase inhibitors</i>	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 ESTROGENS	RESULTS INCONSISTENT	... SEEM TO BE ANXIOLYTIC AND ANTIDEPRESSIVE	... SEEM TO BE ANXIOLYTIC
<i>High systemic P /P increase</i>	F			↓	↓ during cognition ↑ during arousal		?		
<i>Exogenous P/ PR agonist</i>	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
<i>Systemic high T/T increase</i>	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. ↑ during cognition ↑ during arousal		?		↑ depression
<i>Exogenous T/DHT</i>	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
<i>Systemic low T/T loss</i>	M	GDX: ↓ cell survival ↔ cell proliferation		Klinefelter: ↓	Klinefelter: ↓ during word gen.	↓ spatial WM	Aging: ↓ memory	↑ anxiety ↑ depression	↑ depression
<i>Blockade of DHT synthesis</i>	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			Animal studies			Human studies
NOTE: LACK OF STUDIES DIRECTLY COMPARING M AND F		... MOSTLY DECREASE NG IN FEMALES; 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	Acute: ↓ Chronic: ↓	Acute: ↓ during encoding of cognitive material ↑ during encoding of emotional material ↓ during retrieval Chronic: ↓
	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: ↓				
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 Chronic: ↓ dendritic length and branching points in CA1/3 ↓ density in CA1/3	Acute: ↓ Chronic: ↓	Acute: ↓ during encoding of cognitive material ↑ during encoding of emotional material ↓ during retrieval 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 oestrous 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 diestrus/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 exogenous 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 Melleo 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 women 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, rendering 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.

Acknowledgements

This research was in part funded by the Austrian Science Fund (P28261, P32276).

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yfrne.2019.100796>.

References

- Abercrombie, H.C., Jahn, A.L., Davidson, R.J., Kern, S., Kirschbaum, C., Halverson, J., 2011. Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. *J. Psychiatr. Res.* 45, 15–23.
- Abplanalp, J.M., Livingston, L., Rose, R.M., Sandwisch, D., 1977. Cortisol and growth hormone responses to psychological stress during the menstrual cycle. *Psychosom. Med.* 39, 158–177.
- Abrous, D.N., Koehl, M., Le Moal, M., 2005. Adult neurogenesis: from precursors to network and physiology. *Physiol. Rev.* 85, 523–569.
- Admon, R., Treadway, M.T., Valeri, L., Mehta, M., Douglas, S., Pizzagalli, D.A., 2017. Distinct trajectories of cortisol response to prolonged acute stress are linked to affective responses and hippocampal gray matter volume in healthy females. *J. Neurosci.* 37, 7994–8002.
- Ahmed-Leitao, F., Spies, G., van den Heuvel, L., Seedat, S., 2016. Hippocampal and amygdala volumes in adults with posttraumatic stress disorder secondary to childhood abuse or maltreatment: a systematic review. *Psychiatry Res. Neuroimaging* 256, 33–43.
- Aikey, J.L., Nyby, J.G., Anmuth, D.M., James, P.J., 2002. Testosterone rapidly reduces anxiety in male house mice (*Mus musculus*). *Horm. Behav.* 42, 448–460.
- Aimone, J.B., Wiles, J., Gage, F.H., 2009. Computational influence of adult neurogenesis on memory encoding. *Neuron* 61, 187–202.
- Akers, K.G., Martinez-Canabal, A., Restivo, L., Yiu, A.P., De Cristofaro, A., Hsiang, H.L., Wheeler, A.L., Guskjolen, A., Niibori, Y., Shoji, H., Ohira, K., Richards, B.A., Miyakawa, T., Josselyn, S.A., Frankland, P.W., 2014. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science* 344, 598–602.
- Albert, P.R., 2015. Why is depression more prevalent in women? *J. Psychiatry Neurosci.* 40, 219–221.
- Albert, K., Hiscox, J., Boyd, B., Dumas, J., Taylor, W., Newhouse, P., 2017. Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. *Neurobiol. Aging* 56, 1–6.
- Allen, K.M., Fung, S.J., Rothmond, D.A., Noble, P.L., Weickert, C.S., 2014. Gonadectomy increases neurogenesis in the male adolescent rhesus macaque hippocampus. *Hippocampus* 24, 225–238.
- Altemus, M., Redwine, L.S., Leong, Y.M., Frye, C.A., Porges, S.W., Carter, C.S., 2001. Responses to laboratory psychosocial stress in postpartum women. *Psychosom. Med.* 63, 814–821.
- Amanatkar, H.R., Chibnall, J.T., Seo, B.W., Manepalli, J.N., Grossberg, G.T., 2014. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ann. Clin. Psychiatry* 26, 19–32.
- Andreano, J.M., Cahill, L., 2009. Sex influences on the neurobiology of learning and memory. *Learn. Mem.* 16, 248–266.
- Andreano, J.M., Cahill, L., 2010. Menstrual cycle modulation of medial temporal activity evoked by negative emotion. *Neuroimage* 53, 1286–1293.
- Angst, J., Gamma, A., Gastpar, M., Lepine, J.P., Mendlewicz, J., Tylee, A., 2002. Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. *Eur. Arch. Psychiatry Clin. Neurosci.* 252, 201–209.
- Apple, A.C., Ryals, A.J., Alpert, K.I., Wagner, L.I., Shih, P.A., Dokucu, M., Cella, D., Penedo, F.J., Voss, J.L., Wang, L., 2017. Subtle hippocampal deformities in breast cancer survivors with reduced episodic memory and self-reported cognitive concerns. *Neuroimage Clin.* 14, 685–691.
- Apple, A.C., Schroeder, M.P., Ryals, A.J., Wagner, L.I., Cella, D., Shih, P.A., Reilly, J., Penedo, F.J., Voss, J.L., Wang, L., 2018. Hippocampal functional connectivity is related to self-reported cognitive concerns in breast cancer patients undergoing adjuvant therapy. *Neuroimage Clin.* 20, 110–118.
- Arelin, K., Mueller, K., Barth, C., Rekkas, P.V., Kratzsch, J., Burmann, I., Villringer, A., Sacher, J., 2015. Progesterone mediates brain functional connectivity changes during the menstrual cycle: a pilot resting state MRI study. *Front. Neurosci.* 9, 44.
- Ashby, M.C., Maier, S.R., Nishimune, A., Henley, J.M., 2006. Lateral diffusion drives constitutive exchange of AMPA receptors at dendritic spines and is regulated by spine morphology. *J. Neurosci.* 26, 7046–7055.
- Attwell, D., Buchan, A.M., Charpak, S., Lauritzen, M., Macvicar, B.A., Newman, E.A., 2010. Glial and neuronal control of brain blood flow. *Nature* 468, 232–243.
- Axelsson, D.A., Doraiswamy, P.M., McDonald, W.M., Boyko, O.B., Tupler, L.A., Patterson, L.J., Nemeroff, C.B., Ellinwood Jr., E.H., Krishnan, K.R., 1993. Hypercortisolemia and hippocampal changes in depression. *Psychiatry Res.* 47, 163–173.
- Babson, K.A., Woodward, S.H., Schaer, M., Sephton, S.E., Kaloupek, D.G., 2017. Salivary cortisol and regional brain volumes among veterans with and without posttraumatic stress disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 2, 372–379.
- Baek, S.B., Bahn, G., Moon, S.J., Lee, J., Kim, K.H., Ko, I.G., Kim, S.E., Sung, Y.H., Kim, B.K., Kim, T.S., Kim, C.J., Shin, M.S., 2011. The phosphodiesterase type-5 inhibitor, tadalafil, improves depressive symptoms, ameliorates memory impairment, as well as suppresses apoptosis and enhances cell proliferation in the hippocampus of maternal-separated rat pups. *Neurosci. Lett.* 488, 26–30.
- Baek, S.S., Jun, T.W., Kim, K.J., Shin, M.S., Kang, S.Y., Kim, C.J., 2012. Effects of postnatal treadmill exercise on apoptotic neuronal cell death and cell proliferation of maternal-separated rat pups. *Brain Dev.* 34, 45–56.
- Bali, N., Arimoto, J.M., Iwata, N., Lin, S.W., Zhao, L., Brinton, R.D., Morgan, T.E., Finch, C.E., 2012. Differential responses of progesterone receptor membrane component-1 (Pgrmc1) and the classical progesterone receptor (Pgr) to 17beta-estradiol and progesterone in hippocampal subregions that support synaptic remodeling and neurogenesis. *Endocrinology* 153, 759–769.
- Banasr, M., Hery, M., Brezun, J.M., Daszuta, A., 2001. Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus. *Eur. J. Neurosci.* 14, 1417–1424.
- Barha, C.K., Lieblich, S.E., Galea, L.A., 2009. Different forms of oestrogen rapidly upregulate cell proliferation in the dentate gyrus of adult female rats. *J. Neuroendocrinol.* 21, 155–166.
- Barha, C.K., Brummelte, S., Lieblich, S.E., Galea, L.A., 2011. Chronic restraint stress in adolescence differentially influences hypothalamic-pituitary-adrenal axis function and adult hippocampal neurogenesis in male and female rats. *Hippocampus* 21, 1216–1227.
- Barha, C.K., Ishrat, T., Epp, J.R., Galea, L.A., Stein, D.G., 2011. Progesterone treatment normalizes the levels of cell proliferation and cell death in the dentate gyrus of the hippocampus after traumatic brain injury. *Exp. Neurol.* 231, 72–81.
- Barha, C.K., Galea, L.A., 2011. Motherhood alters the cellular response to estrogens in the hippocampus later in life. *Neurobiol. Aging* 32, 2091–2095.
- Barker, J.M., Galea, L.A., 2008. Repeated estradiol administration alters different aspects of neurogenesis and cell death in the hippocampus of female, but not male, rats. *Neuroscience* 152, 888–902.
- Barnes, L.L., Wilson, R.S., Bienias, J.L., Schneider, J.A., Evans, D.A., Bennett, D.A., 2005. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch. Gen. Psychiatry* 62, 685–691.
- Bartessaghi, R., Guidi, S., Severi, S., Contestabile, A., Ciani, E., 2003. Sex differences in the hippocampal dentate gyrus of the guinea-pig before puberty. *Neuroscience* 121, 327–339.
- Barth, C., Steele, C.J., Mueller, K., Rekkas, P.V., Arelin, K., Pampel, A., Burmann, I., Kratzsch, J., Villringer, A., Sacher, J., 2016. In-vivo dynamics of the human hippocampus across the menstrual cycle. *Sci. Rep.* 6, 32833.
- Baum, L.W., 2005. Sex, hormones, and Alzheimer's disease. *J. Gerontol. Ser. A, Biol. Sci. Med. Sci.* 60, 736–743.
- Bayer, J., Rune, G., Kutsche, K., Schwarze, U., Kalisch, R., Buchel, C., Sommer, T., 2013. Estrogen and the male hippocampus: genetic variation in the aromatase gene predicting serum estrogen is associated with hippocampal gray matter volume in men. *Hippocampus* 23, 117–121.
- Bayer, J., Schultz, H., Gamer, M., Sommer, T., 2014. Menstrual-cycle dependent fluctuations in ovarian hormones affect emotional memory. *Neurobiol. Learn. Mem.* 110, 55–63.
- Bayer, J., Rune, G., Schultz, H., Tobia, M.J., Mebes, I., Katzler, O., Sommer, T., 2015. The effect of estrogen synthesis inhibition on hippocampal memory. *Psychoneuroendocrinology* 56, 213–225.
- Bayer, J., Glascher, J., Finsterbusch, J., Schulte, L.H., Sommer, T., 2018. Linear and inverted U-shaped dose-response functions describe estrogen effects on hippocampal activity in young women. *Nat. Commun.* 9, 1220.
- Beiko, J., Lander, R., Hampson, E., Boon, F., Cain, D.P., 2004. Contribution of sex differences in the acute stress response to sex differences in water maze performance in the rat. *Behav. Brain Res.* 151, 239–253.
- Beinhoff, U., Tuman, H., Bretschneider, J., Bittner, D., Riepe, M.W., 2008. Gender-specificities in Alzheimer's disease and mild cognitive impairment. *J. Neurol.* 255, 117–122.
- Bekku, N., Yoshimura, H., 2005. Animal model of menopausal depressive-like state in female mice: prolongation of immobility time in the forced swimming test following ovariectomy. *Psychopharmacology* 183, 300–307.
- Bellace, M., Williams, J.M., Mohamed, F.B., Faro, S.H., 2013. An fMRI study of the activation of the hippocampus by emotional memory. *Int. J. Neurosci.* 123, 121–127.
- Belnoue, L., Grosjean, N., Ladeveze, E., Abrous, D.N., Koehl, M., 2013. Prenatal stress inhibits hippocampal neurogenesis but spares olfactory bulb neurogenesis. *PLoS ONE* 8, e72972.
- Benson, S., Kattoor, J., Kullmann, J.S., Hofmann, S., Engler, H., Forsting, M., Gizewski, E.R., Elsenbruch, S., 2014. Towards understanding sex differences in visceral pain: enhanced reactivation of classically-conditioned fear in healthy women. *Neurobiol. Learn. Mem.* 109, 113–121.
- Bentz, D., Michael, T., Wilhelm, F.H., Hartmann, F.R., Kunz, S., von Rohr, I.R., de Quervain, D.J., 2013. Influence of stress on fear memory processes in an aversive differential conditioning paradigm in humans. *Psychoneuroendocrinology* 38, 1186–1197.
- Berent-Spillon, A., Persad, C.C., Love, T., Tkaczyk, A., Wang, H., Reame, N.K., Frey, K.A., Zubieta, J.K., Smith, Y.R., 2010. Early menopausal hormone use influences brain regions used for visual working memory. *Menopause* 17, 692–699.
- Berent-Spillon, A., Briceño, E., Pinsky, A., Simmen, A., Persad, C.C., Zubieta, J.K., Smith, Y.R., 2015. Distinct cognitive effects of estrogen and progesterone in menopausal women. *Psychoneuroendocrinology* 59, 25–36.
- Bettis, T., Jacobs, L.F., 2012. Sex differences in object recognition are modulated by

- object similarity. *Behav. Brain Res.* 233, 288–292.
- Beylin, A.V., Gandhi, C.C., Wood, G.E., Talk, A.C., Matzel, L.D., Shors, T.J., 2001. The role of the hippocampus in trace conditioning: temporal discontinuity or task difficulty? *Neurobiol. Learn. Mem.* 76, 447–461.
- Bhatia, S., Bookheimer, S.Y., Gaillard, W.D., Theodore, W.H., 1993. Measurement of whole temporal lobe and hippocampus for MR volumetry: normative data. *Neurology* 43, 2006–2010.
- Bimonte-Nelson, H.A., Singleton, R.S., Williams, B.J., Granholm, A.C., 2004. Ovarian hormones and cognition in the aged female rat: II. progesterone supplementation reverses the cognitive enhancing effects of ovariectomy. *Behav. Neurosci.* 118, 707–714.
- Boldrini, M., Underwood, M.D., Hen, R., Rosoklija, G.B., Dwork, A.J., John Mann, J., Arango, V., 2009. Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacol. Off. Publ. Am. College Neuropsychopharmacol.* 34, 2376–2389.
- Boldrini, M., Hen, R., Underwood, M.D., Rosoklija, G.B., Dwork, A.J., Mann, J.J., Arango, V., 2012. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. *Biol. Psychiatry* 72, 562–571.
- Bos, P.A., Montoya, E.R., Terburg, D., van Honk, J., 2014. Cortisol administration increases hippocampal activation to infant crying in males depending on childhood neglect. *Hum. Brain Mapp.* 35, 5116–5126.
- Bouma, E.M., Riese, H., Ormel, J., Verhulst, F.C., Oldehinkel, A.J., 2009. Adolescents' cortisol responses to awakening and social stress; effects of gender, menstrual phase and oral contraceptives. The TRAILS study. *Psychoneuroendocrinology* 34, 884–893.
- Bourne, J., Harris, K.M., 2007. Do thin spines learn to be mushroom spines that remember? *Curr. Opin. Neurobiol.* 17, 381–386.
- Bowers, J.M., Waddell, J., McCarthy, M.M., 2010. A developmental sex difference in hippocampal neurogenesis is mediated by endogenous oestradiol. *Biol. Sex Differ.* 1, 8.
- Bowman, R.E., Zrull, M.C., Luine, V.N., 2001. Chronic restraint stress enhances radial arm maze performance in female rats. *Brain Res.* 904, 279–289.
- Braden, B.B., Dassel, K.B., Bimonte-Nelson, H.A., O'Rourke, H.P., Connor, D.J., Moorhous, S., Sabbagh, M.N., Caselli, R.J., Baxter, L.C., 2017. Sex and post-menopause hormone therapy effects on hippocampal volume and verbal memory. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 24, 227–246.
- Brailoiu, E., Dun, S.L., Brailoiu, G.C., Mizuo, K., Sklar, L.A., Oprea, T.I., Prossnitz, E.R., Dun, N.J., 2007. Distribution and characterization of estrogen receptor G protein-coupled receptor 30 in the rat central nervous system. *J. Endocrinol.* 193, 311–321.
- Bramen, J.E., Hranilovich, J.A., Dahl, R.E., Forbes, E.E., Chen, J., Toga, A.W., Dinov, I.D., Worthman, C.M., Sowell, E.R., 2011. Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cereb. Cortex* 21, 636–646.
- Brandt, N., Vierk, R., Rune, G.M., 2013. Sexual dimorphism in estrogen-induced synaptogenesis in the adult hippocampus. *Int. J. Dev. Biol.* 57, 351–356.
- Brännvall, K., Bogdanovic, N., Korhonen, L., Lindholm, D., 2005. 19-Nortestosterone influences neural stem cell proliferation and neurogenesis in the rat brain. *Eur. J. Neurosci.* 21, 871–878.
- Bremner, J.D., 2005. Effects of traumatic stress on brain structure and function: relevance to early responses to trauma. *J. Trauma Dissoc.* 6, 51–68.
- Bremner, J.D., 2006. Traumatic stress: effects on the brain. *Dialogues Clin. Neurosci.* 8, 445–461.
- Breslau, N., Schultz, L., Peterson, E., 1995. Sex differences in depression: a role for pre-existing anxiety. *Psychiatry Res.* 58, 1–12.
- Brinton, R.D., Thompson, R.F., Foy, M.R., Baudry, M., Wang, J., Finch, C.E., Morgan, T.E., Pike, C.J., Mack, W.J., Stanczyk, F.Z., Nilsen, J., 2008. Progesterone receptors: form and function in brain. *Front. Neuroendocrinol.* 29, 313–339.
- Brown, E.S., Woolston, D.J., Frol, A., Bobadilla, L., Khan, D.A., Hanczyk, M., Rush, A.J., Fleckenstein, J., Babcock, E., Cullum, C.M., 2004. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biol. Psychiatry* 55 (5), 538–545.
- Brown, E.S., Lu, H., Denniston, D., Uh, J., Thomas, B.P., Carmody, T.J., Auchus, R.J., Diaz-Arastia, R., Tamminga, C., 2013. A randomized, placebo-controlled proof-of-concept, crossover trial of phenytoin for hydrocortisone-induced declarative memory changes. *J. Affect. Disord.* 150, 551–558.
- Brown, E.S., Jeon-Slaughter, H., Lu, H., Jamadar, R., Issac, S., Shad, M., Denniston, D., Tamminga, C., Nakamura, A., Thomas, B.P., 2015. Hippocampal volume in healthy controls given 3-day stress doses of hydrocortisone. *Neuropsychopharmacology* 40, 1216–1221.
- Brummelte, S., Galea, L.A., 2010. Chronic high corticosterone reduces neurogenesis in the dentate gyrus of adult male and female rats. *Neuroscience* 168, 680–690.
- Brummelte, S., Pawluski, J.L., Galea, L.A., 2006. High post-partum levels of corticosterone given to dams influence postnatal hippocampal cell proliferation and behavior of offspring: a model of post-partum stress and possible depression. *Horm. Behav.* 50, 370–382.
- Buchanan, T.W., Kern, S., Allen, J.S., Tranel, D., Kirschbaum, C., 2004. Circadian regulation of cortisol after hippocampal damage in humans. *Biol. Psychiatry* 56, 651–656.
- Buchanan, T.W., Tranel, D., Kirschbaum, C., 2009. Hippocampal damage abolishes the cortisol response to psychosocial stress in humans. *Horm. Behav.* 56, 44–50.
- Buddenberg, T.E., Komorowski, M., Ruocco, L.A., Silva, M.A., Topic, B., 2009. Attenuating effects of testosterone on depressive-like behavior in the forced swim test in healthy male rats. *Brain Res. Bull.* 79, 182–186.
- Burkhardt, T., Ludecke, D., Spies, L., Wittmann, L., Westphal, M., Flitsch, J., 2015. Hippocampal and cerebellar atrophy in patients with Cushing's disease. *Neurosurg. Focus* 39, E5.
- Butz, M., Lehmann, K., Dammasch, I.E., Teuchert-Noodt, G., 2006. A theoretical network model to analyse neurogenesis and synaptogenesis in the dentate gyrus. *Neural Netw. Off. J. Int. Neural Netw. Soc.* 19, 1490–1505.
- Buwald, B., van der Borgh, K., Koolhaas, J.M., McEwen, B.S., 2010. Testosterone decrease does not play a major role in the suppression of hippocampal cell proliferation following social defeat stress in rats. *Physiol. Behav.* 101, 719–725.
- Cahill, L., 2006. Why sex matters for neuroscience. *Nat. Rev. Neurosci.* 7, 477–484.
- Calem, M., Bromis, K., McGuire, P., Morgan, C., Kempton, M.J., 2017. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. *Neuroimage Clin.* 14, 471–479.
- Cameron, H.A., Gould, E., 1994. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* 61, 203–209.
- Cameron, C.A., McKay, S., Susman, E.J., Wynne-Edwards, K., Wright, J.M., Weinberg, J., 2017. Cortisol stress response variability in early adolescence: attachment, affect and sex. *J. Youth Adolesc.* 46, 104–120.
- Cameron, H.A., Schoenfeld, T.J., 2018. Behavioral and structural adaptations to stress. *Front. Neuroendocrinol.*
- Capitani, E., Laiacona, M., Basso, A., 1998. Phonetically cued word-fluency, gender differences and aging: a reappraisal. *Cortex* 34, 779–783.
- Capitani, E., Barbarotto, R., Laiacona, M., 2005. Gender differences and the brain representation of semantic knowledge. *Brain Lang.* 95, 56–57.
- Carey, M.P., Deterd, C.H., de Koning, J., Helmerhorst, F., de Kloet, E.R., 1995. The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat. *J. Endocrinol.* 144, 311–321.
- Carrier, N., Kabbaj, M., 2012. Testosterone and imipramine have antidepressant effects in socially isolated male but not female rats. *Horm. Behav.* 61, 678–685.
- Carrier, N., Kabbaj, M., 2012. Extracellular signal-regulated kinase 2 signaling in the hippocampal dentate gyrus mediates the antidepressant effects of testosterone. *Biol. Psychiatry* 71, 642–651.
- Celec, P., Ostatnikova, D., Hodosy, J., 2015. On the effects of testosterone on brain behavioral functions. *Front. Neurosci.* 9, 12.
- Chaiton, J.A., Wong, S.J., Galea, L.A., 2019. Chronic aromatase inhibition increases ventral hippocampal neurogenesis in middle-aged female mice. *Psychoneuroendocrinology* 106, 111–116.
- Chan, M., Chow, C., Hamson, D.K., Lieblich, S.E., Galea, L.A., 2014. Effects of chronic oestradiol, progesterone and medroxyprogesterone acetate on hippocampal neurogenesis and adrenal mass in adult female rats. *J. Neuroendocrinol.* 26, 386–399.
- Chen, Y., Dube, C.M., Rice, C.J., Baram, T.Z., 2008. Rapid loss of dendritic spines after stress involves derangement of spine dynamics by corticotropin-releasing hormone. *J. Neurosci.* 28, 2903–2911.
- Chen, X., He, X., Tao, L., Li, J., Wu, J., Zhu, C., Yu, F., Zhang, L., Zhang, J., Qiu, B., Yu, Y., Wang, K., 2017. The working memory and dorsolateral prefrontal-hippocampal functional connectivity changes in long-term survival breast cancer patients treated with tamoxifen. *Int. J. Neuropsychopharmacol.* 20, 374–382.
- Chen, R., Muetzel, R.L., El Marroun, H., Noppe, G., van Rossum, E.F., Jaddoe, V.W., Verhulst, F.C., White, T., Fang, F., Tiemeier, H., 2016. No association between hair cortisol or cortisone and brain morphology in children. *Psychoneuroendocrinology* 74, 101–110.
- Cherney, I.D., Brabec, C.M., Runco, D.V., 2008. Mapping out spatial ability: sex differences in way-finding navigation. *Percept. Mot. Skills* 107, 747–760.
- Chiang, C.C., Shivacharan, R.S., Wei, X., Gonzalez-Reyes, L.E., Durand, D.M., 2019. Slow periodic activity in the longitudinal hippocampal slice can self-propagate non-synaptically by a mechanism consistent with ephaptic coupling. *J. Physiol.* 597, 249–269.
- Childs, E., Dlugos, A., De Wit, H., 2010. Cardiovascular, hormonal, and emotional responses to the TSST in relation to sex and menstrual cycle phase. *Psychophysiology* 47, 550–559.
- Chow, C., Epp, J.R., Lieblich, S.E., Barha, C.K., Galea, L.A., 2013. Sex differences in neurogenesis and activation of new neurons in response to spatial learning and memory. *Psychoneuroendocrinology* 38, 1236–1250.
- Chung, K.C., Peisen, F., Kogler, L., Radke, S., Turetsky, B., Freiherr, J., Derntl, B., 2016. The influence of menstrual cycle and androstadienone on female stress reactions: an fMRI study. *Front. Hum. Neurosci.* 10, 44.
- Chung, K.C., Peisen, F., Kogler, L., Radke, S., Turetsky, B., Freiherr, J., Derntl, B., 2016. Corrigendum: The influence of menstrual cycle and androstadienone on female stress reactions: an fMRI study. *Front. Hum. Neurosci.* 10, 293.
- Cinini, S.M., Barnabe, G.F., Galvao-Coelho, N., de Medeiros, M.A., Perez-Mendes, P., Sousa, M.B., Covolan, L., Mello, L.E., 2014. Social isolation disrupts hippocampal neurogenesis in young non-human primates. *Front. Neurosci.* 8, 45.
- Clelland, C.D., Choi, M., Romberg, C., Clemenson Jr., G.D., Fragniere, A., Tyers, P., Jessberger, S., Saksida, L.M., Barker, R.A., Gage, F.H., Bussey, T.J., 2009. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 325, 210–213.
- Coe, C.L., Kramer, M., Czeh, B., Gould, E., Reeves, A.J., Kirschbaum, C., Fuchs, E., 2003. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biol. Psychiatry* 54, 1025–1034.
- Coker, L.H., Espeland, M.A., Rapp, S.R., Legault, C., Resnick, S.M., Hogan, P., Gaussoin, S., Dailey, M., Shumaker, S.A., 2010. Postmenopausal hormone therapy and cognitive outcomes: the Women's Health Initiative Memory Study (WHIMS). *J. Steroid Biochem. Mol. Biol.* 118, 304–310.
- Colle, R., Chupin, M., Cury, C., Vandendrie, C., Gressier, F., Hardy, P., Falissard, B., Colliot, O., Ducreux, D., Corruble, E., 2015. Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts. *J. Psychiatr. Res.* 61, 13–18.
- Collip, D., Habets, P., Marcellis, M., Gronenschild, E., Lataster, T., Lardinois, M., Nicolson, N.A., Myin-Germeys, I., 2013. Hippocampal volume as marker of daily life stress sensitivity in psychosis. *Psychol. Med.* 43, 1377–1387.

- Coluccia, D., Wolf, O.T., Kollias, S., Roozendaal, B., Forster, A., de Quervain, D.J., 2008. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. *J. Neurosci.* 28, 3474–3478.
- Conrad, C.D., LeDoux, J.E., Magarinos, A.M., McEwen, B.S., 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behav. Neurosci.* 113, 902–913.
- Conrad, C.D., Jackson, J.L., Wiczorek, L., Baran, S.E., Harman, J.S., Wright, R.L., Korol, D.L., 2004. Acute stress impairs spatial memory in male but not female rats: influence of estrous cycle. *Pharmacol. Biochem. Behav.* 78, 569–579.
- Cordeira, J., Kolluru, S.S., Rosenblatt, H., Kry, J., Strecker, R.E., McCarley, R.W., 2018. Learning and memory are impaired in the object recognition task during metestrus/diestrus and after sleep deprivation. *Behav. Brain Res.* 339, 124–129.
- Corkin, S., 2002. What's new with the amnesic patient H.M.? *Nat. Rev. Neurosci.* 3, 153–160.
- Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol. Psychiatry* 62, 847–855.
- Cox, S.R., MacPherson, S.E., Ferguson, K.J., Royle, N.A., Maniega, S.M., Hernandez Mdel, C., Bastin, M.E., MacLulich, A.M., Wardlaw, J.M., Deary, I.J., 2015. Does white matter structure or hippocampal volume mediate associations between cortisol and cognitive ageing? *Psychoneuroendocrinology* 62, 129–137.
- Cox, S.R., Valdes Hernandez, M.D.C., Kim, J., Royle, N.A., MacPherson, S.E., Ferguson, K.J., Munoz Maniega, S., Anlagan, D., Aribisala, B.S., Bastin, M.E., Park, J., Starr, J.M., Deary, I.J., MacLulich, A.M., Wardlaw, J.M., 2017. Associations between hippocampal morphology, diffusion characteristics, and salivary cortisol in older men. *Psychoneuroendocrinology* 78, 151–158.
- Craft, R.M., Kostick, M.L., Rogers, J.A., White, C.L., Tsutsui, K.T., 2010. Forced swim test behavior in postpartum rats. *Pharmacol. Biochem. Behav.* 96, 402–412.
- Crapo, L., 1979. Cushing's syndrome: a review of diagnostic tests. *Metabolism* 28, 955–977.
- Creer, D.J., Romberg, C., Saksida, L.M., van Praag, H., Bussey, T.J., 2010. Running enhances spatial pattern separation in mice. *PNAS* 107, 2367–2372.
- Cunningham-Bussell, A.C., Root, J.C., Butler, T., Tuescher, O., Pan, H., Epstein, J., Weisholtz, D.S., Pavony, M., Silverman, M.E., Goldstein, M.S., Altemus, M., Cloitre, M., Ledoux, J., McEwen, B., Stern, E., Silbersweig, D., 2009. Diurnal cortisol amplitude and fronto-limbic activity in response to stressful stimuli. *Psychoneuroendocrinology* 34, 694–704.
- Czeh, B., Welt, T., Fischer, A.K., Erhardt, A., Schmitt, W., Muller, M.B., Toschi, N., Fuchs, E., Keck, M.E., 2002. Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. *Biol. Psychiatry* 52, 1057–1065.
- Dabbs, J.M., Chang, E.L., Strong, R.A., Milun, R., 1998. Spatial ability, navigation strategy, and geographic knowledge among men and women. *Evol. Hum. Behav.* 19, 89–98.
- Dahmen, B., Puetz, V.B., Scharke, W., von Polier, G.G., Herpertz-Dahlmann, B., Konrad, K., 2018. Effects of early-life adversity on hippocampal structures and associated HPA axis functions. *Dev. Neurosci.* 40, 13–22.
- Dalla, C., Antoniou, K., Drossopoulou, G., Xagoraris, M., Kokras, N., Sfakakis, A., Papadopoulou-Daifoti, Z., 2005. Chronic mild stress impact: are females more vulnerable? *Neuroscience* 135, 703–714.
- Dalla, C., Antoniou, K., Kokras, N., Drossopoulou, G., Papathanasiou, G., Bekris, S., Daskas, S., Papadopoulou-Daifoti, Z., 2008. Sex differences in the effects of two stress paradigms on dopaminergic neurotransmission. *Physiol. Behav.* 93, 595–605.
- Dalla, C., Whetstone, A.S., Hodes, G.E., Shors, T.J., 2009. Stressful experience has opposite effects on dendritic spines in the hippocampus of cycling versus masculinized females. *Neurosci. Lett.* 449, 52–56.
- Dalla, C., Papachristos, E.B., Whetstone, A.S., Shors, T.J., 2009. Female rats learn trace memories better than male rats and consequently retain a greater proportion of new neurons in their hippocampi. *PNAS* 106, 2927–2932.
- Dallak, M.M., Mikhailidis, D.P., Haidara, M.A., Bin-Jalilah, I.M., Tork, O.M., Rateb, M.A., Yassin, H.Z., Al-Refai, Z.A., Ibrahim, I.M., Elawa, S.M., Rashed, L.A., Afifi, N.A., 2008. Oxidative stress as a common mediator for apoptosis induced-cardiac damage in diabetic rats. *Open Cardiovasc. Med. J.* 2, 70–78.
- Davis, E.G., Humphreys, K.L., McEwen, L.M., Sacchet, M.D., Camacho, M.C., MacIsaac, J.L., Lin, D.T.S., Kobor, M.S., Gotlib, I.H., 2017. Accelerated DNA methylation age in adolescent girls: associations with elevated diurnal cortisol and reduced hippocampal volume. *Transl. Psychiatry* 7, e1223.
- de Frias, C.M., Nilsson, L.G., Herlitz, A., 2006. Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 13, 574–587.
- de Voogd, L.D., Klumpers, F., Fernandez, G., Hermans, E.J., 2017. Intrinsic functional connectivity between amygdala and hippocampus during rest predicts enhanced memory under stress. *Psychoneuroendocrinology* 75, 192–202.
- Dedovic, K., Rexroth, M., Wolff, E., Duchesne, A., Scherling, C., Beaudry, T., Lue, S.D., Lord, C., Engert, V., Pruessner, J.C., 2009. Neural correlates of processing stressful information: an event-related fMRI study. *Brain Res.* 1293, 49–60.
- Dedovic, K., Engert, V., Duchesne, A., Lue, S.D., Andrews, J., Efanov, S.I., Beaudry, T., Pruessner, J.C., 2010. Cortisol awakening response and hippocampal volume: vulnerability for major depressive disorder? *Biol. Psychiatry* 68, 847–853.
- den Heijer, T., Geerlings, M.I., Hofman, A., de Jong, F.H., Launer, L.J., Pols, H.A., Breteler, M.M., 2003. Higher estrogen levels are not associated with larger hippocampi and better memory performance. *Arch. Neurol.* 60, 213–220.
- Dennison, M., Whittle, S., Ucel, M., Vijayakumar, N., Kline, A., Simmons, J., Allen, N.B., 2013. Mapping subcortical brain maturation during adolescence: evidence of hemisphere- and sex-specific longitudinal changes. *Dev. Sci.* 16, 772–791.
- Dias, G.P., Bevilacqua, M.C., da Luz, A.C., Fleming, R.L., de Carvalho, L.A., Cocks, G., Beckman, D., Hosken, L.C., de Sant'Anna Machado, W., Correa-e-Castro, A.C., Mousovich-Neto, F., de Castro Gomes, V., Bastos Gde, N., Kubrusly, R.C., da Costa, V.M., Srivastava, D., Landeira-Fernandez, J., Nardi, A.E., Thuret, S., Gardino, P.F., 2014. Hippocampal biomarkers of fear memory in an animal model of generalized anxiety disorder. *Behav. Brain Res.* 263, 34–45.
- Dotson, V.M., Davatzikos, C., Kraut, M.A., Resnick, S.M., 2009. Depressive symptoms and brain volumes in older adults: a longitudinal magnetic resonance imaging study. *J. Psychiatry Neurosci.* 34, 367–375.
- Duan, H., Yuan, Y., Zhang, L., Qin, S., Zhang, K., Buchanan, T.W., Wu, J., 2013. Chronic stress exposure decreases the cortisol awakening response in healthy young men. *Stress* 16, 630–637.
- Duarte-Guterman, P., Yagi, S., Chow, C., Galea, L.A., 2015. Hippocampal learning, memory, and neurogenesis: effects of sex and estrogens across the lifespan in adults. *Horm. Behav.* 74, 37–52.
- Duarte-Guterman, P., Lieblich, S.E., Chow, C., Galea, L.A., 2015. Estradiol and GPER activation differentially affect cell proliferation but not GPER expression in the hippocampus of adult female rats. *PLoS ONE* 10, e0129880.
- Eberling, J.L., Wu, C., Haan, M.N., Mungas, D., Buonocore, M., Jagust, W.J., 2003. Preliminary evidence that estrogen protects against age-related hippocampal atrophy. *Neurobiol. Aging* 24, 725–732.
- Edinger, K.L., Frye, C.A., 2007. Androgens' performance-enhancing effects in the inhibitory avoidance and water maze tasks may involve actions at intracellular androgen receptors in the dorsal hippocampus. *Neurobiol. Learn. Mem.* 87, 201–208.
- Endo, Y., Mizuno, T., Fujita, K., Funabashi, T., Kimura, F., 1994. Soft-diet feeding during development enhances later learning abilities in female rats. *Physiol. Behav.* 56, 629–633.
- Engert, V., Buss, C., Khalili-Mahani, N., Wadiwalla, M., Dedovic, K., Pruessner, J.C., 2010. Investigating the association between early life parental care and stress responsivity in adulthood. *Dev. Neuropsychol.* 35, 570–581.
- Epp, J.R., Spritzer, M.D., Galea, L.A., 2007. Hippocampus-dependent learning promotes survival of new neurons in the dentate gyrus at a specific time during cell maturation. *Neuroscience* 149, 273–285.
- Everaerd, D., Gerritsen, L., Rijpkema, M., Frodl, T., van Oostrom, I., Franke, B., Fernandez, G., Tendolkar, I., 2012. Sex modulates the interactive effect of the serotonin transporter gene polymorphism and childhood adversity on hippocampal volume. *Neuropsychopharmacology* 37, 1848–1855.
- Exner, C., Nehrkorn, B., Martin, V., Huber, M., Shiratori, K., Rief, W., 2008. Sex-dependent hippocampal volume reductions in schizophrenia relate to episodic memory deficits. *J. Neuropsychiatry Clin. Neurosci.* 20, 227–230.
- Ezzati, A., Katz, M.J., Zammit, A.R., Lipton, M.L., Zimmerman, M.E., Sliwinski, M.J., Lipton, R.B., 2016. Differential association of left and right hippocampal volumes with verbal episodic and spatial memory in older adults. *Neuropsychologia* 93, 380–385.
- Falconer, E.M., Galea, L.A., 2003. Sex differences in cell proliferation, cell death and defensive behavior following acute predator odor stress in adult rats. *Brain Res.* 975, 22–36.
- Fanselow, M.S., Dong, H.W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 65, 7–19.
- Faraone, S.V., 2015. Attention deficit hyperactivity disorder and premature death. *Lancet* 385, 2132–2133.
- Farinetti, A., Tomasi, S., Foglio, B., Ferraris, A., Ponti, G., Gotti, S., Peretto, P., Panzica, G.C., 2015. Testosterone and estradiol differentially affect cell proliferation in the subventricular zone of young adult gonadectomized male and female rats. *Neuroscience* 286, 162–170.
- Felmingham, K., Williams, L.M., Kemp, A.H., Liddell, B., Falconer, E., Peduto, A., Bryant, R., 2010. Neural responses to masked fear faces: sex differences and trauma exposure in posttraumatic stress disorder. *J. Abnorm. Psychol.* 119, 241–247.
- Feng, M., Sheng, G., Li, Z., Wang, J., Ren, K., Jin, X., Jiang, K., 2014. Postnatal maternal separation enhances tonic GABA current of cortical layer 5 pyramidal neurons in juvenile rats and promotes genesis of GABAergic neurons in neocortical molecular layer and subventricular zone in adult rats. *Behav. Brain Res.* 260, 74–82.
- Fernandez-Guasti, A., Martinez-Mota, L., 2005. Anxiolytic-like actions of testosterone in the burying behavior test: role of androgen and GABA-benzodiazepine receptors. *Psychoneuroendocrinology* 30, 762–770.
- Ferragud, A., Haro, A., Sylvain, A., Velazquez-Sanchez, C., Hernandez-Rabaza, V., Canales, J.J., 2010. Enhanced habit-based learning and decreased neurogenesis in the adult hippocampus in a murine model of chronic social stress. *Behav. Brain Res.* 210, 134–139.
- Fester, L., Ribeiro-Gouveia, V., Prange-Kiel, J., von Schassen, C., Bottner, M., Jarry, H., Rune, G.M., 2006. Proliferation and apoptosis of hippocampal granule cells require local oestrogen synthesis. *J. Neurochem.* 97, 1136–1144.
- Fester, L., Prange-Kiel, J., Zhou, L., Blittersdorf, B.V., Bohm, J., Jarry, H., Schumacher, M., Rune, G.M., 2012. Estrogen-regulated synaptogenesis in the hippocampus: sexual dimorphism in vivo but not in vitro. *J. Steroid Biochem. Mol. Biol.* 131, 24–29.
- Figueiredo, H.F., Dolgas, C.M., Herman, J.P., 2002. Stress activation of cortex and hippocampus is modulated by sex and stage of estrus. *Endocrinology* 143, 2534–2540.
- Filipek, P.A., Richelme, C., Kennedy, D.N., Caviness Jr., V.S., 1994. The young adult human brain: an MRI-based morphometric analysis. *Cereb. Cortex* 4, 344–360.
- Filkowski, M.M., Olsen, R.M., Duda, B., Wanger, T.J., Sabatinelli, D., 2017. Sex differences in emotional perception: meta analysis of divergent activation. *Neuroimage* 147, 925–933.
- Fisher, P.M., Larsen, C.B., Beliveau, V., Henningsson, S., Pinborg, A., Holst, K.K., Jensen, P.S., Svarer, C., Siebner, H.R., Knudsen, G.M., Frokjaer, V.G., 2017. Pharmacologically induced sex hormone fluctuation effects on resting-state functional connectivity in a risk model for depression: a randomized trial. *Neuropsychopharmacology* 42, 446–453.
- Foland-Ross, L.C., Ross, J.L., Reiss, A.L., 2019. Androgen treatment effects on

- hippocampus structure in boys with Klinefelter syndrome. *Psychoneuroendocrinology* 100, 223–228.
- Fowler, C.D., Johnson, F., Wang, Z., 2005. Estrogen regulation of cell proliferation and distribution of estrogen receptor- α in the brains of adult female prairie and meadow voles. *J. Comp. Neurol.* 489, 166–179.
- Fowler, C.D., Liu, Y., Wang, Z., 2008. Estrogen and adult neurogenesis in the amygdala and hypothalamus. *Brain Res. Rev.* 57, 342–351.
- Frank, T.C., Kim, G.L., Krzemien, A., Van Vugt, D.A., 2010. Effect of menstrual cycle phase on corticolimbic brain activation by visual food cues. *Brain Res.* 1363, 81–92.
- Frazier, J.A., Chiu, S., Breeze, J.L., Makris, N., Lange, N., Kennedy, D.N., Herbert, M.R., Bent, E.K., Koneru, V.K., Dieterich, M.E., Hodge, S.M., Rauch, S.L., Grant, P.E., Cohen, B.M., Seidman, L.J., Caviness, V.S., Biederman, J., 2005. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *Am. J. Psychiatry* 162, 1256–1265.
- Frazier, J.A., Hodge, S.M., Breeze, J.L., Giuliano, A.J., Terry, J.E., Moore, C.M., Kennedy, D.N., Lopez-Larson, M.P., Caviness, V.S., Seidman, L.J., Zablotsky, B., Makris, N., 2008. Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. *Schizophr. Bull.* 34, 37–46.
- Frick, K.M., 2015. Molecular mechanisms underlying the memory-enhancing effects of estradiol. *Horm. Behav.* 74, 4–18.
- Frick, K.M., Kim, J., 2018. Mechanisms underlying the rapid effects of estradiol and progesterone on hippocampal memory consolidation in female rodents. *Horm. Behav.* 104, 100–110.
- Frings, L., Wagner, K., Unterrainer, J., Spreer, J., Halsband, U., Schulze-Bonhage, A., 2006. Gender-related differences in lateralization of hippocampal activation and cognitive strategy. *NeuroReport* 17, 417–421.
- Frodl, T., Meisenzahl, E.M., Zetzsch, T., Born, C., Groll, C., Jager, M., Leinsinger, G., Bottlender, R., Hahn, K., Moller, H.J., 2002. Hippocampal changes in patients with first episode of major depression. *Am. J. Psychiatry* 159, 1112–1118.
- Frodl, T., Carballedo, A., Frey, E.M., O'Keane, V., Skokauskas, N., Morris, D., Gill, M., Hughes, M.M., Harkin, A., Connor, T., 2014. Expression of glucocorticoid inducible genes is associated with reductions in cornu ammonis and dentate gyrus volumes in patients with major depressive disorder. *Dev. Psychopathol.* 26, 1209–1217.
- Frodl, T., Janowitz, D., Schmaal, L., Tozzi, L., Dobrowolny, H., Stein, D.J., Veltman, D.J., Wittfeld, K., van Erp, T.G.M., Jahanshad, N., Block, A., Hegenscheid, K., Volzke, H., Lagopoulos, J., Hatton, S.N., Hickie, I.B., Frey, E.M., Carballedo, A., Brooks, S.J., Vuletic, D., Uhlmann, A., Veer, I.M., Walter, H., Schnell, K., Grotegerd, D., Arolt, V., Kugel, H., Schramm, E., Konrad, C., Zurovski, B., Baune, B.T., van der Wee, N.J.A., van Tol, M.J., Penninx, B., Thompson, P.M., Hibar, D.P., Dannlowski, U., Grabe, H.J., 2017. Childhood adversity impacts on brain subcortical structures relevant to depression. *J. Psychiatr. Res.* 86, 58–65.
- Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiol. Dis.* 52, 24–37.
- Frye, C.A., 1995. Estrus-associated decrements in a water maze task are limited to acquisition. *Physiol. Behav.* 57, 5–14.
- Frye, C.A., 2011. Progesterone attenuates depressive behavior of younger and older adult C57/BL6, wildtype, and progesterone receptor knockout mice. *Pharmacol. Biochem. Behav.* 99, 525–531.
- Frye, C.A., Duffy, C.K., Wolf, A.A., 2007. Estrogens and progestins enhance spatial learning of intact and ovariectomized rats in the object placement task. *Neurobiol. Learn. Mem.* 88, 208–216.
- Frye, C.A., Rhodes, M.E., 2002. Enhancing effects of estrogen on inhibitory avoidance performance may be in part independent of intracellular estrogen receptors in the hippocampus. *Brain Res.* 956, 285–293.
- Frye, C.A., Wolf, A.A., 2009. Depression-like behavior of aged male and female mice is ameliorated with administration of testosterone or its metabolites. *Physiol. Behav.* 97, 266–269.
- Fuentes, N., Silveira, P., 2019. Estrogen receptor signaling mechanisms. *Adv. Protein Chem. Struct. Biol.* 116, 135–170.
- Gabor, C., Lymer, J., Phan, A., Choleris, E., 2015. Rapid effects of the G-protein coupled oestrogen receptor (GPER) on learning and dorsal hippocampus dendritic spines in female mice. *Physiol. Behav.* 149, 53–60.
- Galea, L.A., 2008. Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. *Brain Res. Rev.* 57, 332–341.
- Galea, L.A.M., Frick, K.M., Hampson, E., Sohrabji, F., Choleris, E., 2017. Why estrogens matter for behavior and brain health. *Neurosci. Biobehav. Rev.* 76, 363–379.
- Galea, L.A., Kavaliers, M., Ossenkopp, K.P., 1996. Sexually dimorphic spatial learning in meadow voles *Microtus pennsylvanicus* and deer mice *Peromyscus maniculatus*. *J. Exp. Biol.* 199, 195–200.
- Galea, L., Kimura, D., 1993. Sex differences in route-learning. *Pers. Individ. Dif.* 14, 53–65.
- Galea, L.A., McEwen, B.S., Tanapat, P., Deak, T., Spencer, R.L., Dhabhar, F.S., 1997. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* 81, 689–697.
- Galea, L.A., McEwen, B.S., 1999. Sex and seasonal differences in the rate of cell proliferation in the dentate gyrus of adult wild meadow voles. *Neuroscience* 89, 955–964.
- Galea, L.A., Wide, J.K., Barr, A.M., 2001. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. *Behav. Brain Res.* 122, 1–9.
- Galea, L.A., Wainwright, S.R., Roes, M.M., Duarte-Guterman, P., Chow, C., Hamson, D.K., 2013. Sex, hormones and neurogenesis in the hippocampus: hormonal modulation of neurogenesis and potential functional implications. *J. Neuroendocrinol.* 25, 1039–1061.
- Garcia-Falgueras, A., Junque, C., Gimenez, M., Caldu, X., Segovia, S., Guillon, A., 2006. Sex differences in the human olfactory system. *Brain Res.* 1116, 103–111.
- Gauthier, C.T., Duyme, M., Zanca, M., Capron, C., 2009. Sex and performance level effects on brain activation during a verbal fluency task: a functional magnetic resonance imaging study. *Cortex* 45, 164–176.
- Gerritsen, L., Comijs, H.C., van der Graaf, Y., Knoops, A.J., Penninx, B.W., Geerlings, M.I., 2011. Depression, hypothalamic pituitary adrenal axis, and hippocampal and entorhinal cortex volumes—the SMART Medea study. *Biol. Psychiatry* 70, 373–380.
- Gibbs, R.B., Johnson, D.A., 2008. Sex-specific effects of gonadectomy and hormone treatment on acquisition of a 12-arm radial maze task by Sprague Dawley rats. *Endocrinology* 149, 3176–3183.
- Giedd, J.N., Vaituzis, A.C., Hamburger, S.D., Lange, N., Rajapakse, J.C., Kaysen, D., Vauss, Y.C., Rapoport, J.L., 1996. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. *J. Comp. Neurol.* 366, 223–230.
- Giedd, J.N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., Rapoport, J.L., 1997. Sexual dimorphism of the developing human brain. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 21, 1185–1201.
- Gobinath, A.R., Mahmoud, R., Galea, L.A., 2015. Influence of sex and stress exposure across the lifespan on endophenotypes of depression: focus on behavior, glucocorticoids, and hippocampus. *Front. Neurosci.* 8, 420.
- Gobinath, A.R., Workman, J.L., Chow, C., Lieblich, S.E., Galea, L.A., 2016. Maternal postpartum corticosterone and fluoxetine differentially affect adult male and female offspring on anxiety-like behavior, stress reactivity, and hippocampal neurogenesis. *Neuropharmacology* 101, 165–178.
- Goel, N., Workman, J.L., Lee, T.T., Innala, L., Viau, V., 2014. Sex differences in the HPA axis. *Comprehens. Physiol.* 4, 1121–1155.
- Gold, S.M., Kern, K.C., O'Connor, M.F., Montag, M.J., Kim, A., Yoo, Y.S., Giessler, B.S., Sicotte, N.L., 2010. Smaller cornu ammonis 2–3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. *Biol. Psychiatry* 68, 553–559.
- Goldstat, R., Briganti, E., Tran, J., Wolfe, R., Davis, S.R., 2003. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause* 10, 390–398.
- Goldstein, J.M., Jerram, M., Poldrack, R., Ahern, T., Kennedy, D.N., Seidman, L.J., Makris, N., 2005. Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. *J. Neurosci.* 25, 9309–9316.
- Goldstein, J.M., Jerram, M., Abbs, B., Whitfield-Gabrieli, S., Makris, N., 2010. Sex differences in stress response circuitry activation dependent on female hormonal cycle. *J. Neurosci.* 30, 431–438.
- Golomb, J., de Leon, M.J., Kluger, A., George, A.E., Tarshish, C., Ferris, S.H., 1993. Hippocampal atrophy in normal aging. An association with recent memory impairment. *Arch. Neurol.* 50, 967–973.
- Gonzalez-Burgos, I., Alejandro-Gomez, M., Cervantes, M., 2005. Spine-type densities of hippocampal CA1 neurons vary in proestrus and estrus rats. *Neurosci. Lett.* 379, 52–54.
- Goto, M., Abe, O., Miyati, T., Inano, S., Hayashi, N., Aoki, S., Mori, H., Kabasawa, H., Ino, K., Yano, K., Iida, K., Mima, K., Ohtomo, K., 2011. 3 Tesla MRI detects accelerated hippocampal volume reduction in postmenopausal women. *J. Magn. Reson. Imaging* 33, 48–53.
- Gould, E., Woolley, C.S., Frankfurt, M., McEwen, B.S., 1990. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *J. Neurosci.* 10, 1286–1291.
- Gould, E., McEwen, B.S., Tanapat, P., Galea, L.A., Fuchs, E., 1997. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J. Neurosci.* 17, 2492–2498.
- Gould, E., Tanapat, P., McEwen, B.S., Flugge, G., Fuchs, E., 1998. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc. Natl. Acad. Sci. U S A* 95, 3168–3171.
- Gould, E., Beylin, A., Tanapat, P., Reeves, A., Shors, T.J., 1999. Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.* 2, 260–265.
- Green, A.D., Galea, L.A., 2008. Adult hippocampal cell proliferation is suppressed with estrogen withdrawal after a hormone-simulated pregnancy. *Horm. Behav.* 54, 203–211.
- Grissom, E.M., Hawley, W.R., Hodges, K.S., Fawcett-Patel, J.M., Dohanich, G.P., 2013. Biological sex influences learning strategy preference and muscarinic receptor binding in specific brain regions of prepubertal rats. *Hippocampus* 23, 313–322.
- Grön, G., Wunderlich, A.P., Spitzer, M., Tomczak, R., Riepe, M.W., 2000. Brain activation during human navigation: gender-different neural networks as substrates of performance. *Am. Nat.* 157, 74–88.
- Guadalupe, T., Mathias, S.R., van Erp, T.G.M., Whelan, C.D., Zwiers, M.P., Abe, Y., Abramovic, L., Agartz, I., Andreassen, O.A., Arias-Vasquez, A., Aribasala, B.S., Armstrong, N.J., Arolt, V., Artiges, E., Ayres-Arriola, R., Baboyan, V.G., Banaschewski, T., Barker, G., Bastin, M.E., Baune, B.T., Blangero, J., Bokde, A.L.W., Boedhoe, P.S.W., Bose, A., Brem, S., Brodaty, H., Bromberg, U., Brooks, S., Buchel, C., Builelaar, J., Calhoun, V.D., Cannon, D.M., Cattrell, A., Cheng, Y., Conrod, P.J., Conzelmann, A., Corvin, A., Crespo-Facorro, B., Crivello, F., Dannlowski, U., de Zubicaray, G.I., de Zwart, S.M.C., Deary, I.J., Desrivieres, S., Doan, N.T., Donohoe, G., Doram, E.S., Ehrlich, S., Espeseth, T., Fernandez, G., Flor, H., Fouché, J.P., Frouin, V., Fukunaga, M., Gallinat, J., Garavan, H., Gill, M., Suarez, A.G., Gowland, P., Grabe, H.J., Grotegerd, D., Gruber, O., Hagenaars, S., Hashimoto, R., Hauser, T.U., Heinz, A., Hibar, D.P., Hoekstra, P.J., Hoogman, M., Howells, F.M., Hu, H., Hulshoff Pol, H.E., Huyser, C., Ittermann, B., Jahanshad, N., Jonsson, E.G., Jurk, S., Kahn, R.S., Kelly, S., Kraemer, B., Kugel, H., Kwon, J.S., Lemaitre, H., Lesch, K.P., Lochner, C., Luciano, M., Marquand, A.F., Martin, N.G., Martinez-Zalacain, I., Martinot, J.L., Mataix-Cols, D., Mather, K., McDonald, C., McMahon, K.L., Medland, S.E., Menchon, J.M., Morris, D.W., Mothersill, O., Maniega, S.M., Mwambi, B., et al., 2017. Human subcortical brain asymmetries in 15,847 people worldwide reveal effects of age and sex. *Brain*

- Imaging Behav. 11, 1497–1514.
- Gur, R.C., Gunning-Dixon, F., Bilker, W.B., Gur, R.E., 2002. Sex differences in temporo- limbic and frontal brain volumes of healthy adults. *Cereb. Cortex* 12, 998–1003.
- Gutierrez-Lobos, K., Scherer, M., Anderer, P., Katschnig, H., 2002. The influence of age on the female/male ratio of treated incidence rates in depression. *BMC Psychiatry* 2, 3.
- Hadel, S., Wirth, C., Rapp, M., Gallinat, J., Schubert, F., 2013. Effects of age and sex on the concentrations of glutamate and glutamine in the human brain. *J. Magn. Reson. Imaging* 38, 1480–1487.
- Hajszan, T., Milner, T.A., Leranah, C., 2007. Sex steroids and the dentate gyrus. *Prog. Brain Res.* 163, 399–415.
- Halpern, D.F., 2000. Sex Differences in Cognitive Abilities. I. Erlbaum Associates, Mahwah, N.J.
- Hamann, S., Canli, T., 2004. Individual differences in emotion processing. *Curr. Opin. Neurobiol.* 14, 233–238.
- Hampson, E., 1990. Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn.* 14, 26–43.
- Hamson, D.K., Wainwright, S.R., Taylor, J.R., Jones, B.A., Watson, N.V., Galea, L.A., 2013. Androgens increase survival of adult-born neurons in the dentate gyrus by an androgen receptor-dependent mechanism in male rats. *Endocrinology* 154, 3294–3304.
- Hamson, D.K., Roes, M.M., Galea, L.A., 2016. Sex hormones and cognition: neuroendocrine influences on memory and learning. *Compr. Physiol.* 6, 1295–1337.
- Han, K.M., Choi, S., Jung, J., Na, K.S., Yoon, H.K., Lee, M.S., Ham, B.J., 2014. Cortical thickness, cortical and subcortical volume, and white matter integrity in patients with their first episode of major depression. *J. Affect. Disord.* 155, 42–48.
- Handa, R.J., Burgess, L.H., Kerr, J.E., O'Keefe, J.A., 1994. Gonadal steroid hormone receptors and sex differences in the hypothalamo-pituitary-adrenal axis. *Horm. Behav.* 28, 464–476.
- Hanson, N.D., Owens, M.J., Boss-Williams, K.A., Weiss, J.M., Nemeroff, C.B., 2011. Several stressors fail to reduce adult hippocampal neurogenesis. *Psychoneuroendocrinology* 36, 1520–1529.
- Harburger, L.L., Saadi, A., Frick, K.M., 2009. Dose-dependent effects of post-training estradiol plus progesterone treatment on object memory consolidation and hippocampal extracellular signal-regulated kinase activation in young ovariectomized mice. *Neuroscience* 160, 6–12.
- Harris, K.M., Jensen, F.E., Tsao, B., 1992. Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation. *J. Neurosci.* 12, 2685–2705.
- Harris, T., Scheuringer, A., Pletzer, B., 2019. Perspective and strategy interactively modulate sex differences in a 3D navigation task. *Biol. Sex Differ.* 10, 17.
- Hastings, R.S., Parsey, R.V., Oquendo, M.A., Arango, V., Mann, J.J., 2004. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 29, 952–959.
- Hatanaka, Y., Mukai, H., Mitsuhashi, K., Hojo, Y., Murakami, G., Komatsuzaki, Y., Sato, R., Kawato, S., 2009. Androgen rapidly increases dendritic thorns of CA3 neurons in male rat hippocampus. *Biochem. Biophys. Res. Commun.* 381, 728–732.
- Heany, S.J., van Honk, J., Stein, D.J., Brooks, S.J., 2016. A quantitative and qualitative review of the effects of testosterone on the function and structure of the human social-emotional brain. *Metab. Brain Dis.* 31, 157–167.
- Heine, V.M., Maslam, S., Joels, M., Lucassen, P.J., 2004. Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation. *Neurobiol. Aging* 25, 361–375.
- Helpman, L., Zhu, X., Suarez-Jimenez, B., Lazarov, A., Monk, C., Neria, Y., 2017. Sex differences in trauma-related psychopathology: a critical review of neuroimaging literature (2014–2017). *Curr. Psychiatry Rep.* 19, 104.
- Henckens, M.J., Hermans, E.J., Pu, Z., Joels, M., Fernandez, G., 2009. Stressed memories: how acute stress affects memory formation in humans. *J. Neurosci.* 29, 10111–10119.
- Herbison, C.E., Henley, D., Marsh, J., Atkinson, H., Newnham, J.P., Matthews, S.G., Lye, S.J., Pennell, C.E., 2016. Characterization and novel analyses of acute stress response patterns in a population-based cohort of young adults: influence of gender, smoking, and BMI. *Stress* 19, 139–150.
- Herting, M.M., Gautam, P., Spielberg, J.M., Kan, E., Dahl, R.E., Sowell, E.R., 2014. The role of testosterone and estradiol in brain volume changes across adolescence: a longitudinal structural MRI study. *Hum. Brain Mapp.* 35, 5633–5645.
- Hidalgo, V., Pulopulos, M.M., Puig-Perez, S., Espin, L., Gomez-Amor, J., Salvador, A., 2015. Acute stress affects free recall and recognition of pictures differently depending on age and sex. *Behav. Brain Res.* 292, 393–402.
- Hill, A.C., Laird, A.R., Robinson, J.L., 2014. Gender differences in working memory networks: a BrainMap meta-analysis. *Biol. Psychol.* 102, 18–29.
- Hillner, K.M., Neumann, I.D., Slattery, D.A., 2012. From stress to postpartum mood and anxiety disorders: how chronic peripartum stress can impair maternal adaptations. *Neuroendocrinology* 95, 22–38.
- Hillner, K.M., Neumann, I.D., Couillard-Despres, S., Aigner, L., Slattery, D.A., 2013. Sex-dependent regulation of hippocampal neurogenesis under basal and chronic stress conditions in rats. *Hippocampus* 23, 476–487.
- Hirshstein, M., Coloma Andrews, L., Hausmann, M., 2014. Gender-stereotyping and cognitive sex differences in mixed- and same-sex groups. *Arch. Sex. Behav.* 43, 1663–1673.
- Hlavacova, N., Wawruch, M., Tisonova, J., Jezova, D., 2008. Neuroendocrine activation during combined mental and physical stress in women depends on trait anxiety and the phase of the menstrual cycle. *Ann. N. Y. Acad. Sci.* 1148, 520–525.
- Hodosy, J., Zelmanova, D., Majzunova, M., Filova, B., Malinova, M., Ostasnikova, D., Celec, P., 2012. The anxiolytic effect of testosterone in the rat is mediated via the androgen receptor. *Pharmacol. Biochem. Behav.* 102, 191–195.
- Hoekzema, E., Barba-Muller, E., Pozzobon, C., Picado, M., Lucco, F., Garcia-Garcia, D., Soliva, J.C., Tobena, A., Desco, M., Crone, E.A., Ballesteros, A., Carmona, S., Vilarroja, O., 2017. Pregnancy leads to long-lasting changes in human brain structure. *Nat. Neurosci.* 20, 287–296.
- Hofer, A., Sidentopf, C.M., Ischebeck, A., Rettenbacher, M.A., Verius, M., Felber, S., Wolfgang Fleischhacker, W., 2007. Sex differences in brain activation patterns during processing of positively and negatively valenced emotional words. *Psychol. Med.* 37, 109–119.
- Hogervorst, E., Williams, J., Budge, M., Riedel, W., Jolles, J., 2000. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience* 101, 485–512.
- Hogervorst, E., Bandelow, S., Moffat, S.D., 2005. Increasing testosterone levels and effects on cognitive functions in elderly men and women: a review. *Curr. Drug Targets CNS Neurol. Disord.* 4, 531–540.
- Hojo, Y., Murakami, G., Mukai, H., Higo, S., Hatanaka, Y., Ogiue-Ikeda, M., Ishii, H., Kimoto, T., Kawato, S., 2008. Estrogen synthesis in the brain—role in synaptic plasticity and memory. *Mol. Cell. Endocrinol.* 290, 31–43.
- Hollanders, J.J., van der Voorn, B., Rottevel, J., Finken, M.J.J., 2017. Is HPA axis reactivity in childhood gender-specific? A systematic review. *Biol. Sex Differ.* 8, 23.
- Holsen, L.M., Spaeth, S.B., Lee, J.H., Ogden, L.A., Klibanski, A., Whitfield-Gabrieli, S., Goldstein, J.M., 2011. Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. *J. Affect. Disord.* 131, 379–387.
- Holsen, L.M., Lee, J.H., Spaeth, S.B., Ogden, L.A., Klibanski, A., Whitfield-Gabrieli, S., Sloan, R.P., Goldstein, J.M., 2012. Brain hypoactivation, autonomic nervous system dysregulation, and gonadal hormones in depression: a preliminary study. *Neurosci. Lett.* 514, 57–61.
- Holtmaat, A.J., Trachtenberg, J.T., Wilbrecht, L., Shepherd, G.M., Zhang, X., Knott, G.W., Svoboda, K., 2005. Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* 45, 279–291.
- Hu, L., Yue, Y., Zuo, P.P., Jin, Z.Y., Feng, F., You, H., Li, M.L., Ge, Q.S., 2006. Evaluation of neuroprotective effects of long-term low dose hormone replacement therapy on postmenopausal women brain hippocampus using magnetic resonance scanner. *Chin. Med. Sci. J.* 21, 214–218.
- Huang, Y., Zhou, R., Wu, M., Wang, Q., Zhao, Y., 2015. Premenstrual syndrome is associated with blunted cortisol reactivity to the TSST. *Stress* 18, 160–168.
- Hulshof, H.J., Novati, A., Sgoifo, A., Luiten, P.G., den Boer, J.A., Meerlo, P., 2011. Maternal separation decreases adult hippocampal cell proliferation and impairs cognitive performance but has little effect on stress sensitivity and anxiety in adult Wistar rats. *Behav. Brain Res.* 216, 552–560.
- Iaria, G., Lanyon, L.J., Fox, C.J., Giaschi, D., Barton, J.J., 2008. Navigational skills correlate with hippocampal fractional anisotropy in humans. *Hippocampus* 18, 335–339.
- Irlé, E., Ruhleder, M., Lange, C., Seidler-Brandler, U., Salzer, S., Dechent, P., Weniger, G., Leibing, E., Leichsenring, F., 2010. Reduced amygdalar and hippocampal size in adults with generalized social phobia. *J. Psychiatry Neurosci.* 35, 126–131.
- Irlé, E., Lange, C., Ruhleder, M., Exner, C., Siemerker, J., Weniger, G., 2011. Hippocampal size in women but not men with schizophrenia relates to disorder duration. *Psychiatry Res.* 192, 133–139.
- Irvine, K., Laws, K.R., Gale, T.M., Kondel, T.K., 2012. Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *J. Clin. Exp. Neuropsychol.* 34, 989–998.
- Jacobs, E., D'Esposito, M., 2011. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *J. Neurosci.* 31, 5286–5293.
- Jacobs, E.G., Holsen, L.M., Lancaster, K., Makris, N., Whitfield-Gabrieli, S., Remington, A., Weiss, B., Buka, S., Klibanski, A., Goldstein, J.M., 2015. 17beta-estradiol differentially regulates stress circuitry activity in healthy and depressed women. *Neuropsychopharmacology* 40, 566–576.
- Jacobs, E.G., Weiss, B.K., Makris, N., Whitfield-Gabrieli, S., Buka, S.L., Klibanski, A., Goldstein, J.M., 2016. Impact of sex and menopausal status on episodic memory circuitry in early midlife. *J. Neurosci.* 36, 10163–10173.
- Jacobs, E.G., Weiss, B., Makris, N., Whitfield-Gabrieli, S., Buka, S.L., Klibanski, A., Goldstein, J.M., 2017. Reorganization of functional networks in verbal working memory circuitry in early midlife: the impact of sex and menopausal status. *Cereb. Cortex* 27, 2857–2870.
- Jacome, L.F., Baratei, K., Buitrago, D., Lema, F., Frankfurt, M., Luine, V.N., 2016. Gonadal hormones rapidly enhance spatial memory and increase hippocampal spine density in male rats. *Endocrinology* 157, 1357–1362.
- Jain, A., Huang, G.Z., Woolley, C.S., 2019. Latent sex differences in molecular signaling that underlies excitatory synaptic potentiation in the hippocampus. *J. Neurosci.* 39, 1552–1565.
- Jancke, L., Merillat, S., Liem, F., Hanggi, J., 2015. Brain size, sex, and the aging brain. *Hum. Brain Mapp.* 36, 150–169.
- Jaworska, N., MacMaster, F.P., Yang, X.R., Courtright, A., Pradhan, S., Gaxiola, I., Cortese, F., Goodyear, B., Ramasubbu, R., 2014. Influence of age of onset on limbic and paralimbic structures in depression. *Psychiatry Clin. Neurosci.* 68, 812–820.
- Jessberger, S., Nakashima, K., Clemenson Jr., G.D., Mejia, E., Mathews, E., Ure, K., Ogawa, S., Sinton, C.M., Gage, F.H., Hsieh, J., 2007. Epigenetic modulation of seizure-induced neurogenesis and cognitive decline. *J. Neurosci.: Off. J. Soc. Neurosci.* 27, 5967–5975.
- Jessberger, S., Clark, R.E., Broadbent, N.J., Clemenson Jr., G.D., Consiglio, A., Lie, D.C., Squire, L.R., Gage, F.H., 2009. Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats. *Learn. Memory* 16, 147–154.
- Jezova, D., Jurankova, E., Mosnarova, A., Kriska, M., Skultetyova, I., 1996. Neuroendocrine response during stress with relation to gender differences. *Acta Neurobiol. Exp. (Wars)* 56, 779–785.

- Ji, E., Weickert, C.S., Lenroot, R., Kindler, J., Skilleter, A.J., Vercammen, A., White, C., Gur, R.E., Weickert, T.W., 2016. Adjunctive selective estrogen receptor modulator increases neural activity in the hippocampus and inferior frontal gyrus during emotional face recognition in schizophrenia. *Transl. Psychiatry* 6, e795.
- Jin, R.O., Mason, S., Mellon, S.H., Epel, E.S., Reus, V.I., Mahan, L., Rosser, R.L., Hough, C.M., Burke, H.M., Mueller, S.G., Wolkowitz, O.M., 2016. Cortisol/DHEA ratio and hippocampal volume: a pilot study in major depression and healthy controls. *Psychoneuroendocrinology* 72, 139–146.
- Jonasson, Z., 2005. Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. *Neurosci. Biobehav. Rev.* 28, 811–825.
- Jorge, R.E., Acion, L., Starkstein, S.E., Magnotta, V., 2007. Hippocampal volume and mood disorders after traumatic brain injury. *Biol. Psychiatry* 62, 332–338.
- Kajantie, E., Phillips, D.I., 2006. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology* 31, 151–178.
- Kasai, H., Fukuda, M., Watanabe, S., Hayashi-Takagi, A., Noguchi, J., 2010. Structural dynamics of dendritic spines in memory and cognition. *Trends Neurosci.* 33, 121–129.
- Kaufman, S.B., 2007. Sex differences in mental rotation and spatial visualization ability: Can they be accounted for by differences in working memory capacity? *Intelligence* 35, 211–223.
- Keding, T.J., Herring, R.J., 2015. Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. *Neuropsychopharmacology* 40, 537–545.
- Kee, N., Teixeira, C.M., Wang, A.H., Frankland, P.W., 2007. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nat. Neurosci.* 10, 355–362.
- Keller, J., Gomez, R., Williams, G., Lemke, A., Lazzaroni, L., Murphy Jr., G.M., Schatzberg, A.F., 2017. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol. Psychiatry* 22, 527–536.
- Kesler, S.R., Garrett, A., Bender, B., Yankowitz, J., Zeng, S.M., Reiss, A.L., 2004. Amygdala and hippocampal volumes in Turner syndrome: a high-resolution MRI study of X-monosomy. *Neuropsychologia* 42, 1971–1978.
- Kessler, R.C., 2003. Epidemiology of women and depression. *J. Affect. Disord.* 74, 5–13.
- Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S., 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* 51, 8–19.
- Khaksari, M., Mahmoodi, M., Rezvani, M.E., Sajjadi, M.A., Karam, G.A., Hajizadeh, S., 2005. Differences between male and female students in cardiovascular and endocrine responses to examination stress. *J. Ayub. Med. Coll. Abbottabad* 17, 15–19.
- Khalili-Mahani, N., Dedovic, K., Engert, V., Pruessner, M., Pruessner, J.C., 2010. Hippocampal activation during a cognitive task is associated with subsequent neuroendocrine and cognitive responses to psychological stress. *Hippocampus* 20, 323–334.
- Khairbek, M.A., Klemm, H.C., Sahay, A., Hen, R., 2012. Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. *Nat. Neurosci.* 15, 1613–1620.
- Kikusui, T., Ichikawa, S., Mori, Y., 2009. Maternal deprivation by early weaning increases corticosterone and decreases hippocampal BDNF and neurogenesis in mice. *Psychoneuroendocrinology* 34, 762–772.
- Kim, G.W., Jeong, G.W., 2014. Neural mechanisms underlying sexual arousal in connection with sexual hormone levels: a comparative study of the postoperative male-to-female transsexuals and premenopausal and menopausal women. *NeuroReport* 25, 693–700.
- Kimura, D., Seal, B.N., 2003. Sex differences in recall of real or nonsense words. *Psychol. Rep.* 93, 263–264.
- Kindler, J., Weickert, C.S., Skilleter, A.J., Catts, S.V., Lenroot, R., Weickert, T.W., 2015. Selective estrogen receptor modulation increases hippocampal activity during probabilistic association learning in schizophrenia. *Neuropsychopharmacology* 40, 2388–2397.
- Kirschbaum, C., Wust, S., Hellhammer, D., 1992. Consistent sex differences in cortisol responses to psychological stress. *Psychosom. Med.* 54, 648–657.
- Kirschbaum, C., Kudielka, B.M., Gaab, J., Schommer, N.C., Hellhammer, D.H., 1999. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosom. Med.* 61, 154–162.
- Klaassen, E.B., de Groot, R.H., Evers, E.A., Nicolson, N.A., Veltman, D.J., Jolles, J., 2013. Cortisol and induced cognitive fatigue: effects on memory activation in healthy males. *Biol. Psychol.* 94, 167–174.
- Knoops, A.J., Gerritsen, L., van der Graaf, Y., Mali, W.P., Geerlings, M.I., 2010. Basal hypothalamic pituitary adrenal axis activity and hippocampal volumes: the SMART-Medea study. *Biol. Psychiatry* 67, 1191–1198.
- Kogler, L., Gur, R.C., Derntl, B., 2015. Sex differences in cognitive regulation of psychosocial achievement stress: brain and behavior. *Hum. Brain Mapp.* 36, 1028–1042.
- Kogler, L., Muller, V.I., Seidel, E.M., Boubela, R., Kalcher, K., Moser, E., Habel, U., Gur, R.C., Eickhoff, S.B., Derntl, B., 2016. Sex differences in the functional connectivity of the amygdala in association with cortisol. *Neuroimage* 134, 410–423.
- Kogler, L., Seidel, E.M., Metzler, H., Thaler, H., Boubela, R.N., Pruessner, J.C., Kryspin-Exner, I., Gur, R.C., Windischberger, C., Moser, E., Habel, U., Derntl, B., 2017. Impact of self-esteem and sex on stress reactions. *Sci. Rep.* 7, 17210.
- Kole, M.H., Costoli, T., Koolhaas, J.M., Fuchs, E., 2004. Bidirectional shift in the cornu ammonis 3 pyramidal dendritic organization following brief stress. *Neuroscience* 125, 337–347.
- Komatsuzaki, Y., Murakami, G., Tsurugizawa, T., Mukai, H., Tanabe, N., Mitsuhashi, K., Kawata, M., Kimoto, T., Ooshio, Y., Kawato, S., 2005. Rapid spinogenesis of pyramidal neurons induced by activation of glucocorticoid receptors in adult male rat hippocampus. *Biochem. Biophys. Res. Commun.* 335, 1002–1007.
- Kong, L., Chen, K., Womer, F., Jiang, W., Luo, X., Driesen, N., Liu, J., Blumberg, H., Tang, Y., Xu, K., Wang, F., 2013. Sex differences of gray matter morphology in cortico-limbic-striatal neural system in major depressive disorder. *J. Psychiatr. Res.* 47, 733–739.
- Kong, F., Zhen, Z., Li, J., Huang, L., Wang, X., Song, Y., Liu, J., 2014. Sex-related neuroanatomical basis of emotion regulation ability. *PLoS ONE* 9, e97071.
- Koss, W.A., Frick, K.M., 2017. Sex differences in hippocampal function. *J. Neurosci. Res.* 95, 539–562.
- Kretz, O., Fester, L., Wehrenberg, U., Zhou, L., Brauckmann, S., Zhao, S., Prange-Kiel, J., Naumann, T., Jarry, H., Frotscher, M., Rune, G.M., 2004. Hippocampal synapses depend on hippocampal estrogen synthesis. *J. Neurosci.* 24, 5913–5921.
- Kuipers, S.D., Trentani, A., Westenbroek, C., Bramham, C.R., Korf, J., Kema, I.P., Ter Horst, G.J., Den Boer, J.A., 2006. Unique patterns of FOS, phospho-CREB and BrdU immunoreactivity in the female rat brain following chronic stress and citalopram treatment. *Neuropharmacology* 50, 428–440.
- Kukulja, J., Thiel, C.M., Wolf, O.T., Fink, G.R., 2008. Increased cortisol levels in cognitively challenging situations are beneficial in young but not older subjects. *Psychopharmacology* 201, 293–304.
- Kukulja, J., Klingmüller, D., Maier, W., Fink, G.R., Hurlmann, R., 2011. Noradrenergic-glucocorticoid modulation of emotional memory encoding in the human hippocampus. *Psychol. Med.* 41, 2167–2176.
- Lagace, D.C., Fischer, S.J., Eisch, A.J., 2007. Gender and endogenous levels of estradiol do not influence adult hippocampal neurogenesis in mice. *Hippocampus* 17, 175–180.
- Lajud, N., Roque, A., Cajero, M., Gutierrez-Ospina, G., Torner, L., 2012. Periodic maternal separation decreases hippocampal neurogenesis without affecting basal corticosterone during the stress hypo-responsive period, but alters HPA axis and coping behavior in adulthood. *Psychoneuroendocrinology* 37, 410–420.
- Landre, L., Destrieux, C., Baudry, M., Barantin, L., Cottier, J.P., Martineau, J., Hommet, C., Isingrini, M., Belzung, C., Gaillard, P., Camus, V., El Hage, W., 2010. Preserved subcortical volumes and cortical thickness in women with sexual abuse-related PTSD. *Psychiatry Res.* 183, 181–186.
- Langelaan, S., Bakker, A.B., Schaufeli, W.B., van Rhenen, W., van Doornen, L.J., 2006. Do burned-out and work-engaged employees differ in the functioning of the hypothalamic-pituitary-adrenal axis? *Scand. J. Work Environ. Health* 32, 339–348.
- Lassalle, J.M., Bataille, T., Halley, H., 2000. Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. *Neurobiol. Learn. Mem.* 73, 243–257.
- Lawton, C.A., 1994. Gender differences in way-finding strategies: relationship to spatial ability and spatial anxiety. *Sex Roles* 30, 765–779.
- Lawton, C.A., 2001. Gender and regional differences in spatial referents used in direction giving. *Sex Roles* 44, 321–337.
- Lawton, C., Charleston, S., Zieles, A., 1996. Individual- and gender-related differences in indoor wayfinding. *Environ. Behav.* 28, 204–219.
- Le Mello, J.M., Baker, G., 2004. Role of progesterone and other neuroactive steroids in anxiety disorders. *Expert Rev. Neurother.* 4, 851–860.
- Lebron-Milad, K., Abbs, B., Milad, M.R., Linnman, C., Rougemont-Bucking, A., Zeidan, M.A., Holt, D.J., Goldstein, J.M., 2012. Sex differences in the neurobiology of fear conditioning and extinction: a preliminary fMRI study of shared sex differences with stress-arousal circuitry. *Biol. Mood Anxiety Disord.* 2, 7.
- Lee, J.H., Byun, M.S., Yi, D., Choe, Y.M., Choi, H.J., Baek, H., Sohn, B.K., Lee, J.Y., Kim, H.J., Kim, J.W., Lee, Y., Kim, Y.K., Sohn, C.H., Woo, J.I., Lee, D.Y., Group, K.R., 2017. Sex-specific association of sex hormones and gonadotropins, with brain amyloid and hippocampal neurodegeneration. *Neurobiol. Aging* 58, 34–40.
- Lee, S.J., Campomanes, C.R., Sikat, P.T., Greenfield, A.T., Allen, P.B., McEwen, B.S., 2004. Estrogen induces phosphorylation of cyclic AMP response element binding (pCREB) in primary hippocampal cells in a time-dependent manner. *Neuroscience* 124, 549–560.
- Lee, K.J., Kim, S.J., Kim, S.W., Choi, S.H., Shin, Y.C., Park, S.H., Moon, B.H., Cho, E., Lee, M.S., Choi, S.H., Chun, B.G., Shin, K.H., 2006. Chronic mild stress decreases survival, but not proliferation, of new-born cells in adult rat hippocampus. *Exp. Mol. Med.* 38, 44–54.
- Lemaire, V., Koehl, M., Le Moal, M., Abrous, D.N., 2000. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc. Natl. Acad. Sci. U S A* 97, 11032–11037.
- Leslie, A.T., Akers, K.G., Krakowski, A.D., Stone, S.S., Sakaguchi, M., Arruda-Carvalho, M., Frankland, P.W., 2011. Impact of early adverse experience on complexity of adult-generated neurons. *Transl. Psychiatry* 1, e35.
- Lete, I., Lapuente, O., 2016. Contraceptive options for women with premenstrual dysphoric disorder: current insights and a narrative review. *Open Access J. Contracept* 7, 117–125.
- Leuner, B., Gould, E., Shors, T.J., 2006. Is there a link between adult neurogenesis and learning? *Hippocampus* 16, 216–224.
- Lewin, C., Herlitz, A., 2002. Sex differences in face recognition—women's faces make the difference. *Brain Cogn.* 50, 121–128.
- Li, W., van Tol, M.J., Li, M., Miao, W., Jiao, Y., Heinze, H.J., Bogerts, B., He, H., Walter, M., 2014. Regional specificity of sex effects on subcortical volumes across the lifespan in healthy aging. *Hum. Brain Mapp.* 35, 238–247.
- Lisofsky, N., Martensson, J., Eckert, A., Lindenberg, U., Gallinat, J., Kuhn, S., 2015. Hippocampal volume and functional connectivity changes during the female menstrual cycle. *Neuroimage* 118, 154–162.
- Lisofsky, N., Lindenberg, U., Kuhn, S., 2015. Amygdala/hippocampal activation during the menstrual cycle: evidence for lateralization of effects across different tasks. *Neuropsychologia* 67, 55–62.
- Liu, J., Chaplin, T.M., Wang, F., Sinha, R., Mayes, L.C., Blumberg, H.P., 2012. Stress

- reactivity and corticolic response to emotional faces in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 51, 304–312.
- Liu, L., Zhao, L., She, H., Chen, S., Wang, J.M., Wong, C., McClure, K., Sitruk-Ware, R., Brinton, R.D., 2010. Clinically relevant progestins regulate neurogenic and neuro-protective responses in vitro and in vivo. *Endocrinology* 151, 5782–5794.
- Logue, M.W., van Rooij, S.J.H., Dennis, E.L., Davis, S.L., Hayes, J.P., Stevens, J.S., Densmore, M., Haswell, C.C., Ipser, J., Koch, S.B.J., Korgaonkar, M., Lebois, L.A.M., Peverill, M., Baker, J.T., Boedhoe, P.S.W., Frijling, J.L., Gruber, S.A., Harpaz-Rotem, I., Jahanshad, N., Koopowitz, S., Levy, I., Nawijn, L., O'Connor, L., Olff, M., Salat, D.H., Sheridan, M.A., Spielberg, J.M., van Zuiden, M., Winternitz, S.R., Wolff, J.D., Wolf, E.J., Wang, X., Wrocklage, K., Abdallah, C.G., Bryant, R.A., Geuze, E., Jovanovic, T., Kaufman, M.L., King, A.P., Krystal, J.H., Lagopoulos, J., Bennett, M., Lanius, R., Liberzon, I., McGlinchey, R.E., McLaughlin, K.A., Milberg, W.P., Miller, M.W., Ressler, K.J., Veltman, D.J., Yucel, M.J., Thomaes, K., Thompson, P.M., Morey, R.A., 2018. Smaller hippocampal volume in posttraumatic stress disorder: a multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. *Biol. Psychiatry* 83, 244–253.
- Lord, C., Buss, C., Lupien, S.J., Pruessner, J.C., 2008. Hippocampal volumes are larger in postmenopausal women using estrogen therapy compared to past users, never users and men: a possible window of opportunity effect. *Neurobiol. Aging* 29, 95–101.
- Lord, C., Engert, V., Lupien, S.J., Pruessner, J.C., 2010. Effect of sex and estrogen therapy on the aging brain: a voxel-based morphometry study. *Menopause* 17, 846–851.
- Lorenzetti, V., Allen, N.B., Fornito, A., Yucel, M.J., 2009. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J. Affect. Disord.* 117, 1–17.
- Lovallo, W.R., Robinson, J.L., Glahn, D.C., Fox, P.T., 2010. Acute effects of hydrocortisone on the human brain: an fMRI study. *Psychoneuroendocrinology* 35, 15–20.
- Luo, J., Wang, T., Liang, S., Hu, X., Li, W., Jin, F., 2013. Experimental gastritis leads to anxiety- and depression-like behaviors in female but not male rats. *Behav. Brain Funct.* 9, 46.
- Lupien, S.J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N.P., Thakur, M., McEwen, B.S., Hauger, R.L., Meaney, M.J., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat. Neurosci.* 1, 69–73.
- Lymer, J., Robinson, A., Winters, B.D., Choleris, E., 2017. Rapid effects of dorsal hippocampal G-protein coupled estrogen receptor on learning in female mice. *Psychoneuroendocrinology* 77, 131–140.
- Mackiewicz, K.L., Sarinopoulos, I., Cleven, K.L., Nitschke, J.B., 2006. The effect of anticipation and the specificity of sex differences for amygdala and hippocampus function in emotional memory. *Proc. Natl. Acad. Sci. U S A* 103, 14200–14205.
- MacLusky, N.J., Luine, V.N., Hajszan, T., Leranthe, C., 2005. The 17 α and 17 β isomers of estradiol both induce rapid spine synapse formation in the CA1 hippocampal subfield of ovariectomized female rats. *Endocrinology* 146, 287–293.
- MacMaster, F.P., Carrey, N., Langevin, L.M., Jaworska, N., Crawford, S., 2014. Disorder-specific volumetric brain difference in adolescent major depressive disorder and bipolar depression. *Brain Imaging Behav.* 8, 119–127.
- Magarinos, A.M., McEwen, B.S., 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience* 69, 89–98.
- Mahmoud, R., Wainwright, S.R., Galea, L.A., 2016. Sex hormones and adult hippocampal neurogenesis: Regulation, implications, and potential mechanisms. *Front. Neuroendocrinol.* 41, 129–152.
- Maki, P.M., 2013. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. *Menopause* 20, 695–709.
- Maki, P.M., Dumas, J., 2009. Mechanisms of action of estrogen in the brain: insights from human neuroimaging and psychopharmacologic studies. *Semin. Reprod. Med.* 27, 250–259.
- Maki, P.M., Dennerstein, L., Clark, M., Guthrie, J., LaMontagne, P., Fornelli, D., Little, D., Henderson, V.W., Resnick, S.M., 2011. Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life. *Brain Res.* 1379, 232–243.
- Maki, P.M., Resnick, S.M., 2000. Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol. Aging* 21, 373–383.
- Maki, P.M., Mordecai, K.L., Rubin, L.H., Sundermann, E., Savarese, A., Eatough, E., Drogos, L., 2015. Menstrual cycle effects on cortisol responsivity and emotional retrieval following a psychosocial stressor. *Horm. Behav.* 74, 201–208.
- Malberg, J.E., Duman, R.S., 2003. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology* 28, 1562–1571.
- Maller, J.J., Reglade-Meslin, C., Anstey, K.J., Sachdev, P., 2006. Sex and symmetry differences in hippocampal volumetrics: before and beyond the opening of the crus of the fornix. *Hippocampus* 16, 80–90.
- Malykhin, N.V., Huang, Y., Hrybouski, S., Olsen, F., 2017. Differential vulnerability of hippocampal subfields and anteroposterior hippocampal subregions in healthy cognitive aging. *Neurobiol. Aging* 59, 121–134.
- Mandyam, C.D., Crawford, E.F., Eisch, A.J., Rivier, C.L., Richardson, H.N., 2008. Stress experienced in utero reduces sexual dichotomies in neurogenesis, microenvironment, and cell death in the adult rat hippocampus. *Dev. Neurobiol.* 68, 575–589.
- Mareckova, K., Holsen, L.M., Admon, R., Makris, N., Seidman, L., Buka, S., Whitfield-Gabrieli, S., Goldstein, J.M., 2016. Brain activity and connectivity in response to negative affective stimuli: impact of dysphoric mood and sex across diagnoses. *Hum. Brain Mapp.* 37 (11), 3733–3744.
- Mareckova, K., Holsen, L., Admon, R., Whitfield-Gabrieli, S., Seidman, L.J., Buka, S.L., Klibanski, A., Goldstein, J.M., 2017. Neural - hormonal responses to negative affective stimuli: impact of dysphoric mood and sex. *J. Affect. Disord.* 222, 88–97.
- Marinari, K.T., Leshner, A.I., Doyle, M.P., 1976. Menstrual cycle status and adrenocortical reactivity to psychological stress. *Psychoneuroendocrinology* 1, 213–218.
- Markham, J.A., McKian, K.P., Stroup, T.S., Juraska, J.M., 2005. Sexually dimorphic aging of dendritic morphology in CA1 of hippocampus. *Hippocampus* 15, 97–103.
- Markowska, A.L., 1999. Sex dimorphisms in the rate of age-related decline in spatial memory: relevance to alterations in the estrous cycle. *J. Neurosci.: Off. J. Soc. Neurosci.* 19, 8122–8133.
- Mazzucco, C.A., Lieblich, S.E., Bingham, B.I., Williamson, M.A., Viau, V., Galea, L.A., 2006. Both estrogen receptor alpha and estrogen receptor beta agonists enhance cell proliferation in the dentate gyrus of adult female rats. *Neuroscience* 141, 1793–1800.
- McClure, R.E., Barha, C.K., Galea, L.A., 2013. 17 β -Estradiol, but not estrone, increases the survival and activation of new neurons in the hippocampus in response to spatial memory in adult female rats. *Horm. Behav.* 63, 144–157.
- McCormick, C.M., Nixon, F., Thomas, C., Lowie, B., Dyck, J., 2010. Hippocampal cell proliferation and spatial memory performance after social instability stress in adolescence in female rats. *Behav. Brain Res.* 208, 23–29.
- McCormick, C.M., Thomas, C.M., Sheridan, C.S., Nixon, F., Flynn, J.A., Mathews, I.Z., 2012. Social instability stress in adolescent male rats alters hippocampal neurogenesis and produces deficits in spatial location memory in adulthood. *Hippocampus* 22, 1300–1312.
- McEwen, B.S., Woolley, C.S., 1994. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. *Exp. Gerontol.* 29, 431–436.
- McHugh, T.L., Saykin, A.J., Wishart, H.A., Flashman, L.A., Cleavinger, H.B., Rabin, L.A., Mamourian, A.C., Shen, L., 2007. Hippocampal volume and shape analysis in an older adult population. *Clin. Neuropsychol.* 21, 130–145.
- McIntyre, R.S., Mancini, D., Einfeld, B.S., Soczynska, J.K., Grupp, L., Konarski, J.Z., Kennedy, S.H., 2006. Calculated bioavailable testosterone levels and depression in middle-aged men. *Psychoneuroendocrinology* 31, 1029–1035.
- McKinnon, M.C., Yucel, K., Nazarov, A., MacQueen, G.M., 2009. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J. Psychiatry Neurosci.* 34, 41–54.
- McKittrick, C.R., Magarinos, A.M., Blanchard, D.C., Blanchard, R.J., McEwen, B.S., Sakai, R.R., 2000. Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites. *Synapse* 36, 85–94.
- McLean, C.P., Asnaani, A., Litz, B.T., Hofmann, S.G., 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *J. Psychiatr. Res.* 45, 1027–1035.
- Merz, C.J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., Wolf, O.T., 2010. Investigating the impact of sex and cortisol on implicit fear conditioning with fMRI. *Psychoneuroendocrinology* 35, 33–46.
- Merz, C.J., Wolf, O.T., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., 2013. Stress differentially affects fear conditioning in men and women. *Psychoneuroendocrinology* 38, 2529–2541.
- Merz, C.J., Hamacher-Dang, T.C., Stark, R., Wolf, O.T., Hermann, A., 2018. Neural underpinnings of cortisol effects on fear extinction. *Neuropsychopharmacology* 43, 384–392.
- Merz, C.J., Wolf, O.T., 2017. Sex differences in stress effects on emotional learning. *J. Neurosci. Res.* 95, 93–105.
- Meyer, C.E., Kurth, F., Lepore, S., Gao, J.L., Johnsonbaugh, H., Oberoi, M.R., Sawiak, S.J., MacKenzie-Graham, A., 2017. In vivo magnetic resonance images reveal neuroanatomical sex differences through the application of voxel-based morphometry in C57BL/6 mice. *Neuroimage* 163, 197–205.
- Milad, M.R., Igwe, A.S., Lebron-Milad, K., Novales, J.E., 2009. Estrous cycle phase and gonadal hormones influence conditioned fear extinction. *Neuroscience* 164, 887–895.
- Miller, K.K., Perlis, R.H., Papakostas, G.I., Mischoulon, D., Losifescu, D.V., Brick, D.J., Fava, M., 2009. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. *CNS Spectr.* 14, 688–694.
- Milne, A.M., MacQueen, G.M., Hall, G.B., 2012. Abnormal hippocampal activation in patients with extensive history of major depression: an fMRI study. *J. Psychiatry Neurosci.* 37, 28–36.
- Mirescu, C., Peters, J.D., Gould, E., 2004. Early life experience alters response of adult neurogenesis to stress. *Nat. Neurosci.* 7, 841–846.
- Moffat, S.D., Resnick, S.M., 2007. Long-term measures of free testosterone predict regional cerebral blood flow patterns in elderly men. *Neurobiol. Aging* 28, 914–920.
- Moffat, S.D., Zonderman, A.B., Metter, E.J., Kawas, C., Blackman, M.R., Harman, S.M., Resnick, S.M., 2004. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 62, 188–193.
- Montero-Lopez, E., Santos-Ruiz, A., Garcia-Rios, M.C., Rodriguez-Blazquez, M., Rogers, H.L., Peralta-Ramirez, M.I., 2018. The relationship between the menstrual cycle and cortisol secretion: daily and stress-invoked cortisol patterns. *Int. J. Psychophysiol.* 131, 67–72.
- Moon, C.M., Kim, G.W., Jeong, G.W., 2014. Whole-brain gray matter volume abnormalities in patients with generalized anxiety disorder: voxel-based morphometry. *NeuroReport* 25, 184–189.
- Morris, R.G., Garrud, P., Rawlins, J.N., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* 297, 681–683.
- Moses-Kolko, E.L., Berga, S.L., Kalro, B., Sit, D.K., Wisner, K.L., 2009. Transdermal estradiol for postpartum depression: a promising treatment option. *Clin. Obstet. Gynecol.* 52, 516–529.
- Mueller, S.C., 2013. Magnetic resonance imaging in paediatric psychoneuroendocrinology: a new frontier for understanding the impact of hormones on emotion and cognition. *J. Neuroendocrinol.* 25, 762–770.
- Mueller, S.C., Mandell, D., Leschek, E.W., Pine, D.S., Merke, D.P., Ernst, M., 2009. Early hyperandrogenism affects the development of hippocampal function: preliminary evidence from a functional magnetic resonance imaging study of boys with familial male precocious puberty. *J. Child Adolesc. Psychopharmacol.* 19, 41–50.

- Mukai, H., Tsurugizawa, T., Murakami, G., Kominami, S., Ishii, H., Ogiue-Ikeda, M., Takata, N., Tanabe, N., Furukawa, A., Hojo, Y., Ooishi, Y., Morrison, J.H., Janssen, W.G., Rose, J.A., Chambon, P., Kato, S., Izumi, S., Yamazaki, T., Kimoto, T., Kawato, S., 2007. Rapid modulation of long-term depression and spinogenesis via synaptic estrogen receptors in hippocampal principal neurons. *J. Neurochem.* 100, 950–967.
- Murphy, D.G., DeCarli, C., McIntosh, A.R., Daly, E., Mentis, M.J., Pietrini, P., Szczepanik, J., Schapiro, M.B., Grady, C.L., Horwitz, B., Rapoport, S.I., 1996. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Arch. Gen. Psychiatry* 53, 585–594.
- Murray, F., Smith, D.W., Hutson, P.H., 2008. Chronic low dose corticosterone exposure decreased hippocampal cell proliferation, volume and induced anxiety and depression like behaviours in mice. *Eur. J. Pharmacol.* 583, 115–127.
- Naghdi, N., Nafisy, N., Majlessi, N., 2001. The effects of intrahippocampal testosterone and flutamide on spatial localization in the Morris water maze. *Brain Res.* 897, 44–51.
- Nagy, A.J., Ormerod, B.K., Mazzucco, C.A., Galea, L.A., 2006. Estradiol-induced enhancement in cell proliferation is mediated through estrogen receptors in the dentate gyrus of adult female rats. *Drug Develop. Res.* 66, 142–149.
- Nakajima, M., Allen, S., Al'Absi, M., 2019. Influences of the Menstrual phase on cortisol response to stress in nicotine dependent women: a preliminary examination. *Nicotine Tob. Res.* 21, 617–622.
- Naninck, E.F., Hoeijmakers, L., Kakava-Georgiadou, N., Meesters, A., Lazic, S.E., Lucassen, P.J., Korosi, A., 2014. Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus* 25, 309–328.
- Naninck, E.F., Hoeijmakers, L., Kakava-Georgiadou, N., Meesters, A., Lazic, S.E., Lucassen, P.J., Korosi, A., 2015. Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus* 25, 309–328.
- Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G.R., Konrad, K., 2009. Sex differences and the impact of steroid hormones on the developing human brain. *Cereb. Cortex* 19, 464–473.
- Nguyen, T.V., Lew, J., Albaugh, M.D., Botteron, K.N., Hudziak, J.J., Fonov, V.S., Collins, D.L., Ducharme, S., McCracken, J.T., 2017. Sex-specific associations of testosterone with prefrontal-hippocampal development and executive function. *Psychoneuroendocrinology* 76, 206–217.
- Nini, M., Hongna, Z., Zhiying, L., Li, Y., Xia, W., 2017. Gender differences in dynamic functional connectivity based on resting-state fMRI. In: *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2017, pp. 2940–2943.
- Noack, H., Nolte, L., Nieratschker, V., Habel, U., Derntl, B., 2019. Imaging stress: an overview of stress induction methods in the MR scanner. *J. Neural Transm. (Vienna)*.
- Nordin, K., Herlitz, A., Larsson, E.M., Soderlund, H., 2017. Overlapping effects of age on associative memory and the anterior hippocampus from middle to older age. *Behav. Brain Res.* 317, 350–359.
- Nowakowski, R.S., Hayes, N.L., Galea, L.A., 2008. Numerology of Neurogenesis: Characterizing the Cell Type of Neurostem Cells. Cold Spring Harbour Laboratory Press, Cold Spring Harbour.
- Oberg, C., Larsson, M., Backman, L., 2002. Differential sex effects in olfactory functioning: the role of verbal processing. *J. Int. Neuropsychol. Soc.* 8, 691–698.
- Oberlander, J.G., Woolley, C.S., 2016. 17beta-Estradiol acutely potentiates glutamatergic synaptic transmission in the hippocampus through distinct mechanisms in males and females. *J. Neurosci.* 36, 2677–2690.
- Oei, N.Y., Elzinga, B.M., Wolf, O.T., de Ruiter, M.B., Damoiseaux, J.S., Kuijter, J.P., Veltman, D.J., Scheltens, P., Rombouts, S.A., 2007. Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. *Brain Imaging Behav.* 1, 31–41.
- Ohnishi, T., Matsuda, H., Hirakata, M., Ugawa, Y., 2006. Navigation ability dependent neural activation in the human brain: an fMRI study. *Neurosci. Res.* 55, 361–369.
- Olderbak, S., Wilhelm, O., Hildebrandt, A., Quoidbach, J., 2019. Sex differences in facial emotion perception ability across the lifespan. *Cogn. Emot.* 33, 579–588.
- Olf, M., 2017. Sex and gender differences in post-traumatic stress disorder: an update. *Eur. J. Psychotraumatol.* 8.
- Ooishi, Y., Kawato, S., Hojo, Y., Hatanaka, Y., Higo, S., Murakami, G., Komatsuzaki, Y., Ogiue-Ikeda, M., Kimoto, T., Mukai, H., 2012. Modulation of synaptic plasticity in the hippocampus by hippocampus-derived estrogen and androgen. *J. Steroid Biochem. Mol. Biol.* 131, 37–51.
- Oomen, C.A., Girardi, C.E., Cahyadi, R., Verbeek, E.C., Krugers, H., Joels, M., Lucassen, P.J., 2009. Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS ONE* 4, e3675.
- Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F.N., Manders, E.M., Joels, M., Lucassen, P.J., Krugers, H., 2010. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J. Neurosci.* 30, 6635–6645.
- Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F.N., Manders, E.M., Joels, M., Krugers, H., Lucassen, P.J., 2011. Early maternal deprivation affects dentate gyrus structure and emotional learning in adult female rats. *Psychopharmacology* 214, 249–260.
- Opel, N., Redlich, R., Zwanzger, P., Grotteger, D., Arolt, V., Heindel, W., Konrad, C., Kugel, H., Dannlowski, U., 2014. Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? *Neuropsychopharmacology* 39, 2723–2731.
- Oreland, S., Nylander, I., Pickering, C., 2010. Prolonged maternal separation decreases granule cell number in the dentate gyrus of 3-week-old male rats. *Int. J. Dev. Neurosci.* 28, 139–144.
- Ormerod, B.K., Galea, L.A., 2001. Reproductive status influences cell proliferation and cell survival in the dentate gyrus of adult female meadow voles: a possible regulatory role for estradiol. *Neuroscience* 102, 369–379.
- Ormerod, B.K., Galea, L.A., 2003. Reproductive status influences the survival of new cells in the dentate gyrus of adult male meadow voles. *Neurosci. Lett.* 346, 25–28.
- Ormerod, B.K., Lee, T.T., Galea, L.A., 2003. Estradiol initially enhances but subsequently suppresses (via adrenal steroids) granule cell proliferation in the dentate gyrus of adult female rats. *J. Neurobiol.* 55, 247–260.
- Ormerod, B.K., Lee, T.T., Galea, L.A., 2004. Estradiol enhances neurogenesis in the dentate gyri of adult male meadow voles by increasing the survival of young granule neurons. *Neuroscience* 128, 645–654.
- Orsini, C.A., Moorman, D.E., Young, J.W., Setlow, B., Floresco, S.B., 2015. Neural mechanisms regulating different forms of risk-related decision-making: Insights from animal models. *Neurosci. Biobehav. Rev.* 58, 147–167.
- Palanza, P., 2001. Animal models of anxiety and depression: how are females different? *Neurosci. Biobehav. Rev.* 25, 219–233.
- Panizzon, M.S., Hauger, R.L., Eaves, L.J., Chen, C.H., Dale, A.M., Eyler, L.T., Fischl, B., Fennema-Notestine, C., Franz, C.E., Grant, M.D., Jacobson, K.C., Jak, A.J., Lyons, M.J., Mendoza, S.P., Neale, M.C., Prom-Wormley, E., Seidman, L.J., Tsuang, M.T., Xian, H., Kremen, W.S., 2012. Genetic influences on hippocampal volume differ as a function of testosterone level in middle-aged men. *Neuroimage* 59, 1123–1131.
- Pawluski, J.L., Brummelte, S., Barha, C.K., Crozier, T.M., Galea, L.A., 2009. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. *Front. Neuroendocrinol.* 30, 343–357.
- Pegues, M.P., Rogers, L.J., Amend, D., Vinogradov, S., Deicken, R.F., 2003. Anterior hippocampal volume reduction in male patients with schizophrenia. *Schizophr. Res.* 60, 105–115.
- Perani, C.V., Slattery, D.A., 2014. Using animal models to study post-partum psychiatric disorders. *Br. J. Pharmacol.* 171, 4539–4555.
- Perez-Martin, M., Azcoitia, I., Trejo, J.L., Sierra, A., Garcia-Segura, L.M., 2003. An antagonist of estrogen receptors blocks the induction of adult neurogenesis by insulin-like growth factor-I in the dentate gyrus of adult female rat. *Eur. J. Neurosci.* 18, 923–930.
- Perez-Martin, M., Salazar, V., Castillo, C., Ariznavarreta, C., Azcoitia, I., Garcia-Segura, L.M., Tresguerras, J.A., 2005. Estradiol and soy extract increase the production of new cells in the dentate gyrus of old rats. *Exp. Gerontol.* 40, 450–453.
- Perl, D.P., 2010. Neuropathology of Alzheimer's disease. *The Mount Sinai J. Med., New York* 77, 32–42.
- Perlaki, G., Orsi, G., Plozer, E., Altbacker, A., Darnai, G., Nagy, S.A., Horvath, R., Toth, A., Doczi, T., Kovacs, N., Bogner, P., Schwarcz, J., Janszky, J., 2014. Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study. *Neurosci. Lett.* 570, 119–123.
- Perrot-Sinal, T.S., Kostenuik, M.A., Ossenkopp, K.P., Kavaliers, M., 1996. Sex differences in performance in the Morris water maze and the effects of initial nonstationary hidden platform training. *Behav. Neurosci.* 110, 1309–1320.
- Persson, J., Herlitz, A., Engman, J., Morell, A., Sjolie, D., Wikstrom, J., Soderlund, H., 2013. Remembering our origin: gender differences in spatial memory are reflected in gender differences in hippocampal lateralization. *Behav. Brain Res.* 256, 219–228.
- Persson, J., Spreng, R.N., Turner, G., Herlitz, A., Morell, A., Stening, E., Wahlund, L.O., Wikstrom, J., Soderlund, H., 2014. Sex differences in volume and structural covariance of the anterior and posterior hippocampus. *Neuroimage* 99, 215–225.
- Pham, K., Nacher, J., Hof, P.R., McEwen, B.S., 2003. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur. J. Neurosci.* 17, 879–886.
- Phan, A., Lancaster, K.E., Armstrong, J.N., MacLusky, N.J., Choleris, E., 2011. Rapid effects of estrogen receptor alpha and beta selective agonists on learning and dendritic spines in female mice. *Endocrinology* 152, 1492–1502.
- Phan, A., Gabor, C.S., Favaro, K.J., Kaschack, S., Armstrong, J.N., MacLusky, N.J., Choleris, E., 2012. Low doses of 17beta-estradiol rapidly improve learning and increase hippocampal dendritic spines. *Neuropsychopharmacology* 37, 2299–2309.
- Phan, A., Suschkov, S., Molinaro, L., Reynolds, K., Lymer, J.M., Bailey, C.D., Kow, L.M., MacLusky, N.J., Pfaff, D.W., Choleris, E., 2015. Rapid increases in immature synapses parallel estrogen-induced hippocampal learning enhancements. *Proc. Natl. Acad. Sci. U S A* 112, 16018–16023.
- Pibiri, F., Nelson, M., Guidotti, A., Costa, E., Pinna, G., 2008. Decreased corticolimbic allopregnanolone expression during social isolation enhances contextual fear: a model relevant for posttraumatic stress disorder. *Proc. Natl. Acad. Sci. U S A* 105, 5567–5572.
- Pillemer, D.B., Wink, P., DiDonato, T.E., Sanborn, R.L., 2003. Gender differences in autobiographical memory styles of older adults. *Memory* 11, 525–532.
- Pintzka, C.W., Evensmoen, H.R., Lehn, H., Haberg, A.K., 2016. Changes in spatial cognition and brain activity after a single dose of testosterone in healthy women. *Behav. Brain Res.* 298, 78–90.
- Pintzka, C.W., Haberg, A.K., 2015. Perimenopausal hormone therapy is associated with regional sparing of the CA1 subfield: a HUNT MRI study. *Neurobiol. Aging* 36, 2555–2562.
- Pletzer, B., 2014. Sex-specific strategy use and global-local processing: a perspective toward integrating sex differences in cognition. *Front. Neurosci.* 8, 425.
- Pletzer, B., 2019. Sex hormones and gender role relate to grey matter volumes in sexually dimorphic brain areas. *Front. Neurosci.*
- Pletzer, B., Kronbichler, M., Aichhorn, M., Bergmann, J., Ladurner, G., Kerschbaum, H., 2010. Menstrual cycle and hormonal contraceptive use modulate human brain structure. *Brain Res.* 1348, 55–62.
- Pletzer, B., Kronbichler, M., Kerschbaum, H., 2015. Differential effects of androgenic and anti-androgenic progestins on fusiform and frontal gray matter volume and face

- recognition performance. *Brain Res.* 1596, 108–115.
- Pletzer, B., Harris, T., Hidalgo-Lopez, E., 2018. Subcortical structural changes along the menstrual cycle: beyond the hippocampus. *Sci. Rep.* 8.
- Pletzer, B., Harris, T.A., Scheuringer, A., Hidalgo-Lopez, E., 2019. The cycling brain: menstrual cycle related fluctuations in hippocampal and fronto-striatal activation and connectivity during cognitive tasks. *Neuropsychopharmacology*.
- Pletzer, B., Harris, T., Hidalgo-Lopez, E., 2019. Previous contraceptive treatment relates to grey matter volumes in the hippocampus and basal ganglia. *Sci. Rep.* 9, 11003.
- Powers, S.I., Laurent, H.K., Gunlicks-Stoessel, M., Balaban, S., Bent, E., 2016. Depression and anxiety predict sex-specific cortisol responses to interpersonal stress. *Psychoneuroendocrinology* 69, 172–179.
- Protopopescu, X., Butler, T., Pan, H., Root, J., Altemus, M., Polancovsky, M., McEwen, B., Silbersweig, D., Stern, E., 2008. Hippocampal structural changes across the menstrual cycle. *Hippocampus* 18, 985–988.
- Pruessner, J.C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., Dagher, A., Meaney, M.J., Lupien, S., 2008. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol. Psychiatry* 63, 234–240.
- Pruessner, J.C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., Lupien, S.J., 2008. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations -2008 Curt Richter Award Winner. *Psychoneuroendocrinology* 35 (2010), 179–191.
- Pruessner, M., Pruessner, J.C., Hellhammer, D.H., Bruce Pike, G., Lupien, S.J., 2007. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. *Psychiatry Res.* 155, 1–10.
- Pruessner, M., Lepage, M., Collins, D.L., Pruessner, J.C., Joobar, R., Malla, A.K., 2015. Reduced hippocampal volume and hypothalamus-pituitary-adrenal axis function in first episode psychosis: evidence for sex differences. *Neuroimage Clin.* 7, 195–202.
- Pulopulos, M.M., Hidalgo, V., Puig-Perez, S., Salvador, A., 2018. Psychophysiological response to social stressors: relevance of sex and age. *Psicothema* 30, 171–176.
- Quas, J.A., Castro, A., Bryce, C.I., Granger, D.A., 2018. Stress physiology and memory for emotional information: moderation by individual differences in pubertal hormones. *Dev. Psychol.* 54, 1606–1620.
- Rayen, I., Gemmel, M., Pauley, G., Steinbusch, H.W., Pawlusi, J.L., 2015. Developmental exposure to SSRIs, in addition to maternal stress, has long-term sex-dependent effects on hippocampal plasticity. *Psychopharmacology* 232, 1231–1244.
- Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K.M., Williamson, A., Acker, J.D., 2004. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol. Aging* 25, 377–396.
- Redlich, R., Almeida, J.J., Grotegerd, D., Opel, N., Kugel, H., Heindel, W., Arolt, V., Phillips, M.L., Dannlowski, U., 2014. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. *JAMA Psychiatry* 71, 1222–1230.
- Reschke-Hernandez, A.E., Okerstrom, K.L., Bowles Edwards, A., Tranel, D., 2017. Sex and stress: Men and women show different cortisol responses to psychological stress induced by the Trier social stress test and the Iowa singing social stress test. *J. Neurosci. Res.* 95, 106–114.
- Resnick, S.M., Espeland, M.A., Jaramillo, S.A., Hirsch, C., Stefanick, M.L., Murray, A.M., Ockene, J., Davatzikos, C., 2009. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI study. *Neurology* 72, 135–142.
- Revest, J.M., Dupret, D., Koehl, M., Funk-Reiter, C., Grosjean, N., Piazza, P.V., Abrous, D.N., 2009. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. *Mol. Psychiatry* 14, 959–967.
- Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., Hancock, G.R., 2018. Protracted hippocampal development is associated with age-related improvements in memory during early childhood. *Neuroimage* 174, 127–137.
- Roberts, A.D., Wessely, S., Chalder, T., Papadopoulos, A., Cleare, A.J., 2004. Salivary cortisol response to awakening in chronic fatigue syndrome. *Br. J. Psychiatry* 184, 136–141.
- Roca, C.A., Schmidt, P.J., Altemus, M., Deuster, P., Danaceau, M.A., Putnam, K., Rubinow, D.R., 2003. Differential menstrual cycle regulation of hypothalamic-pituitary-adrenal axis in women with premenstrual syndrome and controls. *J. Clin. Endocrinol. Metab.* 88, 3057–3063.
- Romeo, R.D., Lee, S.J., McEwen, B.S., 2004. Differential stress reactivity in intact and ovariectomized prepubertal and adult female rats. *Neuroendocrinology* 80, 387–393.
- Romer, B., Pfeiffer, N., Lewicka, S., Ben-Abdallah, N., Vogt, M.A., Deuschle, M., Vollmayr, B., Gass, P., 2010. Finasteride treatment inhibits adult hippocampal neurogenesis in male mice. *Pharmacopsychiatry* 43, 174–178.
- Rosario, E.R., Chang, L., Head, E.H., Stanczyk, F.Z., Pike, C.J., 2011. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol. Aging* 32, 604–613.
- Ruigrok, A.N., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. *Neurosci. Biobehav. Rev.* 39, 34–50.
- Rummel, J., Epp, J.R., Galea, L.A., 2010. Estradiol does not influence strategy choice but place strategy choice is associated with increased cell proliferation in the hippocampus of female rats. *Horm. Behav.* 58, 582–590.
- Rutkowski, J.M., Wallace, B.K., Wise, P.M., O'Donnell, M.E., 2011. Effects of estradiol on ischemic factor-induced astrocyte swelling and AQP4 protein abundance. *Am. J. Physiol. Cell Physiol.* 301, C204–C212.
- Sah, A., Schmuckermair, C., Sartori, S.B., Gaburro, S., Kandasamy, M., Irschick, R., Klimaschewski, L., Landgraf, R., Aigner, L., Singewald, N., 2012. Anxiety- rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. *Transl. Psychiatry* 2, e171.
- Sahay, A., Scobie, K.N., Hill, A.S., O'Carroll, C.M., Kheirbek, M.A., Burghardt, N.S., Fenton, A.A., Dranovsky, A., Hen, R., 2011. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472, 466–470.
- Samplin, E., Ikuta, T., Malhotra, A.K., Szeszko, P.R., Derosse, P., 2013. Sex differences in resilience to childhood maltreatment: effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. *J. Psychiatr. Res.* 47, 1174–1179.
- Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805–809.
- Sapolsky, R.M., Meaney, M.J., 1986. Maturation of the adrenocortical stress response: neuroendocrine control mechanisms and the stress hyporesponsive period. *Brain Res.* 396, 64–76.
- Saravia, F., Beauquis, J., Pietranera, L., De Nicola, A.F., 2007. Neuroprotective effects of estradiol in hippocampal neurons and glia of middle age mice. *Psychoneuroendocrinology* 32, 480–492.
- Satterthwaite, T.D., Vandekar, S., Wolf, D.H., Ruparel, K., Roalf, D.R., Jackson, C., Elliott, M.A., Bilker, W.B., Calkins, M.E., Prabhakaran, K., Davatzikos, C., Hakonarson, H., Gur, R.E., Gur, R.C., 2014. Sex differences in the effect of puberty on hippocampal morphology. *J. Am. Acad. Child Adolesc. Psychiatry* 53 341–50e1.
- Saucier, D.M., Green, S.M., Leason, J., MacFadden, A., Bell, S., Elias, L.J., 2002. Are sex differences in navigation caused by sexually dimorphic strategies or by differences in the ability to use the strategies? *Behav. Neurosci.* 116, 403–410.
- Scharfman, H.E., MacLusky, N.J., 2017. Sex differences in hippocampal area CA3 pyramidal cells. *J. Neurosci. Res.* 95, 563–575.
- Scharfman, H.E., Myers, C.E., 2016. Corruption of the dentate gyrus by “dominant” granule cells: Implications for dentate gyrus function in health and disease. *Neurobiol. Learn. Mem.* 129, 69–82.
- Scheff, S.W., Price, D.A., Schmitt, F.A., Mufson, E.J., 2006. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* 27, 1372–1384.
- Schlott, W., Hellhammer, J., Schulz, P., Stone, A.A., 2004. Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response. *Psychosom. Med.* 66, 207–214.
- Schmaal, L., Yucel, M., Ellis, R., Vijayakumar, N., Simmons, J.G., Allen, N.B., Whittle, S., 2017. Brain structural signatures of adolescent depressive symptom trajectories: a longitudinal magnetic resonance imaging study. *J. Am. Acad. Child Adolesc. Psychiatry* 56 593–601 e9.
- Schoning, S., Engelen, A., Kugel, H., Schafer, S., Schiffbauer, H., Zwitserlood, P., Pletzer, E., Beizai, P., Kersting, A., Ohrmann, P., Greb, R.R., Lehmann, W., Heindel, W., Arolt, V., Konrad, C., 2007. Functional anatomy of visuo-spatial working memory during mental rotation is influenced by sex, menstrual cycle, and sex steroid hormones. *Neuropsychologia* 45, 3203–3214.
- Schuck, R.K., Flores, R.E., Fung, L.K., 2019. Brief report: sex/gender differences in symptomatology and camouflaging in adults with autism spectrum disorder. *J. Autism Dev. Disord.* 49, 2597–2604.
- Schuhmacher, A., Mossner, R., Jessen, F., Scheef, L., Block, W., Belloche, A.C., Lennertz, L., Welper, H., Hofels, S., Pfeiffer, U., Wagner, M., Maier, W., Schwab, S., Zobel, A., 2012. Association of amygdala volumes with cortisol secretion in unipolar depressed patients. *Psychiatry Res.* 202, 96–103.
- Schwabe, L., Tegenthoff, M., Hoffken, O., Wolf, O.T., 2013. Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. *Biol. Psychiatry* 74, 801–808.
- Schwabe, L., Wolf, O.T., 2012. Stress modulates the engagement of multiple memory systems in classification learning. *J. Neurosci.* 32, 11042–11049.
- Sebastian, V., Estil, J.B., Chen, D., Schrott, L.M., Serrano, P.A., 2013. Acute physiological stress promotes clustering of synaptic markers and alters spine morphology in the hippocampus. *PLoS ONE* 8, e79077.
- Seeman, M.V., 1997. Psychopathology in women and men: focus on female hormones. *Am. J. Psychiatry* 154, 1641–1647.
- Seeman, T.E., McEwen, B.S., Singer, B.H., Albert, M.S., Rowe, J.W., 1997. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *J. Clin. Endocrinol. Metab.* 82, 2458–2465.
- Seiger, R., Hahn, A., Hummer, A., Kranz, G.S., Ganger, S., Woletz, M., Kraus, C., Sladky, R., Kautzky, A., Kasper, S., Windischberger, C., Lanzenberger, R., 2016. Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration. *Psychoneuroendocrinology* 74, 371–379.
- Seo, D., Jia, Z., Lacadie, C.M., Tsou, K.A., Bergquist, K., Sinha, R., 2011. Sex differences in neural responses to stress and alcohol context cues. *Hum. Brain Mapp.* 32, 1998–2013.
- Seo, D., Rabinowitz, A.G., Douglas, R.J., Sinha, R., 2019. Limbic response to stress linking life trauma and hypothalamus-pituitary-adrenal axis function. *Psychoneuroendocrinology* 99, 38–46.
- Shafir, T., Love, T., Berent-Spillon, A., Persad, C.C., Wang, H., Reame, N.K., Frey, K.A., Zubieta, J.K., Smith, Y.R., 2012. Postmenopausal hormone use impact on emotion processing circuitry. *Behav. Brain Res.* 226, 147–153.
- Sheline, Y.I., Sanghavi, M., Mintun, M.A., Gado, M.H., 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* 19, 5034–5043.
- Sheppard, P.A.S., Choleris, E., Galea, L.A.M., 2019. Structural plasticity of the hippocampus in response to estrogens in female rodents. *Mol. Brain* 12, 22.
- Sheridan, M.A., How, J., Araujo, M., Schamberg, M.A., Nelson, C.A., 2013. What are the links between maternal social status, hippocampal function, and HPA axis function in children? *Dev Sci* 16, 665–675.
- Shima, N., Yamaguchi, Y., Yuri, K., 2003. Distribution of estrogen receptor beta mRNA-containing cells in ovariectomized and estrogen-treated female rat brain. *Anat. Sci.*

- Int. 78, 85–97.
- Shin, N.Y., Bak, Y., Nah, Y., Han, S., Kim, D.J., Kim, S.J., Lee, J.E., Lee, S.G., Lee, S.K., 2018. Author correction: disturbed retrieval network and prospective memory decline in postpartum women. *Sci. Rep.* 8, 14437.
- Shin, N.Y., Bak, Y., Nah, Y., Han, S., Kim, D.J., Kim, S.J., Lee, J.E., Lee, S.G., Lee, S.K., 2018. Disturbed retrieval network and prospective memory decline in postpartum women. *Sci. Rep.* 8, 5476.
- Shinohara, Y., Hirase, H., Watanabe, M., Itakura, M., Takahashi, M., Shigemoto, R., 2008. Left-right asymmetry of the hippocampal synapses with differential subunit allocation of glutamate receptors. *Proc. Natl. Acad. Sci. U S A* 105, 19498–19503.
- Shores, M.M., Sloan, K.L., Matsumoto, A.M., Mocerri, V.M., Felker, B., Kivlahan, D.R., 2004. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch. Gen. Psychiatry* 61, 162–167.
- Shores, M.M., Mocerri, V.M., Sloan, K.L., Matsumoto, A.M., Kivlahan, D.R., 2005. Low testosterone levels predict incident depressive illness in older men: effects of age and medical morbidity. *J. Clin. Psychiatry* 66, 7–14.
- Shores, M.M., Kivlahan, D.R., Sadak, T.I., Li, E.J., Matsumoto, A.M., 2009. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J. Clin. Psychiatry* 70, 1009–1016.
- Shors, T.J., Chua, C., Falduto, J., 2001. Sex differences and opposite effects of stress on dendritic spine density in the male versus female hippocampus. *J. Neurosci.* 21, 6292–6297.
- Shors, T.J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., Gould, E., 2001. Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410, 372–376.
- Shors, T.J., Mathew, J., Sisti, H.M., Edgcomb, C., Beckoff, S., Dalla, C., 2007. Neurogenesis and helplessness are mediated by controllability in males but not in females. *Biol. Psychiatry* 62, 487–495.
- Shughrue, P.J., Lane, M.V., Merchenthaler, I., 1997. Comparative distribution of estrogen receptor- α and - β mRNA in the rat central nervous system. *J. Comp. Neurol.* 388, 507–525.
- Siddiqui, A., Romeo, R.D., 2019. Sex differences and similarities in hippocampal cellular proliferation and the number of immature neurons during adolescence in rats. *Dev. Neurosci.* 41, 132–138.
- Silva-Gomez, A.B., Aguilar-Salgado, Y., Reyes-Hernandez, D.O., Flores, G., 2013. Dexamethasone induces different morphological changes in the dorsal and ventral hippocampus of rats. *J. Chem. Neuroanat.* 47, 71–78.
- Silverman, I.L., Choi, J., Mackewn, A., Fisher, M., Moro, J., Olshansky, E., 2000. Evolved mechanisms underlying wayfinding. Further studies on the hunter-gatherer theory of spatial sex differences. *Evol. Hum. Behav.* 21, 201–213.
- Sivakumar, P.T., Kalmady, S.V., Venkatasubramanian, G., Bharath, S., Reddy, N.N., Rao, N.P., Kovoor, J.M., Jain, S., Varghese, M., 2015. Volumetric analysis of hippocampal sub-regions in late onset depression: a 3 tesla magnetic resonance imaging study. *Asian J. Psychiatry* 13, 38–43.
- Skakkebaek, A., Gravholt, C.H., Rasmussen, P.M., Bojesen, A., Jensen, J.S., Fedder, J., Laurberg, P., Hertz, J.M., Ostergaard, J.R., Pedersen, A.D., Wallentin, M., 2014. Neuroanatomical correlates of Klinefelter syndrome studied in relation to the neuropsychological profile. *Neuroimage Clin.* 4, 1–9.
- Slavich, G.M., Sacher, J., 2019. Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. *Psychopharmacology*.
- Smith, C.C., McMahon, L.L., 2006. Estradiol-induced increase in the magnitude of long-term potentiation is prevented by blocking NR2B-containing receptors. *J. Neurosci.: Off. J. Soc. Neurosci.* 26, 8517–8522.
- Sneider, J.T., Sava, S., Rogowska, J., Yurgelun-Todd, D.A., 2011. A preliminary study of sex differences in brain activation during a spatial navigation task in healthy adults. *Percept. Mot. Skills* 113, 461–480.
- Sneider, J.T., Cohen-Gilbert, J.E., Hamilton, D.A., Stein, E.R., Golan, N., Oot, E.N., Seraika, A.M., Rohan, M.L., Harris, S.K., Nickerson, L.D., Silveri, M.M., 2018. Adolescent hippocampal and prefrontal brain activation during performance of the virtual morris water task. *Front. Hum. Neurosci.* 12, 238.
- Soleman, R.S., Schagen, S.E., Veltman, D.J., Kreukels, B.P., Cohen-Kettenis, P.T., Lambalk, C.B., Wouters, F., Delemarre-van de Waal, H.A., 2013. Sex differences in verbal fluency during adolescence: a functional magnetic resonance imaging study in gender dysphoric and control boys and girls. *J. Sex Med.* 10, 1969–1977.
- Sousa, N., Lukyanov, N.V., Madeira, M.D., Almeida, O.F., Paula-Barbosa, M.M., 2000. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience* 97, 253–266.
- Sovijit, W.N., Sovijit, W.E., Pu, S., Usuda, K., Inoue, R., Watanabe, G., Yamaguchi, H., Nagaoka, K., 2019. Ovarian progesterone suppresses depression and anxiety-like behaviors by increasing the Lactobacillus population of gut microbiota in ovariectomized mice. *Neurosci. Res.*
- Spalletta, G., Piras, F., Caltagirone, C., Fagioli, S., 2014. Hippocampal multimodal structural changes and subclinical depression in healthy individuals. *J. Affect. Disord.* 152–154, 105–112.
- Spritzer, M.D., Galea, L.A., 2007. Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. *Dev. Neurobiol.* 67, 1321–1333.
- Spritzer, M.D., Gill, M., Weinberg, A., Galea, L.A., 2008. Castration differentially affects spatial working and reference memory in male rats. *Arch. Sex. Behav.* 37, 19–29.
- Spritzer, M.D., Ibler, E., Inglis, W., Curtis, M.G., 2011. Testosterone and social isolation influence adult neurogenesis in the dentate gyrus of male rats. *Neuroscience* 195, 180–190.
- Starkman, M.N., Giordani, B., Gebarski, S.S., Schteingart, D.E., 2003. Improvement in learning associated with increase in hippocampal formation volume. *Biol. Psychiatry* 53, 233–238.
- Steinman, K., Ross, J., Lai, S., Reiss, A., Hoeft, F., 2009. Structural and functional neuroimaging in Klinefelter (47, XXY) syndrome: a review of the literature and preliminary results from a functional magnetic resonance imaging study of language. *Dev. Disabil. Res. Rev.* 15, 295–308.
- Stephens, M.A., Mahon, P.B., McCaul, M.E., Wand, G.S., 2016. Hypothalamic-pituitary-adrenal axis response to acute psychosocial stress: Effects of biological sex and circulating sex hormones. *Psychoneuroendocrinology* 66, 47–55.
- Stomby, A., Boraxbekk, C.J., Lundquist, A., Nordin, A., Nilsson, L.G., Adolfsson, R., Nyberg, L., Olsson, T., 2016. Higher diurnal salivary cortisol levels are related to smaller prefrontal cortex surface area in elderly men and women. *Eur. J. Endocrinol.* 175, 117–126.
- Stroud, L.R., Papandonatos, G.D., D'Angelo, C.M., Brush, B., Lloyd-Richardson, E.E., 2017. Sex differences in biological response to peer rejection and performance challenge across development: a pilot study. *Physiol. Behav.* 169, 224–233.
- Suda, S., Segi-Nishida, E., Newton, S.S., Duman, R.S., 2008. A postpartum model in rat: behavioral and gene expression changes induced by ovarian steroid deprivation. *Biol. Psychiatry* 64, 311–319.
- Sudheimer, K.D., O'Hara, R., Spiegel, D., Powers, B., Kraemer, H.C., Neri, E., Weiner, M., Hardan, A., Hallmayer, J., Dhabhar, F.S., 2014. Cortisol, cytokines, and hippocampal volume interactions in the elderly. *Front. Aging Neurosci.* 6, 153.
- Sundstrom Poromaa, I., Gingnell, M., 2014. Menstrual cycle influence on cognitive function and emotion processing from a reproductive perspective. *Front. Neurosci.* 8, 380.
- Suri, D., Veenit, V., Sarkar, A., Thiagarajan, D., Kumar, A., Nestler, E.J., Galante, S., Vaidya, V.A., 2013. Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. *Biol. Psychiatry* 73, 658–666.
- Suzuki, M., Hagino, H., Nohara, S., Zhou, S.Y., Kawasaki, Y., Takahashi, T., Matsui, M., Seto, H., Ono, T., Kurachi, M., 2005. Male-specific volume expansion of the human hippocampus during adolescence. *Cereb. Cortex* 15, 187–193.
- Szeszko, P.R., Lehner, A., Yehuda, R., 2018. Glucocorticoids and hippocampal structure and function in PTSD. *Harv. Rev. Psychiatry* 26, 142–157.
- Tan, A., Ma, W., Vira, A., Marwha, D., Eliot, L., 2016. The human hippocampus is not sexually-dimorphic: meta-analysis of structural MRI volumes. *Neuroimage* 124, 350–366.
- Tanapat, P., Hastings, N.B., Reeves, A.J., Gould, E., 1999. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. *J. Neurosci.: Off. J. Soc. Neurosci.* 19, 5792–5801.
- Tanapat, P., Hastings, N.B., Rydel, T.A., Galea, L.A., Gould, E., 2001. Exposure to fox odor inhibits cell proliferation in the hippocampus of adult rats via an adrenal hormone-dependent mechanism. *J. Comp. Neurol.* 437, 496–504.
- Tanapat, P., Hastings, N.B., Gould, E., 2005. Ovarian steroids influence cell proliferation in the dentate gyrus of the adult female rat in a dose- and time-dependent manner. *J. Comp. Neurol.* 481, 252–265.
- Tang, S.S., Ren, Y., Ren, X.Q., Cao, J.R., Hong, H., Ji, H., Hu, Q.H., 2019. ER α and/or ER β activation ameliorates cognitive impairment, neurogenesis and apoptosis in type 2 diabetes mellitus mice. *Exp. Neurol.* 311, 33–43.
- Taylor, W.D., Steffens, D.C., Payne, M.E., MacFall, J.R., Marchuk, D.A., Svenson, I.K., Krishnan, K.R., 2005. Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late-life depression. *Arch. Gen. Psychiatry* 62, 537–544.
- Tessner, K.D., Walker, E.F., Dhruv, S.H., Hochman, K., Hamann, S., 2007. The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. *Brain Res.* 1179, 70–78.
- Thomas, R.M., Hotsenpiller, G., Peterson, D.A., 2007. Acute psychosocial stress reduces cell survival in adult hippocampal neurogenesis without altering proliferation. *J. Neurosci.* 27, 2734–2743.
- Thomason, M.E., Tocco, M.A., Quednau, K.A., Bedway, A.R., Carre, J.M., 2013. Idle behaviors of the hippocampus reflect endogenous cortisol levels in youth. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 642–652.
- Toffol, E., Heikkinen, O., Partonen, T., 2015. Hormone therapy and mood in perimenopausal and postmenopausal women: a narrative review. *Menopause* 22, 564–578.
- Torner, L., Karg, S., Blume, A., Kandasamy, M., Kuhn, H.G., Winkler, J., Aigner, L., Neumann, I.D., 2009. Prolactin prevents chronic stress-induced decrease of adult hippocampal neurogenesis and promotes neuronal fate. *J. Neurosci.* 29, 1826–1833.
- Totterman, T.H., Carlsson, M., Simonsson, B., Bengtsson, M., Nilsson, K., 1989. T-cell activation and subset patterns are altered in B-CLL and correlate with the stage of the disease. *Blood* 74, 786–792.
- Toufexis, D.J., Davis, C., Hammond, A., Davis, M., 2004. Progesterone attenuates corticotropin-releasing factor-enhanced but not fear-potentiated startle via the activity of its neuroactive metabolite, allopregnanolone. *J. Neurosci.* 24, 10280–10287.
- Toufexis, D., Rivarola, M.A., Lara, H., Viau, V., 2014. Stress and the reproductive axis. *J. Neuroendocrinol.* 26, 573–586.
- Travis, S.G., Coupland, N.J., Hegadoren, K., Silverstone, P.H., Huang, Y., Carter, R., Fujiwara, E., Seres, P., Malykhin, N.V., 2016. Effects of cortisol on hippocampal subfields volumes and memory performance in healthy control subjects and patients with major depressive disorder. *J. Affect. Disord.* 201, 34–41.
- Tsurugizawa, T., Mukai, H., Tanabe, N., Murakami, G., Hojo, Y., Kominami, S., Mitsuhashi, K., Komatsuzaki, Y., Morrison, J.H., Janssen, W.G., Kimoto, T., Kawato, S., 2005. Estrogen induces rapid decrease in dendritic thorns of CA3 pyramidal neurons in adult male rat hippocampus. *Biochem. Biophys. Res. Commun.* 337, 1345–1352.
- Tuscher, J.J., Luine, V., Frankfurt, M., Frick, K.M., 2016. Estradiol-mediated spine changes in the dorsal hippocampus and medial prefrontal cortex of ovariectomized female mice depend on ERK and mTOR activation in the dorsal hippocampus. *J. Neurosci.* 36, 1483–1489.

- Uno, H., Tarara, R., Else, J.G., Suleman, M.A., Sapolsky, R.M., 1989. Hippocampal damage associated with prolonged and fatal stress in primates. *J. Neurosci.* 9, 1705–1711.
- Vachon-Presseau, E., Roy, M., Martel, M.O., Caron, E., Marin, M.F., Chen, J., Albouy, G., Plante, I., Sullivan, M.J., Lupien, S.J., Rainville, P., 2013. The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans. *Brain* 136, 815–827.
- Valli, I., Crossley, N.A., Day, F., Stone, J., Tognin, S., Mondelli, V., Howes, O., Valmaggia, L., Pariante, C., McGuire, P., 2016. HPA-axis function and grey matter volume reductions: imaging the diathesis-stress model in individuals at ultra-high risk of psychosis. *Transl. Psychiatry* 6, e797.
- van Stegeren, A.H., 2009. Imaging stress effects on memory: a review of neuroimaging studies. *Can. J. Psychiatry* 54, 16–27.
- van Stegeren, A.H., Roozendaal, B., Kindt, M., Wolf, O.T., Joels, M., 2010. Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiol. Learn. Mem.* 93, 56–65.
- van Wingen, G., van Broekhoven, F., Verkes, R.J., Petersson, K.M., Backstrom, T., Buitelaar, J., Fernandez, G., 2007. How progesterone impairs memory for biologically salient stimuli in healthy young women. *J. Neurosci.* 27, 11416–11423.
- van Wingen, G., Mattern, C., Verkes, R.J., Buitelaar, J., Fernandez, G., 2008. Testosterone biases automatic memory processes in women towards potential mates. *Neuroimage* 43, 114–120.
- Via, V., Meaney, M.J., 1991. Variations in the hypothalamic-pituitary-adrenal response to stress during the estrous cycle in the rat. *Endocrinology* 129, 2503–2511.
- Victor, T.A., Drevets, W.C., Misaki, M., Bodurka, J., Savitz, J., 2017. Sex differences in neural responses to subliminal sad and happy faces in healthy individuals: implications for depression. *J. Neurosci. Res.* 95, 703–710.
- Vierk, R., Glassmeier, G., Zhou, L., Brandt, N., Fester, L., Dudzinski, D., Wilkars, W., Bender, R.A., Lewerenz, M., Gloger, S., Graser, L., Schwarz, J., Rune, G.M., 2012. Aromatase inhibition abolishes LTP generation in female but not in male mice. *J. Neurosci.* 32, 8116–8126.
- Vogel, S., Klumpers, F., Kroes, M.C., Oplaat, K.T., Krugers, H.J., Oitzl, M.S., Joels, M., Fernandez, G., 2015. A stress-induced shift from trace to delay conditioning depends on the mineralocorticoid receptor. *Biol. Psychiatry* 78, 830–839.
- Vogel, S., Klun, L.M., Fernandez, G., Schwabe, L., 2018. Stress leads to aberrant hippocampal involvement when processing schema-related information. *Learn. Mem.* 25, 21–30.
- Voyer, D., Bryden, M.P., 1990. Gender, level of spatial ability, and lateralization of mental rotation. *Brain Cogn.* 13, 18–29.
- Voyer, D., Voyer, S., Bryden, M.P., 1995. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychol. Bull.* 117, 250–270.
- Voyer, D., Postma, A., Brake, B., Imperato-McGinley, J., 2007. Gender differences in object location memory: a meta-analysis. *Psychon. Bull. Rev.* 14, 23–38.
- Vythilingam, M., Vermetten, E., Anderson, G.M., Luckenbaugh, D., Anderson, E.R., Snow, J., Staib, L.H., Charney, D.S., Bremner, J.D., 2004. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol. Psychiatry* 56, 101–112.
- Waddell, J., Bowers, J.M., Edwards, N.S., Jordan, C.L., McCarthy, M.M., 2013. Dysregulation of neonatal hippocampal cell genesis in the androgen insensitive Tfm rat. *Horm. Behav.* 64, 144–152.
- Wainwright, S.R., Workman, J.L., Tehrani, A., Hamson, D.K., Chow, C., Lieblich, S.E., Galea, L.A., 2016. Testosterone has antidepressant-like efficacy and facilitates imipramine-induced neuroplasticity in male rats exposed to chronic unpredictable stress. *Horm. Behav.* 79, 58–69.
- Walf, A.A., Frye, C.A., 2006. A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. *Neuropsychopharm.: Off. Publ. Am. Coll. Neuropsychopharm.* 31, 1097–1111.
- Walf, A.A., Frye, C.A., 2007. Administration of estrogen receptor beta-specific selective estrogen receptor modulators to the hippocampus decrease anxiety and depressive behavior of ovariectomized rats. *Pharmacol. Biochem. Behav.* 86, 407–414.
- Walf, A.A., Frye, C.A., 2007. Estradiol decreases anxiety behavior and enhances inhibitory avoidance and gestational stress produces opposite effects. *Stress* 10, 251–260.
- Walf, A.A., Frye, C.A., 2009. Effects of two estradiol regimens on anxiety and depressive behaviors and trophic effects in peripheral tissues in a rodent model. *Gend. Med.* 6, 300–311.
- Walf, A.A., Sumida, K., Frye, C.A., 2006. Inhibiting 5alpha-reductase in the amygdala attenuates anxiety and antidepressant behavior of naturally receptive and hormone-primed ovariectomized rats. *Psychopharmacology* 186, 302–311.
- Wang, Y., Xu, Q., Li, S., Li, G., Zuo, C., Liao, S., Long, Y., Li, S., Joshi, R.M., 2018. Gender differences in anomalous subcortical morphology for children with ADHD. *Neurosci. Lett.* 665, 176–181.
- Warren, S.G., Juraska, J.M., 1997. Spatial and nonspatial learning across the rat estrous cycle. *Behav. Neurosci.* 111, 259–266.
- Warren, S.G., Humphreys, A.G., Juraska, J.M., Greenough, W.T., 1995. LTP varies across the estrous cycle: enhanced synaptic plasticity in proestrus rats. *Brain Res.* 703, 26–30.
- Watanabe, R., Kakeda, S., Watanabe, K., Liu, X., Katsuki, A., Umeno-Nakano, W., Hori, H., Abe, O., Yoshimura, R., Korogi, Y., 2017. Relationship between the hippocampal shape abnormality and serum cortisol levels in first-episode and drug-naïve major depressive disorder patients. *Depress Anxiety* 34, 401–409.
- Weerden, R., Muehlhan, M., Wolf, O.T., Thiel, C.M., 2010. Effects of acute psychosocial stress on working memory related brain activity in men. *Hum. Brain Mapp.* 31, 1418–1429.
- Wegman, J., Fonteijn, H.M., van Ekert, J., Tyborowska, A., Jansen, C., Janzen, G., 2014. Gray and white matter correlates of navigational ability in humans. *Hum. Brain Mapp.* 35, 2561–2572.
- Wei, S.M., Baller, E.B., Kohn, P.D., Kippenhan, J.S., Kolachana, B., Soldin, S.J., Rubinow, D.R., Schmidt, P.J., Berman, K.F., 2018. Brain-derived neurotrophic factor Val(66) Met genotype and ovarian steroids interactively modulate working memory-related hippocampal function in women: a multimodal neuroimaging study. *Mol. Psychiatry* 23, 1066–1075.
- Weinstock, M., 2016. Prenatal stressors in rodents: Effects on behavior. *Neurobiol. Stress* 6, 3–13.
- Wessa, M., Rohleder, N., Kirschbaum, C., Flor, H., 2006. Altered cortisol awakening response in posttraumatic stress disorder. *Psychoneuroendocrinology* 31, 209–215.
- Westenbroek, C., Den Boer, J.A., Veenhuis, M., Ter Horst, G.J., 2004. Chronic stress and social housing differentially affect neurogenesis in male and female rats. *Brain Res. Bull.* 64, 303–308.
- Whittle, S., Yap, M.B., Sheeber, L., Dudgeon, P., Yucel, M., Pantelis, C., Simmons, J.G., Allen, N.B., 2011. Hippocampal volume and sensitivity to maternal aggressive behavior: a prospective study of adolescent depressive symptoms. *Dev. Psychopathol.* 23, 115–129.
- Wick, A., 2011. Oestradiol and psychosis: clinical findings and biological mechanisms. *Curr. Top. Behav. Neurosci.* 8, 173–187.
- Wierenga, L.M., Bos, M.G.N., Schreuders, E., Vd Kamp, F., Peper, J.S., Tamnes, C.K., Crone, E.A., 2018. Unraveling age, puberty and testosterone effects on subcortical brain development across adolescence. *Psychoneuroendocrinology* 91, 105–114.
- Williams, C.L., Barnett, A.M., Meck, W.H., 1990. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. *Behav. Neurosci.* 104, 84–97.
- Wisse, L.E., Biessels, G.J., Stegenga, B.T., Kooistra, M., van der Veen, P.H., Zwanenburg, J.J., van der Graaf, Y., Geerlings, M.I., 2015. Major depressive episodes over the course of 7 years and hippocampal subfield volumes at 7 tesla MRI: the PREDICT-MR study. *J. Affect. Disord.* 175, 1–7.
- Wolf, O.T., 2009. Stress and memory in humans: twelve years of progress? *Brain Res.* 1293, 142–154.
- Wolf, O.T., Convit, A., de Leon, M.J., Caraos, C., Qadri, S.F., 2002. Basal hypothalamo-pituitary-adrenal axis activity and corticotropin feedback in young and older men: relationships to magnetic resonance imaging-derived hippocampus and cingulate gyrus volumes. *Neuroendocrinology* 75, 241–249.
- Wolfram, M., Bellingrath, S., Kudielka, B.M., 2011. The cortisol awakening response (CAR) across the female menstrual cycle. *Psychoneuroendocrinology* 36, 905–912.
- Woolley, C.S., McEwen, B.S., 1993. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *J. Comp. Neurol.* 336, 293–306.
- Woolley, C.S., Gould, E., McEwen, B.S., 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res.* 531, 225–231.
- Woolley, C.S., Gould, E., Frankfurt, M., McEwen, B.S., 1990. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. *J. Neurosci.* 10, 4035–4039.
- Woolley, D.G., Vermaerck, B., Op de Beeck, H., Wagemans, J., Gantois, I., D'Hooge, R., Swinnen, S.P., Wenderoth, N., 2010. Sex differences in human virtual water maze performance: novel measures reveal the relative contribution of directional responding and spatial knowledge. *Behav. Brain Res.* 208, 408–414.
- Woon, F., Hedges, D.W., 2011. Gender does not moderate hippocampal volume deficits in adults with posttraumatic stress disorder: a meta-analysis. *Hippocampus* 21, 243–252.
- Wust, S., Federenko, I., Hellhammer, D.H., Kirschbaum, C., 2000. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology* 25, 707–720.
- Wust, S., Wolf, J., Hellhammer, D.H., Federenko, I., Schommer, N., Kirschbaum, C., 2000. The cortisol awakening response - normal values and confounds. *Noise Health* 2, 79–88.
- Xiao, L., Jordan, C.L., 2002. Sex differences, laterality, and hormonal regulation of androgen receptor immunoreactivity in rat hippocampus. *Horm. Behav.* 42, 327–336.
- Yagi, S., Galea, L.A.M., 2019. Sex differences in hippocampal cognition and neurogenesis. *Neuropsychopharmacology* 44, 200–213.
- Yagi, S., Drewczynski, D., Wainwright, S.R., Barha, C.K., Hershorn, O., Galea, L.A.M., 2017. Sex and estrous cycle differences in immediate early gene activation in the hippocampus and the dorsal striatum after the cue competition task. *Horm. Behav.* 87, 69–79.
- Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., Tochigi, M., Rogers, M., Aoki, S., Kato, N., Kasai, K., 2008. Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits. *Cereb. Cortex* 18, 46–52.
- Yao, S., Song, J., Gao, J., Lin, P., Yang, M., Zahid, K.R., Yan, Y., Cao, C., Ma, P., Zhang, H., Li, Z., Huang, C., Ding, H., Xu, G., 2017. Cognitive function and serum hormone levels are associated with gray matter volume decline in female patients with prolactinomas. *Front. Neurol.* 8, 742.
- Yap, J.J., Takase, L.F., Kochman, L.J., Fornal, C.A., Miczek, K.A., Jacobs, B.L., 2006. Repeated brief social defeat episodes in mice: effects on cell proliferation in the dentate gyrus. *Behav. Brain Res.* 172, 344–350.
- Ycaza Herrera, A., Mather, M., 2015. Actions and interactions of estradiol and glucocorticoids in cognition and the brain: Implications for aging women. *Neurosci. Biobehav. Rev.* 55, 36–52.
- Yonker, J.E., Eriksson, E., Nilsson, L.G., Herlitz, A., 2003. Sex differences in episodic memory: minimal influence of estradiol. *Brain Cogn.* 52, 231–238.
- Yoshiya, M., Komatsuzaki, Y., Hojo, Y., Ikeda, M., Mukai, H., Hatanaka, Y., Murakami, G., Kawata, M., Kimoto, T., Kawato, S., 2013. Corticosterone rapidly increases thorns of CA3 neurons via synaptic/extranuclear glucocorticoid receptor in rat hippocampus. *Front. Neural Circuits* 7, 191.
- Young, K.D., Bellgowan, P.S., Bodurka, J., Drevets, W.C., 2013. Functional neuroimaging

- of sex differences in autobiographical memory recall. *Hum. Brain Mapp.* 34, 3320–3332.
- Yue, Y., Hu, L., Tian, Q.J., Jiang, J.M., Dong, Y.L., Jin, Z.Y., Cheng, Y.H., Hong, X., Ge, Q.S., Zuo, P.P., 2007. Effects of long-term, low-dose sex hormone replacement therapy on hippocampus and cognition of postmenopausal women of different apoE genotypes. *Acta Pharmacol. Sin.* 28, 1129–1135.
- Yuste, R., Bonhoeffer, T., 2001. Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu. Rev. Neurosci.* 24, 1071–1089.
- Yuste, R., Bonhoeffer, T., 2004. Genesis of dendritic spines: insights from ultrastructural and imaging studies. *Nat. Rev. Neurosci.* 5, 24–34.
- Zarrouf, F.A., Artz, S., Griffith, J., Sirbu, C., Kommor, M., 2009. Testosterone and depression: systematic review and meta-analysis. *J. Psychiatric Pract.* 15, 289–305.
- Zhang, J.M., Konkle, A.T., Zup, S.L., McCarthy, M.M., 2008. Impact of sex and hormones on new cells in the developing rat hippocampus: a novel source of sex dimorphism? *Eur. J. Neurosci.* 27, 791–800.
- Zhang, Z., Yang, R., Zhou, R., Li, L., Sokabe, M., Chen, L., 2010. Progesterone promotes the survival of newborn neurons in the dentate gyrus of adult male mice. *Hippocampus* 20, 402–412.
- Zhao, Z., Taylor, W.D., Styner, M., Steffens, D.C., Krishnan, K.R., MacFall, J.R., 2008. Hippocampus shape analysis and late-life depression. *PLoS ONE* 3, e1837.
- Zhao, H., Tian, Z., Hao, J., Chen, B., 2005. Extragonadal aromatization increases with time after ovariectomy in rats. *Reprod. Biol. Endocrinol* 3, 6.
- Zhou, L., Fester, L., von Blittersdorff, B., Hassu, B., Nogens, H., Prange-Kiel, J., Jarry, H., Wegscheider, K., Rune, G.M., 2010. Aromatase inhibitors induce spine synapse loss in the hippocampus of ovariectomized mice. *Endocrinology* 151, 1153–1160.
- Zorn, J.V., Schur, R.R., Boks, M.P., Kahn, R.S., Joels, M., Vinkers, C.H., 2017. Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology* 77, 25–36.
- Zuena, A.R., Mairesse, J., Casolini, P., Cinque, C., Alema, G.S., Morley-Fletcher, S., Chiodi, V., Spagnoli, L.G., Gradini, R., Catalani, A., Nicoletti, F., Maccari, S., 2008. Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats. *PLoS ONE* 3, e2170.
- Zuo, Y., Lin, A., Chang, P., Gan, W.B., 2005. Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron* 46, 181–189.