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Review article

Sex differences in the brain: Implications for behavioral and biomedical research

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ABSTRACT

Biological differences between males and females are found at multiple levels. However, females have too often been under-represented in behavioral neuroscience research, which has stymied the study of potential sex differences in neurobiology and behavior. This review focuses on the study of sex differences in the neurobiology of social behavior, memory, emotions, and recovery from brain injury, with particular emphasis on the role of estrogens in regulating forebrain function. This work, presented by the authors at the 2016 meeting of the International Behavioral Neuroscience Society, emphasizes varying approaches from several mammalian species in which sex differences have not only been documented, but also become the focus of efforts to understand the mechanistic basis underlying them. This information may provide readers with useful experimental tools to successfully address recently introduced regulations by granting agencies that either require (e.g. the National Institutes of Health in the United States and the Canadian Institutes of Health Research in Canada) or recommend (e.g. Horizon 2020 in Europe) the inclusion of both sexes in biomedical research.

1. Introduction

Considerable interest has been directed towards understanding differences in how male and female physiology can contribute to sex differences in disease incidence, manifestation, and outcome. This review begins with an overview of an evolutionary explanation of why sex differences in different traits may have developed, with an eye towards understanding how studying an evolutionary perspective can aid in our understanding of sex differences in the regulation of social behavior, cognition, and recovery from stroke.

1.1. Brief History of the Evolution of Sex Differences

Species in which two distinct cell types, the gametes, must fuse together to produce offspring (i.e. species with sexual reproduction) are typified by two distinct sexes each producing morphologically different reproductive cells. Further sex differences evolve when different evolutionary pressures exist for each sex, the exact nature of which depends upon a species' particular ecology (recently reviewed in Morrow, 2015). Charles Darwin, in his 1871 two-volume book entitled "The Descent of Man, and Selection in Relation to Sex", formulated the theory of sexual selection to explain the existence of a considerable number of species with behavioral and morphological sexual dimorphisms. According to Darwin's theory of sexual selection, two factors can skew reproductive success towards one sex versus the other. The first, intrasexual competition (often among males) is heightened when access to reproduction is limited to few members of a sex. The second, intersexual choice, drives sex differences when the mating preferences of one sex (often the female sex) cause the evolution of specific traits in the opposite sex. Although sexual selection can explain traits that affect mating success in a number of species including *Homo sapiens* (Geary, 2010, 2016), it is less suitable for explaining sex differences in traits, such as foraging strategies, that may not be directly involved in intrasexual competition or intersexual mating choices. For these traits, differences in the selective pressures acting on the two sexes can better explain the evolution of sex differences (Lande, 1980; Morrow, 2015). In this regard, the evolution of sex differences can be seen as driven by differences in the life history strategies that enable males and females to maximize reproductive success over a lifetime (Morrow, 2015).

A number of proximal mechanisms for the evolution of sex differences have been investigated, including the hormonal or genetic sex-

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dependent regulation of functions (Arnold, 2017), sex-specific epigenetic regulation of genes (e.g. different DNA methylation patterns in males and females; Day and Bonduriansky, 2004; Naumova et al., 2013; reviewed in McCarthy and Nugent, 2013), and alternative splicing of gene transcripts (McIntyre et al., 2006), as well as sex chromosome-linked genes (reviewed in Arnold, 2017; Ellegren and Parsch, 2007; Wyman et al., 2012). When present, sex differences in traits have implications for a number of phenotypes, from physiological to behavioral, as well as for susceptibility to stressors, pathogens, and disease (Hamilton and Zuk, 1982; reviewed in Morrow, 2015; Roved et al., 2017).

1.2. Why Studying Evolutionary causes of Sex Differences in Traits Matters

The evolutionary causes of sex differences may aid our understanding of sex differences in disease and can inform sex-targeted and sex-appropriate medical interventions. The approach of using evolutionary theory to better understand medical conditions has been formulated in the field of medicine often referred to as "Evolutionary or Darwinian Medicine" (Nesse and Williams, 1996; Nesse et al., 2010) and can be applied to the understanding of sex differences in disease, mortality, and lifespan (e.g. Gilks et al., 2014; Kruger and Nesse, 2006).

Sex differences in psychiatric disorders may be rooted in sex differences in brain and behavior that are frequently found in a number of species including humans and rodents (Earls, 1987; see recent meta-analysis in Ruigrok et al., 2014). For example, females of these species tend to be more sensitive and responsive to potential threats, showing enhanced stress responses and defensive behaviors (Blanchard et al., 1991; Craske, 2003; Jolles et al., 2015; reviewed in Palanza, 2001; Shors, 2016). This reaction appears evolutionarily adaptive in view of the greater reproductive and parental investment by mammalian females, whereby greater evolutionary costs (i.e. reduced offspring survival) are associated with the loss of females than the loss of males. The evolutionarily adaptive female advantage in risk aversion in humans (Betzig, 2012; Maner et al., 2007) may explain female predominance in psychiatric disorders related to the activation of the stress systems such as anxiety disorders, phobias, depressive disorders, (Rutter et al., 2003), and post-traumatic stress disorders (Craske, 2003; Klabunde et al., 2016).

On the other hand, the males of many species tend to show greater levels of active patrolling of a territory (Gaulin and Fitzgerald, 1986; Jacobs et al., 1990; reviewed in Geary, 2010), and better spatial ability than females (Spritzer et al., 2005). Those males also tend to display more aggressive behaviors related to defending territories and gaining exclusive or priority access to important resources. This male advantage in social competition, territoriality, and active territory use is common in many species (Wilson and Daly, 1985; reviewed in Ervin et al., 2015a; Geary, 2016; Marlowe, 2005), and may be linked to the higher incidence and/or severity in men of risk-taking disorders, impulsive behaviors, and disorders of social behavior such as autism spectrum disorders (Lai et al., 2013), early onset schizophrenia (Shepherd et al., 2012), and violence and impulsive aggression (Caspi et al., 2014; Rice, 2015).

Steroid hormones such as estrogens, progestins, and androgens are involved in driving the development and subsequent regulation of sexually different structures, function, and behavior throughout life. Developmental (also termed "organizational") actions of hormones lead to the often sexually different life-long epigenetic regulation of genes (reviewed in McCarthy and Nugent, 2013). So called "activational" effects of hormones are also seen at puberty (Schulz and Sisk, 2016) and in adulthood, as hormones continue to regulate and modulate multiple behaviors and cognitive functions (reviewed in Arnold, 2017, Ervin et al., 2013; Gillies and McArthur, 2010). The laboratories of the speakers of the symposium "Sex Differences in the Brain: Implications for Behavioral and Biomedical Research" presented at the 2016 conference of the International Behavioral Neuroscience Society have devoted considerable effort to understanding the activational role of hormones in various behaviors, brain functions, brain health, and the molecular functioning of brain cells. These investigations have often demonstrated sex differences in the way that estrogens, progesterone, and androgens affect those biological systems. Below, Drs. Elena Choleris, Liisa Galea, Karyn Frick, and Farida Sohrabji summarize their findings showing sex differences in, and hormonal regulation of, rodent social behavior, pattern separation and spatial learning, as well as the molecular mechanisms of memory and recovery from stroke. We first review literature on sex differences and hormonal underpinnings of social behavior (Section 2), with a focus on brain regions underlying regulation of key social cognitive skills, social recognition, social learning, as well as known sexual dimorphisms in social interactions and aggression. We subsequently review literature on sex differences in spatial cognition (Section 3), with a focus on the brain plasticity and hormonal mechanisms underlying pattern separation and spatial learning. In Section 4, we focus on the molecular mechanisms through which estrogens and progesterone regulate memory formation in females and discuss emerging data suggesting sex differences in these mechanisms. In Section 5, we present an overview of sex differences in the outcome and therapy of strokes deriving from research with humans and animal models. Finally, this review concludes with some general thoughts about future directions for sex differences research.

2. Sex differences in rodent social behavior: hormonal influences.

Hormones regulate most aspects of social behavior, from reproduction and mate choices, to social cognition, social interactions, and aggression. The regulation of sexual and reproductive behaviors is a well-studied function of androgens, estrogens and progestins (for recent reviews see Georgiadis et al., 2012; Motta-Mena and Puts, 2017). Sex hormones are also involved in regulating the choice of, and preference for, specific mates. Generally, the sex that has the greatest investment in reproduction is also the choosiest when it comes to mating. In mammals, this is typically the female (Edward, 2015; Jennions and Petrie, 1997). Female mating and mating preferences are driven by the phase of the estrous cycle. In rodents, females are sexually receptive and proceptive only when both estrogens and progesterone peak, during the proestrous/behavioral estrous phase (Walmer et al., 1992). In humans, even though mating occurs throughout the menstrual cycle, sex drive and preference for traits linked to "good genes" are increased during the fertile phase, with evidence suggesting this is driven by estradiol as well as androgens (reviewed in Motta-Mena and Puts, 2017). Mating preferences in most non-human animals are also driven by androgens (possibly *via* their estrogenic metabolites) in males and both estrogens and androgens in females (reviewed in Adkins-Regan, 1998, 2009).

The choice of specific mates and/or social partners requires the cognitive function of social recognition. Social recognition can be broadly defined as an animal's ability to distinguish between conspecifics, and is important for the establishment of social hierarchies, social bonds, mate choices, territoriality, and the avoidance of infected or sick individuals (reviewed in Choleris et al., 2009, 2012; Ervin et al., 2015a; Sánchez-Andrade and Kendrick, 2011). Social recognition is regulated by sex hormones, especially estrogens. In addition to social recognition, estrogens regulate social learning, which is defined as, "learning that is influenced by observation of, or interaction with, another animal (typically a conspecific) or its products" (such as odor cues; Box, 1984; Galef, 1988; Heyes, 1994). Social learning is evolutionary adaptive in that by "exploiting the expertise of others" (Russon, 1997), it can allow animals to circumvent the costs that may be associated with trial-and-error individual learning (recently reviewed in Matta et al., 2016; Ervin et al., 2015a).

Social recognition also affects how animals interact with conspecifics, which can be investigated in the laboratory by assessing social interactions between cagemates or strangers. Such social interactions

show marked sex differences as reviewed below and in Table 2 and are regulated by sex hormones (reviewed in Ervin et al., 2015a). Sex hormones affect behavior and cognition *via* delayed lasting genomic mechanisms involving direct regulation of gene transcription by hormone receptors. Estrogens also act through quick onset and rapid (minutes) mechanisms that do not involve the regulation of gene transcription by hormone receptors (recently reviewed in Kow and Pfaff, 2016; Schwartz et al., 2016). A number of studies have shown estrogenic regulation of social cognition in mice via both long-term and rapid mechanisms (Ervin et al., 2015a). The Choleris lab at the University of Guelph, and other laboratories elsewhere, has spent the past few years elucidating the role of the three main receptors for estrogens, estrogen receptor alpha (ERα), ERβ, and the G protein-coupled ER (GPER, also known as G protein-coupled receptor 30 or GPR30) in social recognition, social learning, and social interactions. Those findings are briefly summarized below and sex differences are highlighted.

2.1. Social recognition: role of estrogens and androgens in male and female rodents

Social recognition is a critical regulator of most social behavior. In males, social recognition is regulated by androgens and their estrogenic metabolites (reviewed in Gabor et al., 2012; Ervin et al., 2015a; Table 2). In male rats, castration greatly reduces serum testosterone and brain levels of aromatase, the enzyme that converts testosterone to estradiol (reviewed in Sinchak et al., 1996). Castration increases the duration of social recognition memory for juvenile male rats from 0.5–1 h to 2–3 h (Bluthé et al., 1993; Thor, 1980). The androgen receptor (AR) is not involved in the developmental regulation of social recognition in male rats, as prenatal daily treatment with an AR antagonist, flutamide, did not affect social memory (Axelson et al., 1999). Male ArKO mice, in which the *cyp19* gene that codes for aromatase (Ar) is "knocked out" (KO), are impaired in social recognition despite having heightened testosterone (Fisher et al., 1998; Pierman et al., 2008). The impairment can be rescued by combined treatment with the two main metabolites of testosterone, the androgen dihydrotestosterone and the estrogen 17β-estradiol, suggesting that 17β-estradiol is critical for social recognition in male mice.

The involvement of estrogens and their receptors in social recognition has been confirmed in both males and females. Ovariectomy reduces social recognition, and estrogens alone (Hlinák, 1993) or in combination with progesterone (Spiteri and Ågmo, 2009) can restore the impairment in ovariectomized female rats. Studies with ERαKO mice showed impaired social recognition in both males and females (Choleris et al., 2003, 2006; Imwalle et al., 2002; Sánchez-Andrade and Kendrick, 2011), although the male impairment is not always found (Sánchez-Andrade and Kendrick, 2011; see Ervin et al., 2015a for more detail and discussion). ERα regulation of social recognition can be mediated by the medial amygdala, as long-term inhibition of ERα in this region impaired social recognition in female rats (Spiteri et al., 2010). Female and male ERβKO mice are not impaired in social recognition (Choleris et al., 2006; Sánchez-Andrade and Kendrick, 2011), although females may appear impaired depending upon the testing conditions (Choleris et al., 2003, 2006; further discussed in Ervin et al., 2015a). Overall, these studies with long-term inhibition of ER genes show that ERα is involved in social recognition in both sexes, whereas ERβ is not (Table 2).

More recent investigations have highlighted a role for estrogens, ERα, ERβ, and GPER in social recognition through rapid mechanisms of action. Systemic administration of 17β-estradiol, the ERα agonist propyl pyrazole triol (PPT), or the GPER agonist G-1 enhanced social recognition in ovariectomized female mice when learning and testing for social recognition was completed within 40 min of drug administration, suggesting rapid non-genomic facilitation of social recognition by ERα or GPER (Phan et al., 2011, 2012; Gabor et al., 2015). In contrast, administration of the ERβ agonist diarylpropionitrile (DPN) impaired social recognition (Phan et al., 2011). Furthermore, treatments that enhanced social recognition (PPT, G-1, and estradiol) also increased dendritic spines in the CA1 region of the dorsal hippocampus (Phan et al., 2011, 2012; Gabor et al., 2015). Administration of the same treatments directly to the dorsal hippocampus similarly enhanced social recognition in ovariectomized mice (Phan et al., 2015; Lymer et al., 2017). Intriguingly, when applied to *ex-vivo* hippocampal sections from experimentally naïve female mice, 17β-estradiol and PPT, but not DPN, decreased AMPA-mediated miniature excitatory postsynaptic currents frequency in CA1 pyramidal neurons, likely due to the internalization of AMPA receptors. Thus, the same neurons that exhibited increased dendritic spine density after treatment also exhibited new immature synapses in the absence of learning that are silent (Phan et al., 2015). The immature spines may become activated under high stimulation conditions during learning events. Collectively, these findings suggest that both ERα and GPER in the dorsal hippocampus can mediate rapid estrogenic enhancement of social recognition in females. In addition, subsequent investigations administered the same treatments in the medial amygdala and found that 17β-estradiol, PPT, G-1, and DPN, all rapidly enhanced social recognition (). Therefore, social recognition is rapidly mediated by all three ERs in the medial amygdala, but only by ERα and GPER in the dorsal hippocampus (Table 2).

The neural and hormonal control of social recognition exhibits striking sex differences (Table 2). That is, the lateral septum is more implicated in males (Appenrodt et al., 2002; Everts and Koolhaas, 1999; Landgraf et al., 2003), whereas the medial amygdala plays a critical role in both sexes (Choleris et al., 2007; Ferguson et al., 2001). Androgen effects on social recognition in males are mediated by the neuropeptide arginine vasopressin (AVP), but AVP is not involved in female social recognition. Furthermore, males exhibit greater AVP expression than females in a number of brain regions, including the bed nucleus of the stria terminalis and the amygdala, which project to the lateral septum, a brain region in which AVP is essential for social recognition in males (e.g. Everts and Koolhaas, 1997; Wang et al., 1993). AVP expression is regulated by testosterone via both estrogenic and androgenic mechanisms in male rodents (De Vries et al., 1984; Szot and Dorsa, 1993; reviewed in De Vries, 2008; reviewed in Choleris et al., 2009; Gabor et al., 2012).

Contrary to males, peripheral administration of an AVP antagonist did not impair social recognition in female rats (Bluthé and Dantzer, 1990; Bluthé et al., 1990; Engelmann et al., 1998), suggesting that AVP is necessary for social recognition only in males. In females and castrated males, social recognition is independent of AVP (Bluthé et al., 1990). Instead, estrogenic regulation of social recognition in both males and females may be mediated by action upon the neuropeptide oxytocin (OT) and its receptor (OTR). Even though this estrogen-OT interplay in the regulation of social recognition has not yet been directly demonstrated, it appears plausible. Pharmacological investigations and studies with global and temporary gene KO mice have repeatedly and consistently demonstrated a critical role for OT and OTR in social recognition in both sexes (reviewed in Gabor et al., 2012). OT and the OTR are under estrogenic control, with both brain and plasma OT levels and brain OTRs fluctuating with the estrous cycle, dropping after ovariectomy, and increasing in response to estradiol benzoate administration (Bale et al., 1995; Dellovade et al., 1999; Ho and Lee, 1992; Sarkar et al., 1992). In the paraventricular nucleus of the hypothalamus, which is the main site of OT synthesis and in which ERβ and GPER, but not ERα, are expressed (Hazell et al., 2009; Mitra et al., 2003), ERβ mediates estrogenic regulation of OT production in both males and females (Nomura et al., 2002; Patisaul et al., 2003). Intriguingly, in the PVN of male mice, estrogens also induced an ERβ-mediated reduction of AVP, suggesting opposite roles for ERβ on OT and AVP synthesis (Nomura et al., 2002). In the medial amygdala, where OT, OTR, ERα, ERβ, and GPER mediate social recognition in both sexes (Choleris et al., 2007; Ferguson et al., 2001; Lymer et al., unpublished results; Spiteri et al., 2010), OTR production is regulated

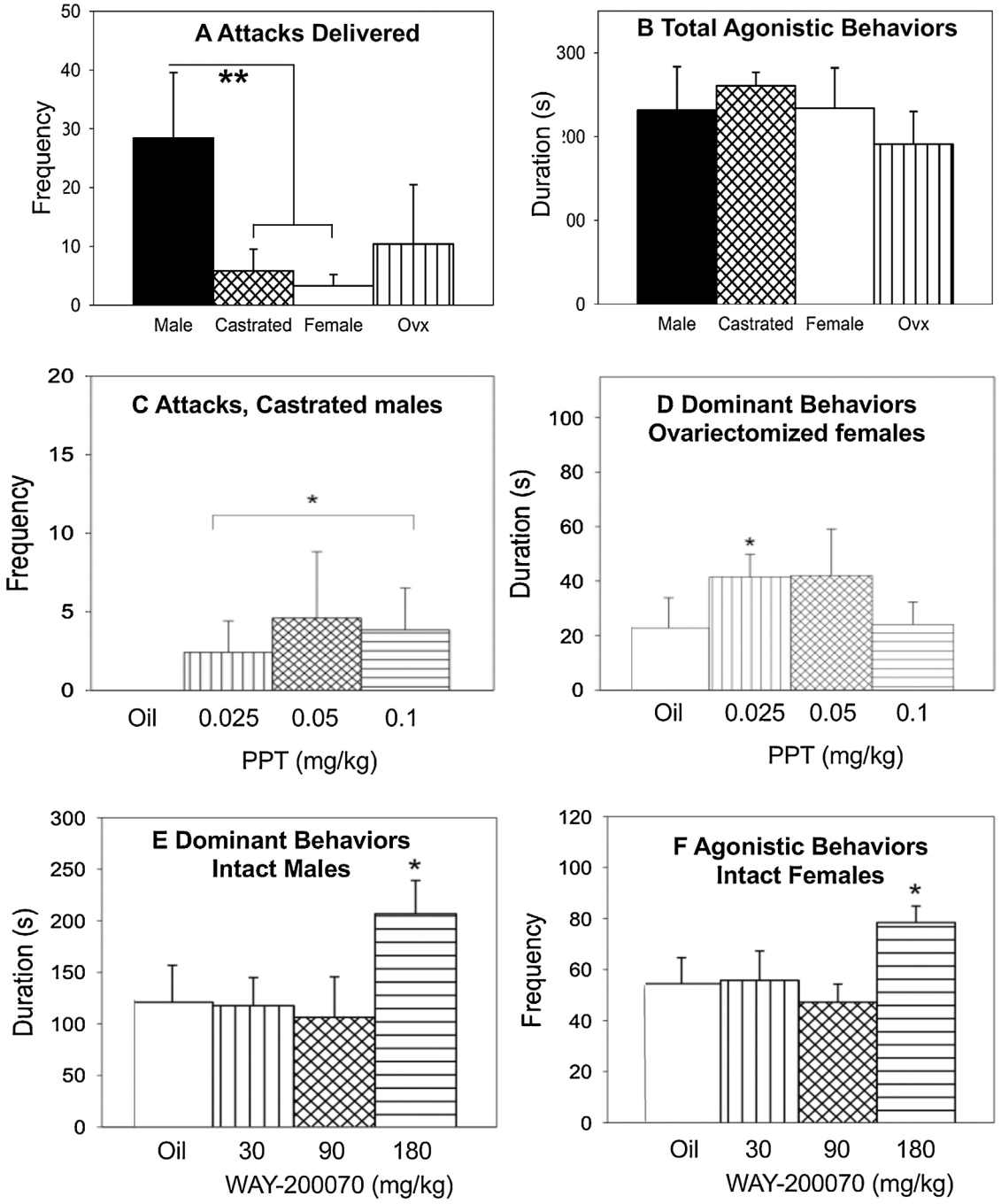

Fig. 1. When males and females were compared in the intruder test of territorial aggression, males performed more attacks than females, which were reduced by castration (A). When dominance-related agonistic behaviors were included, no sex differences were found in total agonistic behaviors (B). Administration of ERα agonist PPT increased attacks in castrated males (C) and dominance aggression in ovariectomized (Ovx) females (D). The ERβ agonist WAY200070 instead only increased dominance in gonadally intact males (E) and overall agonistic behaviors (comprised mostly of dominance behavior) in females (F). * indicates a significant difference from the sesame oil treated control group at $p < 0.05$. ** = $p < 0.01$ in comparison to gonadally intact males. Modified from Clipperton-Allen et al. (2010, 2011).

by ERα and not ERβ (Young et al., 1998). To the best of our knowledge, the interplay between OT and GPER, also found in the paraventricular nucleus of the hypothalamus and the medial amygdala (Hazell et al., 2009), has not been investigated. In summary, it is clear that estrogens play a critical role in the regulation of social recognition in males and females, and intriguing sex differences in the possible downstream mechanisms (AVP or OT) and brain site of action warrant further investigations (Table 2).

2.2. Social learning: role of estrogens in female rodents

Whereas social recognition involves learning *about* others and their characteristics, social learning permits animals to acquire novel adaptive information *from* others. Even though social learning is seen in both males and females, a direct comparison between the sexes is often not investigated and the sex of the animals used is not always reported (reviewed in Choleris and Kavaliers, 1999; Table 2). When sex differences are found, females often outperform males in rodents, birds, and humans (e.g. Brodin and Urhan, 2015; Chipman and Hampson, 2007; Wang et al., 2014a; Wang et al., 2014b; reviewed in Ervin et al.,

2015a). Investigations into the role of the sex hormones in social learning have so far been limited to estrogens in females, and have focused on the social transmission of food preferences, whereby an observer animal develops a food preference during a social interaction with a demonstrator animal that has recently consumed a novel diet (Galef et al., 1984; Valsecchi and Galef, 1989; reviewed in Matta et al., 2016; Ervin et al., 2015a). Natural changes in hormonal states associated with the estrous cycle, pregnancy, and parturition have been associated with enhanced social learning or memory for a socially-acquired food preferences in mice, rats, and gerbils (Choleris et al., 2011, 2012; Fleming et al., 1994; Sánchez-Andrade et al., 2005). In ovariectomized mice, chronic and acute replacement with estradiol benzoate 48 h prior to social learning prolonged the expression of a socially-acquired food preference (Clipperton-Allen et al., 2009). These long-term effects of estrogens on social learning are likely due to action at ERβ, as administration of the ERβ agonist WAY-200070 48 h prior to training also doubled the duration of time the mice showed a socially-learned food preference. The ERα agonist PPT, instead blocked social learning (Clipperton et al., 2008). Conversely, 17β-estradiol and GPER agonist G-1, both rapidly enhanced social learning within 45 min of treatment (G-1 more so than estradiol), whereas PPT and DPN both inhibited it (PPT more so than DPN) (Ervin et al., 2015b). Thus, estrogens promote social learning in female mice, but which receptors mediate the effects depends upon whether those effects are delayed or rapid. ERβ promotes long-term effects of social learning, but inhibits rapid effects of social learning, whereas the GPER promotes social learning rapidly. Instead, ERα activation blocks social learning (Table 2). The specific brain regions underlying these estrogenic actions on social learning are currently unknown. Unpublished data by Kelsy Ervin seem to rule out the dorsal hippocampus and the basolateral amygdala, both of which are regions implicated in social learning (e.g. Carballo-Marquez et al., 2009; Winocur, 1990), suggesting that estrogens may regulate social learning by acting upon regions that are upstream of the hippocampus.

In summary, estrogens play an important role in social learning in females, although the specific receptors involved depend upon the mechanisms of estrogenic action, delayed or rapid. Whether androgens or estrogens similarly mediate social learning in males is, to the best of our knowledge, unknown. Social learning is often greater in females than in males (reviewed in Ervin et al., 2015a) and this sex difference supports a role for sex hormones, but findings also suggest that other underlying neurochemical mechanisms to support social learning may differ between the sexes (Table 2). For example, recent studies showed that dopamine D2-type receptors in the dorsal hippocampus are necessary for social learning in male mice only (Matta et al., 2017 and unpublished results). Conversely, dorsal hippocampal D1 receptors mediate social learning in both male and female mice (Matta et al., 2017). These results suggest that more investigations into possible sex differences in the neurobiology of social learning should be conducted.

2.3. Social interactions and aggression: role of estrogens and androgens in male and female rodents

Males of many species typically show higher levels of overt territorial aggression (i.e. attacks, bites, lock fights) towards an unfamiliar intruder than females (Fig. 1A. reviewed in Parmigiani et al., 1998; Ervin et al., 2015a; Table 2). However, this finding should not suggest that females are not aggressive. Females are aggressive, but they typically show a predominance of non-overt dominance-related aggression (e.g. chasing an opponent or pushing it down during allogrooming), and fewer or no direct attacks. As a consequence, females are underrepresented in laboratory investigations of aggressive behavior that typically focus on overt aggression (reviewed in Ervin et al., 2015a). When non-overt aggression is investigated, female mice are found to spend as much time as males, if not more, in agonistic interactions with an unfamiliar same-sex intruder (Fig. 1B. e.g. Clipperton-Allen et al., 2010, 2011). Thus, sex differences in aggression are expressed by the *type* of aggression, with males showing more overt aggression and females showing more non-overt aggression to an unfamiliar same sex intruder. Whether overt or dominance-type aggression is predominant has important functional implications: overt aggression can result in injury and, unless it deescalates to dominance-type, overt aggression often causes the loser to leave the territory of the winner. Hence, overt aggression can lead to reduced levels of sociality, with territorial animals spacing themselves apart *via* the exclusion of unfamiliar intruders. Non-overt aggression instead typically leads to the formation of dominance hierarchies that regulate the social dynamics of a group, for example by controlling access to critical resources, while at the same time enabling cohabitation among group members (reviewed in Ervin et al., 2015a).

Social interactions are affected by social recognition: animals will interact differently with a familiar versus an unfamiliar conspecific (reviewed in Ervin et al., 2015a). When overt and dominance-type aggression were assessed in same-sex cagemates, overall levels of overt aggression were very low in both males and females, confirming an important role of familiarity in social interactions. Sex differences were still evident however, as male cagemates were more agonistic (e.g., boxed for longer, delivered more attacks and had greater dominance) than females, who instead engaged in more submissive-type behaviors and displayed more non-aggressive social investigations than males (Matta et al., 2017). Thus, even when interactions are with cohabiting conspecifics, the amount and type of agonistic behaviors differ in male and female mice.

Intriguing sex differences have been described in the brain mechanisms underlying overt and dominance aggression in Syrian hamsters. Serotonin receptor 5-HT1a activation in the hypothalamus enhanced aggression in females and inhibited aggression in males (Terranova et al., 2016). Further, the establishment of dominance in females was associated with activation of serotonergic neurons in the dorsal raphe but not in males (Terranova et al., 2016). Conversely, AVP reduced aggression in females and enhanced it in males, and the establishment of dominance was linked to activation of hypothalamic AVP neurons in males (Terranova et al., 2016). These sex differences support a role for the sex hormones in aggression. Overt and dominance-type aggression are both regulated by testosterone and estrogens. Gonadectomy reduces aggression in males and females of a number of species. In mouse studies that directly compared the sexes, castration reduced overt aggression and shifted towards dominance-type aggression, whereas in females, ovariectomy only reduced dominance aggression (Fig. 1B. Clipperton-Allen et al., 2010, 2011). Androgens, as well as estrogens, can reinstate aggression in adults of both sexes (e.g. Brain and Haug, 1992; Simon and Whalen, 1986; Trainor et al., 2007; reviewed in Ervin et al., 2015a). These effects of hormones on aggression are organizational (e.g. Berretti et al., 2014; vom Saal, 1979) and activational (e.g. Brain and Haug, 1992), and are mediated *via* long-term genomic as well as rapid mechanisms (reviewed below and in Ervin et al., 2015a; Ogawa, 2004). Thus, notwithstanding the baseline sex difference in the type of aggression spontaneously displayed by mice towards an unfamiliar intruder (more overt in males; more dominance-type in females), hormonal regulation of aggression is similar in both sexes. However, interesting sex differences emerge in the mechanisms of how hormones influence aggression in males and females.

Studies, have highlighted intriguing sex differences, including a critical and *opposite* role for ERα, and possibly even ERβ, in male and female aggression towards unfamiliar intruders. ERα promotes male, and inhibits female, territorial aggression (reviewed in Ogawa, 2004; Scordalakes and Rissman, 2004). In the ventral medial nucleus of the hypothalamus (VMH), ablation of neurons that co-express ERα and the progesterone receptor (Yang et al., 2013), or long-term inhibition of ERα gene expression (Sano et al., 2013), reduced both aggression and sexual behavior in male mice. Interestingly, long-term inhibition of ERα

in the VMH of female rats increased overt aggression towards juvenile intruders (Spiteri et al., 2010). This finding supports an opposite role for ERα in male and female aggression, even within the same brain region (Table 2). Similarly, global gene KO studies suggest that ERβ inhibits male aggression and enhances female aggression (reviewed in Ogawa, 2004). Thus, ERα and ERβ seem to play opposite roles in male aggression and, like for ERα, an opposite role for ERβ in male and female aggression is suggested. However, effects in ERβKO males were transient and the type of aggression studied in ERβKO females was different than that of males (postpartum maternal vs territorial). Hence, the conclusion of a sex difference in ERβ involvement in mouse aggression is tentative at this point. Finally, studies with long-term treatment with PPT and DPN in beach mice *Peromyscus polionotus* lead to the conclusion that both ERα and ERβ regulate male territorial aggression in this species (Trainor et al., 2007), suggesting important species differences in long-term ER regulation of male aggression.

Two studies investigated sex differences in the role of long-term ER action on aggression towards an unfamiliar same-sex intruder using acute treatments of PPT and ERβ agonist WAY-200070 two and three days prior to testing. In both sexes, ERα activation increased sex-typical aggressive behavior (attacks in males and dominance in females) in gonadectomized, but not in gonadally-intact, mice (Fig. 1C and D, Clipperton-Allen et al., 2011). ERβ activation instead only enhanced dominance-type aggression (not attacks) in both sexes and only in gonadally intact mice (Fig. 1E and F, Clipperton-Allen et al., 2010). Thus, ERα activation was capable of inducing sex-typical aggression in the absence of circulating gonadal hormones, suggesting, again, a critical role for ERα in aggression. ERβ activation instead only affected aggression when circulating hormones were present, suggesting a lesser, modulatory, role for ERβ in aggression.

A few studies, so far only in males, have also investigated the role of estrogens in aggression *via* rapid non-genomic mechanisms. A single injection of 17β-estradiol 15 min prior to a 10-min intruder test restored attacks that had been eliminated by chronic treatment with an aromatase inhibitor in California mice *Peromyscus californicus* housed under short-day conditions (Trainor et al., 2007, 2008). 17β-estradiol however did not reverse the enhancing effects on aggression of the aromatase inhibitor under long-day conditions, suggesting that the rapid estrogenic regulation of aggression is specific for short-day, winter-like photoperiods. In male golden hamsters (a.k.a. Syrian hamsters, *Mesocricetus auratus*,) anterior hypothalamic infusions of 17β-estradiol did not affect aggression but did rapidly enhance territorial scent marking, whereas androgen infusions were ineffective in influencing aggression (Hayden-Hixson and Ferris, 1991). Rather, systemic testosterone rapidly inhibited urine scent marking in subordinate but not dominant male white-footed mice (*Peromyscus leucops*, Fuxjager et al., 2015). Thus, studies on rapid effects suggest that estradiol enhances various manifestations of male aggression in different species. They also indicate that these rapid effects are more flexible than genomic effects in that they can be modulated by environmental factors such as day length and even the type of bedding in the cage (discussed in Laredo et al., 2014).

In summary, despite a common sex difference in the type of aggression displayed, estrogenic and androgenic mechanisms regulate aggression in both males and females, both rapidly and dynamically and through long-term genomic action. ERα and ERβ may have opposite effects on aggression *via* long term mechanisms, and these effects also appear opposite in males and females. In addition, ERα in mice seems more specifically involved in overt aggression, whereas ERβ may be more implicated in dominance aggression. Whether these differences in ERα and ERβ involvement correspond to different brain regions implicated in different types of aggression in males and females remains to be investigated. Similarly, the involvement of other ERs, like GPER and the putative membrane ER called Gq-mER, in aggression remains uninvestigated.

2.4. Making sense of sex differences and hormonal regulation of rodent social behavior

Overall, hormones, especially estrogens, are highly involved in social behavior, affecting social recognition, social learning, and social interactions in males and females. Some intriguing sex differences in these processes have been observed, such as the different brain regions and downstream effectors of hormonal action in social recognition; that is, AVP in males and OT in both sexes (Everts and Koolhaas, 1997; Wang et al., 1993; reviewed in Gabor et al., 2012). Studies also show that different social behaviors can be differently regulated by the three main ERs. For example, ERα is critically involved in sexual behavior, mate choices, aggression, and social recognition, whereas it blocks social learning (Clipperton et al., 2008; Ervin et al., 2015b; Ogawa, 2004; Phan et al., 2012, 2015), suggesting that ERα may act as a switch that inhibits certain hormonally-driven social behaviors when others take priority. In the case of a prototypical sexually different social behavior – agonistic interactions – ERα seems implicated in both males and females, though differently (Ogawa, 2004; Scordalakes and Rissman, 2004). ERα selective activation enhanced sex-typical agonistic behaviors: overt attacks in males and dominance related behaviors in females (Clipperton-Allen et al., 2010, 2011). In addition, long-term and rapid hormonal manipulations do not always yield the same results. For example, single-treatment, acute, activation of ERβ prolonged the expression of a socially-learned food preference when administered 72 h before testing (i.e. long-term effect), whereas it had a small impairing effect on social learning when administered 15 min before testing (i.e. rapid effects) (Clipperton et al., 2008; Ervin et al., 2015b). Conversely, the long-term and rapid mechanisms of hormone action seem to similarly contribute to other social behaviors. For example, ERα appears involved in social recognition in both long-term gene KO studies and in rapid studies with ERα specific agonists (Choleris et al., 2006; Imwalle et al., 2002; Phan et al., 2012; 2015; Sánchez-Andrade and Kendrick, 2011). Finally, investigations into the brain regions involved find that the hippocampus can drive many of the rapid effects of estrogens on social behavior, except social learning (Ervin et al., unpublished results; Lymer et al., 2017; Phan et al., 2015). Other brain areas currently under investigation (e.g. the medial amygdala) also appear to be involved (Lymer et al., in preparation). In the case of aggression, two studies on the VMH suggest that the same receptor, ERα, may regulate aggression in opposite directions in males and females, suggesting profound sex differences in the functioning of this brain region (Sano et al., 2013; Spiteri et al., 2010). Overall, receptor-specific roles are being identified in the regulation of social behavior by estrogens and these may be reflected in the network of brain regions involved in each of these social behaviors in males and females.

3. Sex differences in pattern separation and spatial learning: relationship to neurogenesis

3.1. Are there sex differences in cognition?

Sex differences in various aspects of cognition have been seen across a number of species and in humans, with women on average exhibiting greater verbal ability, and perceptual speed while men on average exhibiting better spatial ability than women (reviewed in Hyde, 2016). However, it is important to be aware that these sex differences often have small effect sizes and there are no indications that there are large sex differences in IQ (Hyde, 2016). Nevertheless, the largest sex difference, with males outperforming females, is seen in spatial ability, and meta-analyses indicate that spatial superiority in males exist in both rodents and primates (Jonasson, 2005; Voyer et al., 2016). From an evolutionary perspective, it has been speculated that the male superiority in spatial ability would be more prominent when there was pressure for males to traverse larger areas in order to gain access to mates (Gaulin et al., 1990). Indeed, in promiscuous strains of voles in

which males traverse larger areas than females during the breeding season, better spatial ability is noted in males (for review see Galea et al., 1996; Gaulin et al., 1990). However, in monogamous strains of voles in which there is no sex difference in home range size and voles form pair bonds, no sex difference in spatial ability is observed (Gaulin et al., 1990). These findings can inform studies of possible mechanisms and pressures that drive sex differences in spatial ability.

Intriguingly, sex differences also exist in vulnerability and manifestation of neurological diseases that involve cognitive disruption such as Alzheimer's Disease (AD) with women more likely to be afflicted with AD, and men more likely to be afflicted with schizophrenia (Jackson et al., 2013; Mendrek and Mancini-Marïe, 2016; Snyder et al., 2016). Cognitive disturbances associated with these diseases also show sex differences, the direction of which depend on the disease. For example, women are more likely to suffer from AD, and show greater cognitive deficits and a more severe decline in memory function with AD (Irvine et al., 2012). On the other hand, men are more likely to suffer earlier in life from schizophrenia than women, and show more severe cognitive symptoms with the disease (Jackson et al., 2013; Mendrek and Mancini-Marïe, 2016; Zhang et al., 2014; Zhang et al., 2015). Thus, one reason it is important to study sex differences in cognition is to understand the involvement of sex as a factor in the severity of cognitive disturbances with disease, as this can lead to clues about how the manifestation and/or treatment of the disease may need differ between the sexes.

3.2. Sex differences in the hippocampus: function and neurogenesis

Although there are a number of brain areas and brain networks that are implicated in cognition, the hippocampus is a widely studied area in memory research for a number of reasons. In line with this review, there are at least three reasons for extensive research on the involvement of the hippocampus on sex differences in memory research. One reason is that the hippocampus possesses notable plasticity, including long term potentiation (LTP), changes to spine density, spine size and type, and the ability to produce new neurons throughout adulthood in all mammalian species studied to date (Connor and Wang, 2016; Howland and Wang, 2008; Leuner and Gould, 2010). Another reason is that the hippocampus contains an abundance of steroid hormone receptors including ERα, ERβ, GPER, and AR (Duarte-Guterman et al., 2015; Hajszan et al., 2007). Finally, the integrity of the hippocampus is compromised in disorders that involve sex differences in cognitive disturbances such as AD and schizophrenia (Leal and Yassa, 2013; Mendrek and Mancini-Marïe, 2016). Although a meta-analysis suggests that men have larger hippocampal volumes than women, this advantage disappears when hippocampal volume is adjusted for total brain or intracranial volume (Tan et al., 2016). The specific role of the hippocampus in cognition is hotly debated, however, it is widely held that the integrity of the hippocampus is important for spatial ability (Buzsáki and Moser, 2013). Thus, this section will focus on hippocampal-dependent spatial learning and memory and its associated effects on adult neurogenesis in the hippocampus.

Adult neurogenesis in the dentate gyrus is seen in most mammalian species, including rodents and humans (Leuner and Gould, 2010; Spalding et al., 2013). Neurogenesis is a process that involves the proliferation, differentiation, migration/integration, and survival of new neurons that are produced. In adulthood, progenitor cells reside in the border between the hilus and the granule cell layer in the dentate gyrus of the hippocampus. When activated, these progenitor/neural stem cells will generate two daughter cells, and at least one of these daughter cells will become a new neuron. Although a significant number of these new neurons do not survive to maturity, numerous factors can promote the survival of new neurons, including exposure to sex hormones (see review Mahmoud et al., 2016). However, much like the lack of a sex difference in overall hippocampal volume, sex differences in neurogenesis levels are not generally observed in rodents (Chow et al., 2013; Barker and Galea, 2008; Dalla et al., 2009). When sex differences are seen in hippocampal neurogenesis, they appear to be limited to the ventral dentate gyrus, with greater levels of new neurons in males (Dalla et al., 2009), or in cell proliferation only when comparing proestrus females to males (Tanapat et al., 1999; see review in Mahmoud et al., 2016). To our knowledge, only one study has investigated sex differences in neurogenesis in the dentate gyrus of humans. Epp et al. (2013) found that women, but not men, with depression showed a greater ratio of immature to mature neurons than controls in response to prescribed antidepressants. These findings, collectively, suggest that despite no overt sex difference in the amount of neurogenesis at any given time, sex differences in neurogenesis may emerge in response to pharmacological treatment or hormones.

One of the most common methods used to assess spatial ability in rodents is the Morris water maze. Males typically outperform females in acquisition of this task, with males reaching asymptotic performance just prior to females (for review see Hamson et al., 2016). However, no sex differences are generally seen in memory for this task (as assessed during the probe trial). Furthermore, sufficient pre-training can eliminate the male advantage in acquisition, indicating a role for stress and/or acclimation in this sex difference (Perrot-Sinal et al., 1996). Indeed, it is intriguing that acute stress and exposure to corticosterone can enhance hippocampus-dependent learning in male rats, but impair hippocampus-dependent learning in female rats (Wood and Shors, 1998; Workman et al., 2015).

In past research using seasonal breeders, such as deer mice and meadow voles, work by Liisa Galea and colleagues has consistently found a slight, but statistically significant, sex difference, with males outperforming females, in acquisition of the Morris water maze even when the animals were pre-trained (Galea et al., 1994; Galea et al., 1995; Chow et al., 2013). Interestingly, this sex difference was observed only when comparing females to males during periods when females were exposed to higher levels of estradiol (i.e., during the breeding season). Thus, high endogenous levels of estradiol in females were negatively associated with performance, whereas low endogenous levels of estradiol were associated with no sex difference (Galea et al., 1994; Galea et al., 1995). Indeed, many studies using exogenous manipulations of estradiol in females or androgens in males find a greater influence of estradiol in female performance and strategy use than of androgens in male performance, indicating a greater activational role of estrogens in female spatial performance than in male spatial performance. Notable sex differences in strategy use exist as well, with males showing more spatial strategy use than females (Locklear and Kritzer, 2014; Yagi et al., 2016, 2017), but a thorough discussion of this topic is beyond the scope of this review.

3.3. Relating sex differences in spatial ability and neurogenesis

In one recent study of rats, sex differences favouring males were observed during learning of the hidden platform version of the Morris water maze, but no sex differences were observed in spatial memory (probe trial performance) (Chow et al., 2013). This study also examined neurogenesis in response to spatial Morris water maze training and activation of new neurons with immediate early genes in response to spatial memory retrieval. Consistent with a number of other studies (Gould et al., 1999; Epp et al., 2007), Chow et al. (2013) found increased levels of hippocampal neurogenesis in response to spatial or cued water maze training in male rats, but not in female rats. In addition, spatially-trained rats exhibited greater co-expression of immediate early genes in new neurons in response to spatial memory retrieval compared to cue-trained rats, suggesting that regardless of sex, spatial training elicited greater activation of new neurons in the dentate gyrus. Surprisingly, however, a positive relationship between the number of new neurons that co-express an immediate early gene, indicating activity, in the dorsal dentate gyrus (BrdU/Zif268-ir cells) and acquisition of the spatial Morris water maze task was only seen in

females. A number of factors may explain the lack of a correlation in males, including a limited range in performance values in males compared to the larger range seen in females, which would have limited the ability to see a positive relationship in males. The findings from this study suggest that although spatial training and the neurogenesis response to spatial training was superior in males compared to females, activation of these new neurons was associated with performance in females but not in males. This pattern of results suggests that sex differences may be present in the ability of the new neurons to be optimally integrated within the hippocampal circuitry.

Although the function of neurogenesis has been a subject of considerable debate, investigators have made some progress over recent years. Pharmacological reduction in the number of new surviving neurons does not influence spatial acquisition or short-term retention in the Morris water maze, but does negatively influence long-term retention (Snyder et al., 2005; Shors et al., 2001b). Newer genetic techniques to reduce neurogenesis in the dentate gyrus have shown that pattern separation for similar, but not distinct, patterns is severely hampered by a reduction in neurogenesis (Clelland et al., 2009) and that neurogenesis is important for proactive interference (Epp et al., 2016; Swan et al., 2014). Pattern separation is a process by which the brain processes patterns that are distinct or similar. Patterns that are similar are more difficult to process than ones that are distinctly different, and this process involves the dentate gyrus (see Fig. 2). In terms of possible sex differences, male rats exhibited more correct responses than female rats when spatial patterns were similar (i.e., when the choice between two arms of a radial arm maze were separated by no more than 45°) (Yagi et al., 2016). However, there was no sex difference when the spatial patterns were distinct (arms were separated by more than 90°). Furthermore, rats were identified as using a spatial or idiothetic (egocentric, i.e. learning to turn left rather than using spatial cues) strategy to solve the radial arm maze. The sex difference favouring males to correctly identify similar patterns was limited to spatial strategy users. In addition, male spatial strategy users displayed greater survival of new neurons in the dorsal dentate gyrus compared to all other groups. Despite these findings, it was the females, and not males, that showed a positive relationship between learning and neurogenesis. A greater number of new neurons in the ventral dentate gyrus was related to greater accuracy at separating similar patterns in females, but this relationship was not seen in males (Yagi et al., 2016). These findings collectively suggest that hippocampus-dependent learning and survival of new neurons in response to this training is greater in males compared to females. However, females may have better integration of these new neurons into the existing circuitry, as they show a positive relationship between activation or number of new neurons with performance, and this relationship is not always seen in males.

In the studies described above (Chow et al., 2013; Yagi et al., 2016), males outperformed females, but there are, of course, tasks in which the reverse is true. What happens when the relationship between neurogenesis and performance is examined in a task in which females outperform males? Christina Dalla and Tracy Shors found that female rats acquired trace conditioning in fewer trials than males and exhibited a greater training-induced increase in the density of new neurons in the dorsal dentate gyrus, despite training-induced increases in both sexes (Dalla et al., 2009). Furthermore, they found that the density of new neurons in the ventral granule cell layer was increased only in females and the density of new neurons in the ventral dentate gyrus was positively correlated to learning with a stronger correlation in the females compared to males (Dalla et al., 2009). Collectively, these findings suggest that females show a stronger relationship between the number or activation of new neurons with memory than do males. Furthermore, females do not always exhibit increases in absolute number of new neurons with learning, which is often seen in males (Table 2). These findings indicating that females show a stronger relationship between neurogenesis in the hippocampus and learning compared to males may prove important when determining what biological factors render women more vulnerable to cognitive decline in AD (Snyder et al., 2016).

4. Molecular mechanisms underlying the regulation of memory consolidation by estradiol and progesterone

As discussed above, sex differences have been reported in numerous aspects of learning and memory that are mediated, at least in part, by the hippocampus. This brain region has been of enormous interest for the study of sex differences in cognitive function because of its key role in the formation of many types of memories, including spatial, recognition, and contextual memories (Cohen et al., 2013; Kim et al.,

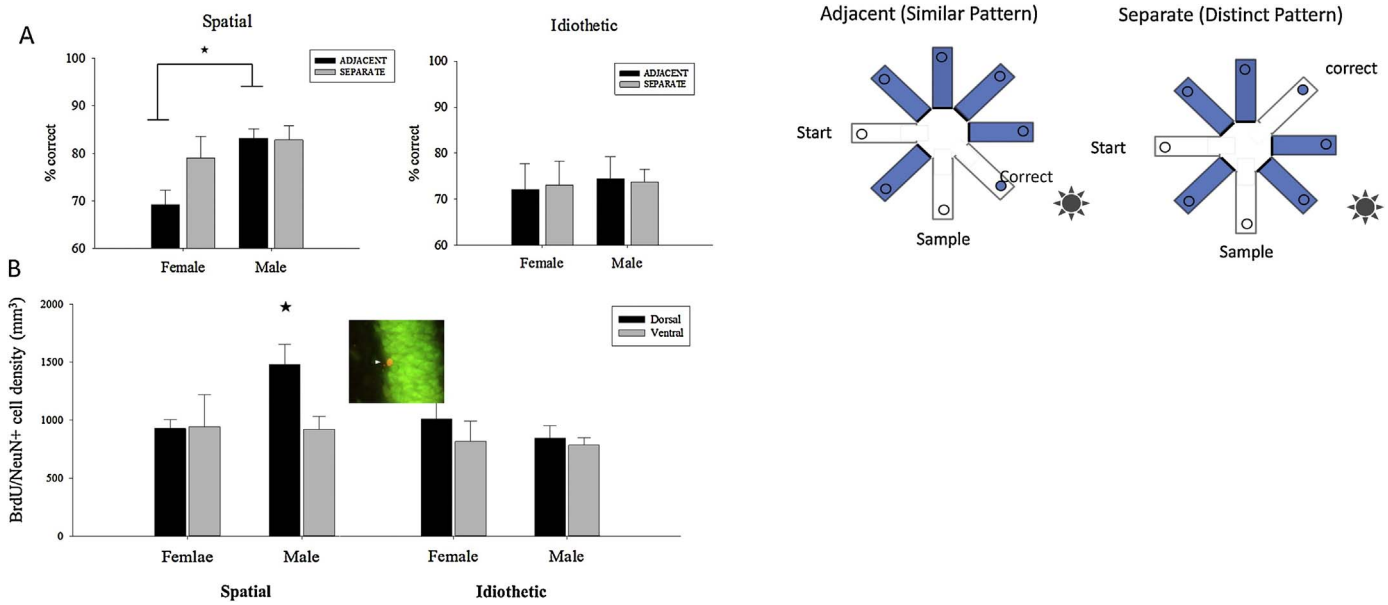

Fig. 2. Male and Female Sprague-Dawley adult rats were trained for 26 days on a delayed non-match to place version of the radial arm maze task with two patterns, with adjacent or separate arms as the correct choices. The sun symbol represents visual cues around the room (see C). A. Male spatial strategy users had a greater percentage of correct responses acquiring similar patters (adjacent arms) than all other groups. There were no sex differences in idiothetic strategy users or when acquiring distinct patterns (separate arms). B. Male strategy users had more new neurons in the dorsal dentate gyrus than all other groups. Asterisks indicates $p < 0.05$. Modified and reprinted with permission from Yagi et al. (2016).

Table 1
Effects of 17β-estradiol and estrogen receptor activation on object memory consolidation and cell-signaling in mice.

		17β-estradiol	ERα, ERβ	GPER
Females	Effect on object memory consolidation	Enhances memory in object recognition and object placement	Enhances memory in object recognition and object placement	Enhances memory in object recognition and object placement
	Cell-signaling pathways involved	PI3K/Akt, PKA, ERK, mTOR	PI3K/Akt, PKA, ERK, mTOR	JNK
	Other receptors involved	NMDA, mGluR1a	mGluR1a	Unknown
	Ages affected	Young and middle-aged, not aged	Young (older ages unknown)	Young (older ages unknown)
Males	Effect on object memory consolidation	Enhances memory in object recognition and object placement	Unknown	Unknown for object memory, but G-1 reduces anxiety in males, not females
	Cell-signaling pathways involved	Unknown, but not ERK	Unknown	Unknown
	Other receptors involved	Unknown	Unknown	Unknown
	Ages affected	Young (older ages unknown)	Unknown	Unknown

1993; Morris et al., 1982). As discussed above, males outperform females in many hippocampal-dependent tasks, including the Morris water maze, radial arm maze, and tests of spatial and object recognition (Jonasson, 2005; Frick and Gresack, 2003). Moreover, the rodent hippocampus is the site of myriad sex differences in such variables as dendritic morphology, synaptic plasticity, and neurogenesis (see (Koss and Frick, 2017) for recent review). For example, LTP in hippocampal CA1 is reportedly more difficult to elicit in female rats than in males (Yang et al., 2004), although this sex difference is influenced by the estrous cycle, such that LTP during the proestrus (high estradiol and progesterone) phase is enhanced relative to males and females in other phases (Good et al., 1999; Warren et al., 1995). In addition, the tetanus required to elicit this enhanced LTP in proestrus rats was considerably lower, because that used in males reliably elicited seizures (Warren et al., 1995). These latter findings suggest a substantial influence of circulating sex steroid hormones on sex differences that is also reflected in synaptic morphology, as CA1 dendritic spine density is also significantly higher in proestrus female rats than in males or females in diestrus (Shors et al., 2001a). Although sex differences in genetic or epigenetic background surely play a role in mediating hippocampal function, the vast majority of research examining sex differences in hippocampal memory has studied the role of hormonal milieu on memory formation, particularly levels of estrogens, progestins, and androgens.

Because the estrous cycle can impact variables such as dendritic spinogenesis and synaptic physiology, most studies have used gonadectomized subjects treated with exogenous hormone replacement. The lion's share of this work has focused on estrogens, particularly 17β-estradiol (estradiol), due to its ability to potently facilitate dendritic spinogenesis, LTP, neurogenesis, cell-signaling, and memory formation (see (Frick, 2015) for recent review). However, some work has focused on progestins and androgens as well (e.g., (Fortress et al., 2015; Leranth et al., 2003; Orr et al., 2012)). Within the context of gonadectomized subjects, the most common approach has been to examine the effects of exogenous hormone treatment on a single sex. Often, this is done with a specific goal in mind, e.g., to try to understand how estradiol regulates memory formation in females. Because estrogen receptor distribution within the hippocampus is largely similar in males and females, at least in the mouse (Mitterling et al., 2010; Waters et al., 2015), the underlying assumption has been that molecular mechanisms regulating memory formation in females will be similar to those in males. However, sex differences may exist at the cellular and molecular level that could have important functional consequences for memory formation in males and females. Thus, it is important to confirm findings from one sex (e.g., female) in the other sex (e.g., males).

This approach of focusing initially on a single sex has been undertaken by numerous laboratories, including that of Karyn Frick at the University of Wisconsin-Milwaukee. For the past several years, the Frick laboratory has endeavored to identify the molecular mechanisms in the hippocampus through which estradiol regulates memory consolidation in females. This work is motivated by sex differences in the risk of AD, which is substantially higher in women than in men (Launer et al., 1999; Zandi et al., 2002). As will be discussed below, estradiol serves a critically important neuroprotective function in the brain, and the loss of this hormone during menopause is thought to render neurons in regions like the hippocampus more vulnerable to Alzheimer's pathology. Nevertheless, hormone replacement has proven largely ineffective as a means of enhancing cognition in post-menopausal women (Espeland et al., in press; McCarrey and Resnick, 2015; Resnick et al., 2009), despite considerable basic research illustrating the memory-enhancing effects of estradiol. To address the apparent disconnect between the basic and clinical literatures, the Frick laboratory has sought to determine how estradiol regulates memory in females in hopes of finding new targets for future drug development that could mimic the beneficial effects of estradiol on memory formation (Frick et al., 2010). Because this work has historically focused on females, progress in females will be reviewed below (see also Table 1). However, new data illustrating sex differences in estrogen receptor utilization by the male and female hippocampus (Oberlander and Woolley, 2016) has laid the groundwork for future investigations in males.

4.1. Estrogenic regulation of one-trial object learning

Numerous studies from the Frick laboratory and others have demonstrated that systemic injection or dorsal hippocampal infusion of estradiol given immediately after training (i.e., post-training) enhances the consolidation of spatial and object recognition memories in ovariectomized mice and rats (see (Tuscher et al., 2015) for recent review). This work has largely used one-trial object learning tasks in which subjects investigate a pair of identical objects for a certain amount of time and then their memory of the object's identity (recognition memory) or location (spatial memory) is assessed anywhere from 1 to 48 h later. In these experiments, the effects of estradiol on memory consolidation have been tested via administration immediately after the initial investigation phase (i.e., training) in order to isolate estradiol's effects on consolidation in the absence of potential confounds resulting from its presence during acquisition. Over two dozen studies from various labs report that post-training administration of estradiol to ovariectomized rats or mice immediately after training enhances memory consolidation in both the object recognition and object location (a.k.a., object placement) tasks (e.g., (Boulware et al., 2013; Inagaki et al., 2010; Kim et al., 2016; Luine et al., 2003; Pereira et al., 2014; Walf et al., 2006); see (Tuscher et al., 2015) for review). Similar effects are observed after systemic injection, dorsal hippocampal infusion, or dorsal third ventricle infusion (Tuscher et al., 2015). Estradiol administration delayed 1–4 h after training does not facilitate memory consolidation (Fernandez et al., 2006; Frye et al., 2007; Walf et al., 2006), indicating that the effects of estradiol on memory occur

Table 2
Sex differences in social, spatial and object-recognition learning.

	Behavior	Neural Regions	Hormonal or sexually different mechanisms
Aggression	M > (overt) F > = (non-overt)	M = F hypothalamus	F, VMH ERα inhibits M, VMH ERα enhances F, hypothalamic 5-HT1a M, hypothalamic AVP
Social Recognition		M, lateral septum M = F, Medial Amygdala M = F hippocampus	M = F ERα, less ERβ F, GPER; M? M, Testosterone-AVP F = M, estrogen-OT
Social Learning	F >	M, Hippocampus; F?	F, GPER, ERβ < βρ > M > F D1R hippocampus
		F, basolateral amygdala; M?	F, D2R hippocampus, not in M
		M, frontal cortex; F?	
Spatial Learning/Pattern Separation	M > spatial acquisition	M > hippocampal neurogenesis	Weakly related to androgens in M Lower E2 improves spatial acquisition in F ERα impairs spatial acquisition in F
	M > pattern separation of similar patterns M = F distinct patterns M = F spatial memory	M > hippocampal neurogenesis when spatial strategy user M = F neurogenesis when idiothetic strategy user	E2 does not modulate performance in F
	F > trace conditioning	F > neurogenesis in dorsal hippocampus	High E2 enhances trace eyeblink conditioning in F
Spatial Recognition	M >	F, dorsal hippocampus M?	F, ERα, ERβ, GPER M?
Object Recognition	M >	F, dorsal hippocampus; M? M, perirhinal cortex, F?	F, ERα, GPER M?

relatively quickly after training. Interestingly, similar memory-enhancing effects of progesterone are observed if administered immediately after training to ovariectomized rats and mice (Fortress et al., 2015; Frye et al., 2007; Orr et al., 2012; Walf et al., 2006). As well, systemic co-administration of estradiol plus progesterone enhances memory in object recognition and object placement tasks in ovariectomized mice and rats (Frye et al., 2007; Harburger et al., 2009; Walf et al., 2006). Thus, post-training treatment with either hormone appears capable of enhancing memory formation, whether given alone or in combination.

4.2. Cell-signaling mechanisms regulating estrogen-induced memory consolidation

The rapid nature of memory formation in one-trial object learning tasks affords the opportunity to discern the molecular mechanisms that govern hormonal regulation of memory consolidation. Much attention has focused on the involvement of cell-signaling pathways in the neural and mnemonic effects of estradiol because cell signaling can be triggered within minutes of estradiol treatment. For example, estradiol can activate the extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways in various cell types, including hippocampal neurons, within 5–10 min (Mannella and Brinton, 2006; Wade and Dorsa, 2003; Wade et al., 2001; Watters et al., 1997; Yokomaku et al., 2003). In hippocampal slices from gonadally-intact male rats, CA1 dendritic spine density is increased and LTP is enhanced by estradiol and androgens in a manner dependent on activation of ERK, protein kinase A (PKA), protein kinase C (PKC), LIM kinase (LIMK), and calcium-calmodulin kinase II (CaMKII) (Hasegawa et al., 2015; Hatanaka et al., 2014; Mukai et al., 2007; Ooishi et al., 2012). In hippocampal slices from both male and female rats, the estradiol-induced increase in dendritic spines is also dependent on activation of the RhoA–RhoA kinase (ROCK)-LIMK-cofilin signaling pathway (Kramár et al., 2009). More recently, the ability of estradiol to increase dendritic spines in the CA1 and prefrontal cortex of ovariectomized mice was shown to depend on activation of ERK and the downstream protein translation pathway mammalian target of rapamycin (mTOR) (Tuscher et al., 2016). As such, the regulation of hippocampal dendritic morphology appears to be dictated by rapid effects of estradiol on cell-signaling pathways. The resulting implications for memory are clear: if activation of cell signaling is necessary for estradiol to increase dendritic spinogenesis, then it is also likely necessary for estradiol to facilitate memory formation.

Indeed, most of the cell-signaling pathways involved in estradiol's effects on hippocampal morphology and physiology are also critical for estradiol to enhance memory consolidation in female mice. In a series of studies using ovariectomized mice as subjects, the Frick laboratory has shown that activation of NMDA receptors, and PKA, PI3K, ERK, and mTOR signaling in the dorsal hippocampus is necessary for estradiol to enhance memory in the object recognition and object placement tasks (Table 1; Boulware et al., 2013; Fernandez et al., 2008; Fortress et al., 2013; Lewis et al., 2008). Rapid phosphorylation of ERK is particularly key; inhibition of PKA or PI3K prevents estradiol from phosphorylating ERK, and inhibition of ERK prevents estradiol from phosphorylating mTOR signaling proteins (Fernandez et al., 2008; Fortress et al., 2013; Lewis et al., 2008). Interestingly, the beneficial effects of post-training progesterone infusion on object recognition in ovariectomized mice are also dependent on ERK and mTOR phosphorylation (Fortress et al., 2015; Orr et al., 2012), suggesting some commonality in the mechanisms underlying the effects of these two sex hormones. As mentioned above, the ability of estradiol to increase CA1 dendritic spine density is dependent on phosphorylation of ERK or mTOR in the dorsal hippocampus (Tuscher et al., 2016), tying the rapid effects of estradiol on ERK-driven cell signaling to its facilitation of spinogenesis and memory consolidation. ERK phosphorylation is also necessary for estradiol to facilitate histone acetylation, an epigenetic process that is essential for estradiol to enhance object recognition memory formation in ovariectomized mice (Zhao et al., 2010). Relevant to menopause, estradiol can rapidly phosphorylate ERK in the dorsal hippocampus of young and middle-aged ovariectomized mice, but not in aged ovariectomized mice (Fan et al., 2010; Fernandez et al., 2008). Similarly, post-training estradiol infusion into the dorsal hippocampus can enhance object recognition memory consolidation in young and middle-aged mice, but not in aged mice (Table 1; Fan et al., 2010; Fernandez et al., 2008). Although it is unclear why the aged brain loses its responsiveness to a single treatment of estradiol, this effect is likely due to age-related alterations in estrogen receptor distribution and expression (Adams et al.,

2002; Waters et al., 2011; Zhang et al., 2011). However, in support of the continued responsiveness of middle-aged females, dorsal hippocampal infusion of estradiol induces similar increases in dorsal hippocampal histone acetylation in young and middle-aged ovariectomized mice (Fortress et al., 2014). Collectively, these data suggest that ERK-mediated cell signaling is necessary for estradiol to rapidly enhance memory consolidation in young and middle-aged females, but that responsiveness to acute treatment with estradiol is lost in the aged female brain.

Numerous studies have also examined the receptors through which estradiol triggers cell signaling. Much of this work has focused on the intracellular receptors ERα and ERβ, and the membrane receptor GPER. Similar to estradiol, dorsal hippocampal infusion of ERα or ERβ agonists enhance object recognition and object placement memory consolidation in ovariectomized mice in a manner dependent on activation of ERK in the dorsal hippocampus (Boulware et al., 2013). Interestingly, this same study found that the ability of estradiol and agonists of ERα and ERβ to enhance memory and increase dorsal hippocampal ERK phosphorylation is dependent on activation of metabotropic glutamate receptor 1a (mGluR1a) in the dorsal hippocampus (Boulware et al., 2013). This finding suggests that ERα and ERβ interact with mGluR1a at the membrane to facilitate the effects of estradiol on ERK phosphorylation and subsequent memory consolidation (Table 1). Indeed, membrane fractionation and co-immunoprecipitation data indicate the direct interaction among mGluR1, ERα, and ERβ at the cell membrane (Boulware et al., 2013), supporting the conclusion that cooperation among intracellular ERs and this specific glutamate receptor at the membrane is essential for estrogenic regulation of memory consolidation in females.

However, not all ERs appear to regulate memory via ERK signaling. Although GPER activation in ovariectomized mice robustly enhances memory consolidation in the object recognition and object placement tasks, ERK phosphorylation is not required (Kim et al., 2016). Indeed, dorsal hippocampal infusion of a GPER agonist (G-1) that enhances memory in females does not increase dorsal hippocampal ERK phosphorylation (Kim et al., 2016). Rather, G-1 increases phosphorylation of c-Jun N-terminal kinase (JNK; Table 1), a mitogen activated protein kinase that activates a somewhat distinct set of transcription factors from ERK (Kim et al., 2016). Interestingly, dorsal hippocampal infusion of estradiol does not activate JNK in the dorsal hippocampus of ovariectomized mice, nor does inhibition of JNK phosphorylation or GPER activation prevent estradiol from enhancing object recognition and object placement memory consolidation (Kim et al., 2016). Thus, the beneficial effects of estradiol on object and spatial memory appear to be independent of GPER and JNK. The lack of effect of G-1 on ERK contradicts other findings from ovariectomized mice indicating that systemic or bath-applied G-1 increases dorsal hippocampal ERK phosphorylation (Hart et al., 2014; Kumar et al., 2015). It is difficult to reconcile these findings at this point because the methods of administering estradiol differed across studies, and so more work is needed to resolve this issue. Interestingly, one of these studies found that systemic G-1 had no effect on ERK in gonadectomized male mice (Hart et al., 2014), suggesting the possibility of sex differences in the biochemical and behavioral response to estradiol.

4.3. Sex differences in molecular mechanisms underlying estrogenic memory modulation

Indeed, such sex differences in response to estradiol have been documented in recent years. For example, in hippocampal cultures from neonatal rats, estradiol interacts with mGluR1a to increase the phosphorylation of the transcription factor cyclic AMP response element binding protein (CREB) in females, but not in males (Boulware et al., 2005). Other studies report differential effects of ERα on memory in male and female mice. In the aforementioned study reporting that G-1 increases ERK phosphorylation in female, but not male, mice, G-1 reduced anxiety in males, but not females (Hart et al., 2014). One recent study suggests that differential effects of estradiol on cell signaling and behavior might result from sex differences in the actions of estrogen receptors. This study examined estrogenic potentiation of glutamate release in the hippocampus of male and female rats. In females, ERβ acted presynaptically to increase the probability of glutamate release, whereas GPER acted postsynaptically to increase glutamate sensitivity (Oberlander and Woolley, 2016). In males, ERα mediated presynaptic glutamate release probability, whereas ERβ regulated postsynaptic glutamate sensitivity (Oberlander and Woolley, 2016). Given this evidence that males and females use different ERs in different parts of the synapse to influence neurotransmitter release, it is possible that the cellular and molecular mechanisms through which estradiol regulates memory differ between the sexes. Preliminary data from the Frick laboratory suggest this may be true, at least in mice. For example, we have found that a post-training dorsal hippocampal infusion of estradiol enhances object recognition and object placement memory consolidation in gonadectomized and gonadally-intact male mice, as it does in ovariectomized mice (Koss and Frick, 2016) (Table 1). However, unlike in females, estradiol infusion does not increase ERK phosphorylation in males (Koss and Frick, 2016), nor does inhibiting ERK phosphorylation prevent estradiol from enhancing memory consolidation in males (), suggesting that estradiol may trigger different cell-signaling pathways to enhance memory in males and females (Table 1). Although the identity of these pathways is not yet known, this is an active area of investigation. Although the scant data cited in this paragraph suggest the intriguing possibility of sex differences in the molecular mechanisms through which estrogens regulate memory formation, considerably more study is needed to definitively support this conclusion.

5. Sex differences in stroke and stroke therapies

Stroke is a cerebrovascular disease caused by interruption of the blood supply to the brain, resulting in rapid death of neurons and, consequently, a range of neurological problems including loss of sensory or motor function, paralysis, depression, dementia, epilepsy, and even death. Stroke is the 5th leading cause of death and leading cause of disability in the United States (Mozaffarian et al., 2015). A principal variable affecting stroke incidence in aging is the biological sex of the patient. Women are more likely to get a stroke (Petrea et al., 2009), to display more non-classical stroke symptoms, and to have worse stroke outcomes (summarized in Table 3). In fact, the rates of stroke-related death have declined over the last 25 years for men but not for women (Silva et al., 2010). A Canadian stroke registry study reported that 10% of women stroke patients were discharged to long-term care as compared to 5% of men (Kapral et al., 2005). Furthermore, because women live longer than men, it is projected that stroke-related disability and institutionalization is likely to affect women more than men (Lai et al., 2005). Although not studied systematically, existing data on preclinical and transitional therapies suggests that there may be sex-specific effects of stroke neuroprotectants and therapies.

5.1. Sex differences in treatment efficacy in clinical studies

Tissue plasminogen activator (tPA; Alteplase) is the only FDA-approved therapy for stroke, and its mode of action consists of proteolytic degradation of the clot, with the goal of re-establishing circulation, known as recanalization. In a study spanning over a decade (1997–2006), men were more likely than women to receive intravenous (IV) tPA, angioplasty/stents, carotid endarterectomy, or cardiac reperfusion. However, towards the end of the study period, sex differences in the use of IV tPA were eliminated (Towfighi et al., 2013), which suggests that greater overall tPA use and an emphasis on early time-to-treatment may decrease sex differences in acute stroke care. Nevertheless, sex-biased therapy persists, as shown in a recent study

Table 3
Sex differences in stroke risk and therapies.

Risk for stroke	Until 45	M > F
	45–54	M = F
	80+	F > M
Severity of stroke	Mortality	F > M
	Longer hospitalization	F > M
	Transfer to assisted living facility	F > M
Preclinical evidence Stroke severity (infarct volume)	Young Aged	M > F F > M
Effect of hormone treatment On females	Estrogen	Decreases infarct volume in young males and females
Cell death pathways	Caspase dependent	Effective target in Females
	Caspase-independent	Effective target in Males
Stroke therapies (Clinical)		
Current FDA approved therapy	tPA effectiveness	M = F
	Likelihood of receiving tPA	M > F
Failed trials	Effectiveness of Tirilazad mesylate	M > F
	Effectiveness of Lazaroids	M > F
Current therapies:	Minocycline	
	Preclinical (effectiveness)	M > F
	Clinical	M > F
Preclinical therapies	PARP inhibitors	Only in males
	Caspase inhibitors	Only in females
	NO deletion/ inhibition	Effective in males, deleterious in females
	microRNA-Let7f	Effective in young females, not in young males, deleterious in middle aged females
	microRNA-363-3p	Effective in females not males

where women were more likely to be excluded from tPA for hypertension as compared to men, suggesting that under-treatment of stroke risk factors in women may further impact stroke therapies as well (Madsen et al., 2015). This disparity is unfortunate, as analyses of data from multiple clinical studies of tPA (ATLANTIS, ECASS II, and CASES) and recombinant prourokinase (r-proUK; Prolyse) (PROACT-2 study) show that thrombolytic therapy has increased therapeutic efficacy in women compared to men (Kent et al., 2005; Kent et al., 2008) (Hill et al., 2006) (Shobha et al., 2010).

Although several drugs have been identified in preclinical studies, only a few of these have made it to clinical trials and none have succeeded (Chacon et al., 2008). These include trials for the free radical scavenger NXY-059 (SAINT I and SAINT II), the lipid peroxidation inhibitor tirilazad mesylate (RANTTAS), and the calcium channel blocker verapamil co-administered with the angiotensin-converting enzyme inhibitor trandolapril (INVEST). Whereas several reasons may explain why the preclinical promise of these drugs was not borne out in clinical trials, in at least one case (tirilazad mesylate), European trials showed the outcomes were much worse in women as compared to men (Tirilizad Steering Committee, 2000). Preclinical studies with these drugs routinely failed to use clinically-relevant animal models, such as aged subjects, or include females and those with comorbid diseases (van der Worp et al., 2005). These and other studies provided the impetus for the STAIR recommendations, which specifically recommends the use of clinically-relevant animal models in studies of stroke (Fisher et al., 2009)

5.2. Sex differences in treatment efficacy in preclinical studies

Sex differences in stroke outcome are also well recognized in preclinical models (summarized in Table 3). Specifically, young females (rats and mice) have a smaller infarct volume and better cerebral blood flow than age-matched males both in normoglycemic (Alkayed et al., 1998) and diabetic (Toung et al., 2000) animals. Although young females sustain a smaller infarct than young males or aged female mice or rats (Selvamani et al., 2014), aging reverses this sex differences, such that aged females show poorer stroke outcomes and significantly more mortality compared to older males (Manwani et al., 2011). In fact, these age effects may be accelerated in females, such that middle aged female rats show worse stroke outcomes than adult female rats, whereas adult and middle-aged males do not differ (Selvamani and Sohrabji, 2010).

This evidence prompted the idea that ovarian estrogens improve stroke outcomes, which is supported by a large number of studies showing that 17β-estradiol, the inactive stereoisomer 17-α estradiol (Simpkins et al., 1997), or conjugated equine estrogens (McCullough et al., 2001) reduce infarct volume in ovariectomized rodents. In contrast, gonadectomy in males reduces infarct volume, suggesting that testosterone, the precursor steroid for estradiol, may be neurotoxic (Yang et al., 2002). Surprisingly, estradiol treatment reduces infarct volume in both younger males and females (Toung et al., 2000). Thus, while availability of estrogens is likely the reason for sex differences in infarct severity in young animals, estradiol treatment is protective for both sexes at this age. Similarly, the peptide hormone, insulin-like growth factor (IGF)-1, is also neuroprotective in both males and older females. These are among the handful of preclinical factors that have been studied in both sexes, where a similar outcome has been observed. In many other instances, studies have shown unexpected sex differences in outcome.

Stroke-related cell death and recovery is multi-factorial, and preclinical studies have, therefore, focused on cell death modulators, immune modulators, and compounds that facilitate recovery through neurogenesis and angiogenesis. The following paragraphs will describe sex differences that have been reported for stroke outcomes using compounds that modulate the inflammatory response and cell death pathways.

5.2.1. Sex differences in anti-inflammatory therapy

Minocycline, a tetracycline antibiotic, represents an excellent example of sex differences in the effects of anti-inflammatory therapy. Minocycline is known to cross the blood–brain barrier, and once in the brain, can attenuate neuronal apoptosis, reduce the inflammation response by reducing microglial activation and migration of T-cells, and inhibit matrix metalloproteinase-9, which remodels extracellular matrix (Yrjanheikki et al., 1999; Machado et al., 2006; Goldstein, 2008; Machado et al., 2009; Matsukawa et al., 2009; Fagan et al., 2011; Switzer et al., 2011; Switzer et al., 2012; Yang et al., 2015). In experimental models of acute ischemic stroke, minocycline shows neuroprotective effects and improved behavioral outcomes in young adult males (Yrjanheikki et al., 1999; Alano et al., 2006; Li and McCullough, 2009). However, in studies where both male and female mice were included, Li and McCullough reported that minocycline is effective in reducing infarct volume only in male mice. Furthermore, minocycline was also ineffective in ovariectomized female mice, even though male and ovariectomized female mice presented similar levels of estrogens (Table 3) (Li and McCullough, 2009).

This paradox was also noted in the clinical literature. Early clinical trials for minocycline showed improved outcomes in the treatment group (Lampl et al., 2007; Padma Srivastava et al., 2012). However, a study by Kohler and colleagues showed that intravenous minocycline treatment given to stroke patients was safe but not efficacious (Kohler et al., 2013). More recently, an open-label evaluator-blinded trial found that oral minocycline (200 mg daily for 5 days) was effective when male and female data were compiled together (Amiri-Nikpour et al.,

2015). However, when the data were analyzed separately for males and females, male patients showed significantly lower (improved) NIH stroke scale (NIHSS) in the minocycline-treated group compared with controls, whereas no significant clinical improvement was seen in female patients relative to control groups (Amiri-Nikpour et al., 2015). This study, along with Li and McCullough's preclinical study, makes a strong case for including both sexes in studies of stroke treatments, and for factoring sex-specific and age-specific analyses into both sample size and statistical analysis.

5.2.2. Sex differences in cell-death pathways

Emerging data suggest that cell-death pathways in ischemic stroke are sexually dimorphic (Reeves et al., 2008; Yuan et al., 2009; Liu et al., 2011; Gibson, 2013). Cell death can result from activation of caspase-dependent and caspase-independent pathways. Studies show that females are more susceptible to caspase-dependent cell death, whereas males are more susceptible to caspase-independent cell death. As a result, compounds that target only one of these pathways display profound sex differences in their efficacy (summarized in Table 3). These pathways are discussed briefly below.

Poly (ADP-ribose) polymerase-1 (PARP-1): Poly (ADP-ribose) polymerase-1 (PARP-1) activation is a major cytotoxic pathway and plays a key role in the pathogenesis of cardiovascular and inflammatory diseases (Beneke, 2008; Peng et al., 2012; Song et al., 2013; Sun et al., 2015). In the previously discussed study (Li and McCullough, 2009), Li et al. additionally reported that minocycline does not impact ischemic injuries in PARP-1 null male mice, indicating that the sexually dimorphic neuroprotective effects may be attributed to PARP-1 inhibition in male mice, whereas the pathway is not affected in females (Hagberg et al., 2004; Mabley et al., 2005; McCullough et al., 2005; Lang and McCullough, 2008; Li and McCullough, 2009; Liu et al., 2011). Downstream pathways of PARP including apoptosis inducing factor (AIF), and poly (ADP-ribose) polymerase (PAR) polymers also mediate cell death after ischemic insult only in males (Yuan et al., 2009). However, a novel water-soluble PARP-1 inhibitor, MP-124, was shown to ameliorate stroke-induced neurological deficits and brain infarct volume in both male and female monkeys (Matsuura et al., 2011), suggesting that species-specific effects may also intersect with sex differences in cell death pathways.

Nitric oxide (NO): Nitric oxide (NO) is synthesized via nitric oxide synthase (NOS) in several cell types in the brain including endothelial cells (eNOS) and neurons (nNOS). Stimulation of nNOS after stroke induces cell death via activation of PARP pathways (Stagliano et al., 1997; Nemoto, 2000; Zhang et al., 2013). Preclinical studies show that reducing nNOS via targeted deletion or by pharmacological inhibitors reduces ischemia-induced cell death (Yoshida et al., 1994; Huang et al., 1994). However, these studies were performed only on young adult? male animals and more recent work, where both sexes were included, confirmed that nNOS deletion/inhibition reduced cell death in males, whereas the same treatment was, paradoxically, deleterious for females (McCullough et al., 2005; Yuan et al., 2009). Female nNOS null mice exhibit a worse outcome after middle cerebral artery occlusion (MCAO) relative to wild-type females, whereas the absence of nNOS in male null littermates produces a better outcome compared to wild-type males, suggesting that neurotoxicity of NO production is restricted to males. Sex steroids may also play a role in the effects of NO. Estradiol, present in both males and females, promotes protection of endothelial function and vascular reactivity (dilation) by enhancing endothelial (e)NOS functionality and NO production, and manipulating endothelium-derived hyperpolarizing factor (EDHF) effectivity. However, testosterone has opposing effects, increasing cerebrovascular inflammation and cerebral artery tone (Krause et al., 2006; Haast et al., 2012). These findings confirm the hypothesis that ischemia induced cell death is more reliant on the NO-PARP pathway in males, whereas the NO pathway may play a beneficial role in females.

Caspases: Although caspase pathways are activated in both sexes after stroke, caspase-dependent cell death pathways are more amenable to treatment in females as compared to males (Siegel et al., 2010; Gibson and Attwood, 2016). Caspase-dependent cell death can be initiated by extrinsic (death receptor mediated) or intrinsic (mitochondria mediated) factors. In the case of ischemia, formation of reactive oxygen species stimulate the release of mitochondrial cytochrome-c to the cytosol. Subsequent formation of the apoptosome, which includes the apoptotic protease activating factor (Apaf)-1, cytochrome c and caspase-9, cleaves procaspase to caspase-3, an executioner caspase. Caspase-3 then cleaves cellular substrates that induce biochemical features of apoptosis, including DNA fragmentation (Cai et al., 1998). In ischemic studies, the pan-caspase inhibitor, quinoline-Val-Asp(Ome)-CH2-O-phenoxy (Q-VD-OPh), shows neuroprotective effects in both neonatal and adult female mice when administered after stroke, but has no effects in males (Renolleau et al., 2007; Liu et al., 2009). Interestingly, pan caspase inhibitors are effective in females that are gonadally intact or ovariectomized (Liu et al., 2011), suggesting that, although this pathway is sexually dimorphic, it's actions may be independent of gonadal steroids.

5.2.3. Sex differences in epigenetic modifiers

A new class of stroke therapies comes from epigenetic regulators, including histone modifiers and non-coding RNA. Compounds that promote histone acetylation, such as HDAC inhibitors, reduce stroke-associated disability in males and females (Langley et al., 2009; Kassis et al., 2016; Park and Sohrabji, 2016). Non-coding RNA, including long non-coding RNA (lnc), microRNA (miRNA), and PIWI-interacting (pi) RNA have been intensely investigated as options for stroke therapy. Of these, miRNAs have been most comprehensively studied. MicroRNAs (miRNAs) are 18–25 nucleotide-long, non-coding RNA molecules that are regulators of mRNA transcript stability (Denli and Hannon, 2003) and translation (Ambros, 2001), and serve as translational repressors. MiRNAs are predicted to control tissue- and cell-specific transcriptomes (Krek et al., 2005; Lim et al., 2005) and to regulate critical biological processes including mitosis, stem cell differentiation, tumorogenesis, and cell death (Croce and Calin, 2005). MiRNA may also perform RNA surveillance and, thus, influence life span and longevity (Montano and Long, 2011).

MiRNA cohorts can change rapidly after acute injury such as stroke, and are actively being studied for their possible role as stroke biomarkers. Particular miRNA species are specific to pathogenic processes, such as miR155 which is associated with hypertension, miR33 with hyperlipidemia, and miR21 and −126 with atherosclerosis (reviewed in (Rink and Khanna, 2011)). MiRNA profiles are altered with stroke, both in humans (Liu da et al., 2016) and in experimental stroke models (Jeyaseelan et al., 2008; Dharap et al., 2009). Plasma levels of miR17 are reported to be significantly elevated in acute stroke patients (Kim et al., 2015), whereas miR-210 levels are lowered in ischemic stroke patients as compared to controls, although stroke outcomes are better in patients where miR-210 levels are higher (Zeng et al., 2011).

MiRNAs have also been shown to mediate neuroprotection in stroke models. Specifically, inhibitors of Let7f, mir-1 (Selvamani et al., 2012), miR200c (Stary et al., 2015) and mir181 (Xu et al., 2015) reduce ischemic injury and improve behavioral function. Most miRNAs have only been studied in one sex (typically male), but in a few instances where both sexes were studied, unexpected differences were noted in efficacy of these compounds, as discussed below.

Let7f: First discovered in *C. elegans* and among the earliest identified non-coding RNAs, Let7f has now been identified in several species including vertebrates and several cell types (Ambros, 2001). Let7f has regulatory roles in a wide variety of gene families, including oncogenes, genes related to cell cycle and differentiation, apoptosis, and immunity. Among the genes targeted by Let7f for translational suppression is IGF-1, a potent stroke neuroprotectant in males and females (reviewed in Sohrabji, 2015). Antagonists to Let7f decreased infarct volume in adult females, and improved post-stroke behavioral impairment (Selvamani

et al., 2012). Paradoxically, anti-Let7f elevated stroke-related disability in middle-aged females and had no effect on ovariectomized females or males (Selvamani et al., 2012). Although the precise explanation underlying the age- and sex-dependent effects of this miRNA are not known, one cautionary note is that each miRNA regulates dozens of genes; some of these genes may have benign effects and others less so. Thus, elevated levels of this miRNA during age may not only suppress translation of IGF-1, but also suppress other genes that may exacerbate stroke disability.

Mir363-3p: Mir363-3p was identified as a potential neuroprotectant based on a comprehensive profiling of serum miRNA. This approach capitalized on the well-known age and sex differences in seen in experimental stroke studies, where adult females typically sustain the smallest infarction compared to age-matched males and middle-aged males and females (Selvamani et al., 2014). Mir363-3p expression was found to be inversely correlated with infarct volume (Selvamani et al., 2014; Selvamani and Sohrabji, 2016), such that it was highly expressed in adult female animals as compared to age-matched males and middle-aged males and females. To assess the functional significance of elevated mir363-3p, adult females were injected with mir363-3p antagonists after stroke. This treatment resulted in increased stroke-induced infarction in a group that typically has small stroke-induced infarction, and increased motor disability as compared to controls that received a scrambled oligo. Reciprocally, middle-aged females were injected with mir363-3p mimics, and this treatment reduced stroke-related infarction and motor disability. Remarkably, although males at both ages had lower levels of mir363-3p, intravenous injections of the mimic did not affect stroke outcomes in either group. A well-validated target of mir363-3p is caspase-3, a cell death effector protein, and in females, the mir363-3p mimic effectively decreased caspase-3 expression and activity, whereas no regulation of this protein was seen in males (Selvamani and Sohrabji, 2016). This finding is consistent with evidence from other caspase-inhibiting compounds (see above) that have also failed to show neuroprotection in males.

Although the molecular mechanisms that make caspase-3 more tractable for stroke in females but not in males are not clearly understood, it should be recognized that estradiol and testosterone have very different effects on caspase-3-mediated cell death. Estradiol reduces caspase-3, however, estradiol treatment also improves stroke outcomes in males where caspase-independent cell death pathways are more critical, suggesting that caspase-mediated cell death is only one of the many ways in which this hormone promotes stroke recovery (Suzuki et al., 2009). In contrast, testosterone exacerbates stroke-induced cell death, and has increases caspase-mediated cell death in a cell-specific manner (Cunningham et al., 2009). The sex difference in caspase-dependent cell death pathways underscores the importance of studying both sexes while new therapies are devised for acute neural diseases.

5.3. Summary

The relatively scarce use of both sexes in preclinical stroke therapy studies may be a critical factor in the lack of success in translating preclinical work to clinical practice. Even though aged women have a higher risk for stroke, worse outcomes, and poorer recovery after ischemia compared to aged men, preclinical studies have routinely failed to utilize clinically relevant animal models (e.g. aged female model) and ignore sexual dimorphisms in underlying mechanisms. Consequently, clinical trials, where inclusion of both sexes is required by law, may fail to include adequate sample sizes for sex-based statistical analysis, resulting in a situation where a drug is deemed a failure, when in fact it might have been effective for one sex, as in the case of 'lazaroids' stroke trial (reviewed in Cahill and Hall, 2017).

6. Conclusions and outlook

Sex differences in morphology, physiology, and behavior are common across the animal kingdom, and are driven and maintained by evolutionary processes that lead to the existence of different proximal mechanisms that govern phenotype in males and females. The prevalence of diverse types of sex differences across multiple species has profound implications for the ways in which researchers must approach behavioral, neurobiological, and biomedical investigations. We have presented here a review of studies in different areas of behavioral neuroscience illustrating sex differences in multiple aspects of behavior, including the ways in which animals relate to conspecifics and learn about their environment, as well as the underlying neurobiological underpinnings of these behaviors. Importantly, this review highlights a critical implication of these sex differences, namely that they form the foundation for sex differences in the risk, severity, and presentation of disease, thus precipitating the need for sex-specific treatments that address the disease as it presents uniquely in each sex. This situation is exemplified by stroke, where sex differences in risk and symptomology lead to sex biases in treatment and disparate efficacies of many stroke treatments in men and women. The literature reviewed here also demonstrates that sex hormones play an important role in the determination and modulation of sex differences. For example, the incidence of Parkinson's disease (PD), which is also an inflammatory disease, is greater in males than females (Wooten et al., 2004). This male bias is attributed, in part, to the protective role played by estrogens in females and also to the toxic effects of testosterone. Both hypotheses receive some support from evidence that oophorectomized females (surgical menopause) have a high incidence of PD that is equal to men (Benedetti et al., 2001; Rocca et al., 2008), and castrated (no gonadal testosterone) male rats have better outcomes after experimental induction of PD as compared to intact males (Murray et al., 2003). In fact, testosterone has also been implicated as a risk factor for developmental neurological disease, due to a higher basal neuroinflammatory state caused by androgen from the fetal testes (McCarthy, 2016).

Collectively, sex differences in basic and clinical research have led to federal policy changes in the United States (at the National Institutes of Health), Canada (at the Canadian Institutes of Health Research) and Europe (the Horizon 2020 initiative) that require sex be considered as a biological variable in biomedical research. In the United States and Canada, it is not required that every proposal include both males and females, but the exclusion of one sex must be scientifically justified in each application (Clayton, 2016). The purpose of this, and related policies, is to rectify the long-standing under-representation of females in biomedical research. Such policies have been challenged on practical grounds, as it has been argued that the inclusion of both sexes increases the cost and scope of research, thereby wasting precious research resources and time (e.g., Eliot and Richardson, 2016). These practical arguments have some merit, particularly because grant budgets have not been adjusted upwards to accommodate additional subjects of the opposite sex. Theoretical arguments against the policies suggest that sex differences in the human brain are rather minimal and pale in comparison to other differences such as species, age, or genetic variation (Joel et al., 2015; Eliot and Richardson, 2016). This view suggests that sex as a variable does not deserve special consideration over other variables that could affect biological function, particularly in preclinical research (Eliot and Richardson, 2016). A cogent counterargument for considering sex as a biological variable in preclinical research is that the purpose of this work is to understand how biological systems function, and examining function in both sexes is paramount in light of the many sex differences that have already been identified (Shansky and Woolley, 2016). Moreover, the paucity of research directly examining sex differences warrants special consideration of sex in biomedical research, especially in light of the fact that sex has been long neglected as a variable in biomedical research (Beery and Zucker, 2011; Shansky and Woolley, 2016). We agree with the perspective that findings discovered in one sex cannot be automatically extrapolated to the other sex and support the view that key results obtained in one sex should be verified in the other. When sex differences are demonstrated

or suspected (e.g., on the basis of the natural history of the species), their genetic and/or hormonal bases should be investigated. These studies should be conducted with sufficient statistical power to allow for the effective inclusions of biological sex, hormonal condition (e.g., estrous cycle), and/or hormone manipulation in statistical models. For additional discussion and practical recommendations on this subject we refer the reader to recent reviews (Galea et al., 2016; Joel and Yankelevitch-Yahav, 2014; Maney, 2016).

Finally, it has been argued, somewhat disdainfully, that sex differences in biomedical research will lead to “blue” and “pink” therapies for various disorders (Eliot and Richardson, 2016; May, 2016). Although this possibility has been viewed with skepticism at the potential sex-specific marketing of pharmaceuticals to men and women, we would argue that the time has finally come to re-examine our “one size fits all” approach to treatment of disease. Sex differences in conditions like stroke warrant the development of sex-specific treatments. If men and women are affected by stroke in considerably different ways, then why would we treat them the same? Indeed, surgical interventions for cardiovascular disease have different outcomes in men versus women, which suggests a careful sex-biased approach to treatment of heart disease (Kodali et al., 2016). We would argue that the extra effort required for the study of sex differences can pay big dividends when it comes to the understanding of the biology of disease and the development of treatment strategies that can lead to more desirable and efficacious medical outcomes in men and women.

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References

Adams, M.M., Fink, S.E., Shah, R.A., Janssen, W.G., Hayashi, S., Milner, T.A., McEwen, B.S., Morrison, J.H., 2002. Estrogen and aging affect the subcellular distribution of estrogen receptor-α in the hippocampus of female rats. J. Neurosci. 22, 3608–3614.
Adkins-Regan, E., 1998. Hormonal mechanisms of mate choice. Amer. Zool. 38, 166–178.
Adkins-Regan, E., 2009. Neuroendocrinology of social behavior. ILAR J. 50, 5–14.
Alano, C.C., Kauppinen, T.M., Valls, A.V., Swanson, R.A., 2006. Minocycline inhibits poly (ADP-ribose) polymerase-1 at nanomolar concentrations. Proc. Natl. Acad. Sci. U. S. A. 103 (25), 9685–9690.
Alkayed, N.J., Harukuni, I., Kimes, A.S., London, E.D., Traystman, R.J., Hurn, P.D., 1998. Gender-linked brain injury in experimental stroke. Stroke J. Cereb. Circ. 29 (1), 159–165 (discussion 166).
Ambros, V., 2001. microRNAs: tiny regulators with great potential. Cell 107, 823–826.
Amiri-Nikpour, M.R., Nazarbaghi, S., Hamdi-Holasou, M., Rezaei, Y., 2015. An open-label evaluator-blinded clinical study of minocycline neuroprotection in ischemic stroke: gender-dependent effect. Acta Neurol. Scandinavica 131 (1), 45–50.
Appenrodt, E., Juszczak, M., Schwarzberg, H., 2002. Septal vasopressin induced preservation of social recognition in rats was abolished by pinealectomy. Behav. Br. Res. 134, 67–73.
Arnold, A.P., 2017. A general theory of sexual differentiation. J. Neurosci. Res. 95, 291–300.
Axelson, J.F., Smith, M., Duarte, M., 1999. Prenatal flutamide treatment eliminates the adult male rat’s dependency upon vasopressin when forming social-olfactory memories. Horm. Behav. 36, 109–118.
Bale, T.L., Dorsa, D.M., Johnston, C.A., 1995. Oxytocin receptor mRNA expression in the ventromedial hypothalamus during the estrous cycle. J. Neurosci. 15, 5058–5064.
Barker, J.M., Galea, L.A.M., 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.
Beery, A.K., Zucker, I., 2011. Sex bias in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 35, 565–572.
Benedetti, M.D., Maraganore, D.M., Bower, J.H., McDonnell, S.K., Peterson, B.J., Ahlskog, J.E., Schaid, D.J., Rocca, W.A., 2001. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. Mov. Disord. Off. J. Mov. Disord. Soc. 16, 830–837.
Beneke, S., 2008. Poly(ADP-ribose) polymerase activity in different pathologies–the link to inflammation and infarction. Exp. Gerontol. 43 (7), 605–614.
Berretti, R., Santoru, F., Locci, A., Sogliano, C., Calza, A., Choleris, E., Porcu, P., Concas, A., 2014. Neonatal exposure to estradiol decreases hypothalamic allopregnanolone concentrations and alters agonistic and sexual but not affective behavior in adult female rats. Horm. Behav. 65, 142–153.
Betzig, L., 2012. Means variances, and ranges in reproductive success: comparative evidence. Evol. Hum. Behav. 33, 309–317.
Blanchard, D.C., Shepherd, J.K., De Padua Carobrez, A., Blanchard, R.J., 1991. Sex effects in defensive behavior: baseline differences and drug interactions. Neurosci. Biobehav. Rev. 15, 461–468.
Bluthé, R.M., Dantzer, R., 1990. Social recognition does not involve vasopressinergic neurotransmission in female rats. Brain Res. 535, 301–304.
Bluthé, R.M., Schoenen, J., Dantzer, R., 1990. Androgen-dependent vasopressinergic neurons are involved in social recognition in rats. Brain. Res. 519, 150–157.
Bluthé, R.M., Gheusi, G., Dantzer, R., 1993. Gonadal-steroids influence the involvement of arginine–vasopressin in social recognition in mice. Psychoneuroendocrinology 18, 323–335.
Boulware, M.I., Weick, J.P., Becklund, B.R., Kuo, S.P., Groth, R.D., Mermelstein, P.G., 2005. Estradiol activates group I and II metabotropic glutamate receptor signaling, leading to opposing influences on cAMP response element-binding protein. J. Neurosci. 25, 5066–5078.
Boulware, M.I., Heisler, J.D., Frick, K.M., 2013. The memory-enhancing effects of hippocampal estrogen receptor activation involve metabotropic glutamate receptor signaling. J. Neurosci. 33, 15184–15194.
Box, H.O., 1984. Primate Behavior and Social Ecology. Chapman & Hall, London.
Brain, P.F., Haug, M., 1992. Hormonal and neurochemical correlates of various forms of animal aggression. Psychoneuroendocrinology 17, 537–551.
Brodin, A., Urhan, A.U., 2015. Sex differences in learning ability in a common songbird, the great tit—females are better observational learners than males. Behav. Ecol. Sociobiol. 69, 237–241.
Buzsáki, G., Moser, E.I., 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat. Neurosci. 16, 130–138.
Cahill, L., Hall, E.D., 2017. Is it time to resurrect lazaroids? J. Neurosci. Res. 95 (1-2), 17–20.
Cai, J., Yang, J., Jones, D., 1998. Mitochondrial control of apoptosis: the role of cytochrome c. Biochim. Biophys. Acta -Bioenergetics. 1366, 139–149.
Carballo-Marquez, A., Vale-Martinez, A., Guillazo-Blanch, G., Marti-Nicolovius, M., 2009. Muscarinic transmission in the basolateral amygdala is necessary for the acquisition of socially transmitted food preferences in rats. Neurobiol. Learn. Mem. 91, 98–101.
Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R., Moffitt, T.E., 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin. Psychol. Sci. 2, 119–137.
Chacon, M.R., Jensen, M.B., Sattin, J.A., Zivin, J.A., 2008. Neuroprotection in cerebral ischemia: emphasis on the SAINT trial. Curr. Cardiol. Rep. 10 (1), 37–42.
Chipman, K., Hampson, E., 2007. A female advantage in the imitation of gestures by preschool children. Dev. Neuropsychol. 31, 137–158.
Choleris, E., Kavaliers, M., 1999. Social learning in animals: sex differences and neurobiological analysis. Pharmacol. Biochem. Behav. 64, 767–776.
Choleris, E., Gustafsson, J.-Å., Korach, K.S., Muglia, L.J., Pfaff, D.W., Ogawa, S., 2003. An estrogen dependent 4-genemicronet regulating social recognition: a study with oxytocin and estrogen receptor-α and -β knockout mice. Proc. Natl. Acad. Sci. U. S. A. 100, 6192–6197.
Choleris, E., Ogawa, S., Kavaliers, M., Gustafsson, J.-Å., Korach, K.-S., Muglia, J., Pfaff, D.W., 2006. Differential involvement of estrogen receptor α, β and oxytocin in social discrimination: a detailed behavioral analysis with knockout mice. Genes Brain Behav. 5, 528–539.
Choleris, E., Little, S.R., Mong, J.A., Puram, S.V., Langer, R., Pfaff, D.W., 2007. Microparticle based delivery of oxytocin receptor antisense DNA in the medial amygdala blocks social recognition in female mice. Proc. Natl. Acad. Sci. U. S. A. 104, 4670–4675.
Choleris, A.E., Clipperton-Allen, A.E., Phan, A., Kavaliers, M., 2009. Neuroendocrinology of social information processing in rats and mice. Front. Neuroendocrinol. 30, 442–459.
Choleris, E., Clipperton-Allen, A.E., Gray, D.G., Diaz-Gonzalez, S., Welsman, R.G., 2011. Differential effects of dopamine receptor D1-type and D2-type antagonists and phase of the estrous cycle on social learning of food preferences, feeding, and social interactions in mice. Neuropsychopharmacology 36, 1689–1702.
Choleris, E., Clipperton-Allen, A.E., Phan, A., Valsecchi, P., Kavaliers, M., 2012. Estrogenic involvement in social learning, social recognition and pathogen avoidance. Front. Neuroendocrinol. 33, 140–159.
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. Psychoneuroendocrin 38, 1236–1250.
Clayton, J.A., 2016. Studying both sexes: a guiding principle for biomedicine. FASEB J. 30, 519–524.
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 (5937), 210–2213.

Clipperton, A.E., Spinato, J.M., Chernets, C., Pfaff, D.W., Choleris, E., 2008. Differential effects of estrogen receptor alpha and beta specific agonists on social learning of food preferences in female mice. Neuropsychopharmacology 33, 2362–2375.
Clipperton-Allen, A.E., Flaxey, I., Webster, H.K., Choleris, E., 2009. Pre-acquisition administration of estradiol benzoate prolongs the preference for a socially transmitted food preference in ovariectomized CD1 mice. Soc. Neurosci. Abstr. 681, 14.
Clipperton-Allen, A.E., Cragg, C.L., Wood, A.J., Pfaff, D.W., Choleris, E., 2010. Agonistic behavior in males and females: effects of an estrogen receptor beta agonist in gonadectomized and gonadally intact mice. Psychoneuroendocrinology 35, 1008–1022.
Clipperton-Allen, A.E., Almey, A., Melichercik, A., Allen, C.P., Choleris, E., 2011. Effects of an estrogen receptor alpha agonist on agonistic behaviour in intact and gonadectomised male and female mice. Psychoneuroendocrinology 36, 981–995.
Cohen, S.J., Munchow, A.H., Rios, L.M., Zhang, G., Asgeirsdottir, H.N., Stackman Jr., R.W., 2013. The rodent hippocampus is essential for nonspatial object memory. Curr. Biol. 23, 1685–1690.
Connor, S.A., Wang, Y.T., 2016. A place at the table: LTD as a mediator of memory genesis. Neuroscientist 22, 359–371.
Craske, M.G., 2003. Origins of Phobias and Anxiety Disorders Why More Women than Men? A Volume in BRAT Series in Clinical Psychology. Elsevier, New York.
Croce, C.M., Calin, G.A., 2005. miRNAs, cancer, and stem cell division. Cell 122 (1), 6–7.
Cunningham, R.L., Giuffrida, A., Roberts, J.L., 2009. Androgens induce dopaminergic neurotoxicity via caspase-3-dependent activation of protein kinase Cdelta. Endocrinology 150 (12), 5539–5548.
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. Proc. Natl. Acad. Sci. U. S. A. 106 (8), 2927–2932.
Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. Prometheus Books, New York.
Day, T., Bonduriansky, R., 2004. Intralocus sexual conflict can drive the evolution of genomic imprinting. Genetics 167, 1537–1546.
De Vries, G.J., Buijs, R.M., Sluiter, A.A., 1984. Gonadal hormone actions on the morphology of the vasopressinergic innervation of the adult rat brain. Brain Res. 298, 141–145.
De Vries, G.J., 2008. Sex differences in vasopressin and oxytocin innervation of the brain. Pr. Brain Res. 170, 17–27.
Dellovade, T.L., Zhu, Y.S., Pfaff, D.W., 1999. Thyroid hormones and estrogen affect oxytocin gene expression in hypothalamic neurons. J. Neuroendocrinol. 11, 1–10.
Denli, A.M., Hannon, G.J., 2003. RNAi: an ever-growing puzzle. Trends Biochem. Sci. 28 (4), 196–201.
Dharap, A., Bowen, K., Place, R., Li, L.C., Vemuganti, R., 2009. Transient focal ischemia induces extensive temporal changes in rat cerebral microRNAome. J. Cerebr. Blood Flow Metabol.: Official Journal of the International Society of Cerebral Blood Flow and Metabolism 29 (4), 675–687.
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 (6), e0129880.
Earls, F., 1987. Sex differences in psychiatric disorders: origins and developmental influences. Psychiatr. Dev. 5, 1–23.
Edward, D.A., 2015. The description of mate choice. Behav. Ecol. 26, 301–310.
Eliot, L., Richardson, S.S., 2016. Sex in context: limitations of animal studies for addressing human Sex/Gender neurobehavioral health disparities. J. Neurosci. 36 (47), 11823–11830.
Ellegren, H., Parsch, J., 2007. The evolution of sex-biased genes and sex-biased gene expression. Nat. Rev. Genet. 8, 689–698.
Engelmann, M., Ebner, K., Wotjak, C.T., Landgraf, R., 1998. Endogenousoxytocin is involved in short-term olfactory memory in female rats. Behav. Brain Res. 90, 89–94.
Epp, J.R., Spritzer, M.D., Galea, L.A.M., 2007. Hippocampus-dependent learning promotes survival of new neurons in the dentate gyrus at a specific time during cell maturation. Neuroscience 149, 273–285.
Epp, J.R., Beasley, C.L., Galea, L.A., 2013. Increased hippocampal neurogenesis and p21 expression in depression: dependent on antidepressants sex, age, and antipsychotic exposure. Neuropsychopharm 38, 2297–2306.
Epp, J.R., Silva Mera, R., Köhlers, S., Josselyn, S.A., Frankland, P.W., 2016. Neurogenesis-mediated forgetting minimizes proactive interference. Nat. Commun. 7, 10838. http://dx.doi.org/10.1038/ncomms10838.
Ervin, S.J.K., Phan, A., Gabor, C.S., Choleris, E., 2013. Rapid oestrogenic regulation of social and non-social learning. J. Neuroendocrinol. 25, 1116–1132.
Ervin, S.J.K., Lymer, J.M., Matta, R., Clipperton-Allen, A.E., Kavaliers, M., Choleris, E., 2015a. Estrogen involvement in social behavior in rodents: rapid and long-term actions. Horm. Behav. 74, 53–76.
Ervin, S.J.K., Mulvale, E., Gallagher, N., Roussel, V., Choleris, E., 2015b. Activation of the G protein-coupled estrogen receptor, but not estrogen receptor α or β, rapidly enhances social learning. Psychoneuroendocrinology 58, 51–66.
Espeland, M.A., Rapp, S.R., Manson, J.E., Goveas, J.S., Shumaker, S.A., Hayden, K.M., Weitlauf, J.C., Gaussoin, S.A., Baker, L.D., Padula, C.B., Hou, L., Resnick, S.M., WHIMSY, WHIMS-ECHO Study Groups, 2017. Long-term effects - on cognitive trajectories of postmenopausal hormone therapy in two age groups. J. Gerontol. A Biol. Sci. Med. Sci. 72, 838–845.
Everts, H.G., Koolhaas, J.M., 1997. Lateral septal vasopressin in rats: role in social and object recognition? Brain Res. 760, 1–7.
Everts, H.G., Koolhaas, J.M., 1999. Differential modulation of lateral septal vasopressin receptor blockade in spatial learning, social recognition, and anxiety-related behaviors in rats. Behav. Brain Res. 99, 7–16.
Fagan, S.C., Cronic, L.E., Hess, D.C., 2011. Minocycline development for acute ischemic stroke. Translat. Stroke Res. 2 (2), 202–208.
Fan, L., Zhao, Z., Orr, P.T., Chambers, C.H., Lewis, M.C., Frick, K.M., 2010. Estradiol-induced object memory consolidation in middle-aged female mice requires dorsal hippocampal extracellular signal-regulated kinase and phosphatidylinositol 3-kinase activation. J. Neurosci. 30, 4390–4400.
Ferguson, J.N., Aldag, J.M., Insel, T.R., Young, L.J., 2001. Oxytocin in the medial amygdala is essential for social recognition in the mouse. J. Neurosci. 21, 8278–8285.
Fernandez, S.M., Lewis, M.C., Frick, K.M., 2006. Differential estrogen receptor mechanisms involved in memory consolidation. Soc Neurosci Abstr (Program # 462.465).
Fernandez, S.M., Lewis, M.C., Pechenino, A.S., Harburger, L.L., Orr, P.T., Gresack, J.E., Schafe, G.E., Frick, K.M., 2008. Estradiol-induced enhancement of object memory consolidation involves hippocampal ERK activation and membrane-bound estrogen receptors. J. Neurosci. 28, 8660–8667.
Fisher, C.R., Graves, K.H., Parlow, A.F., Simpson, E.R., 1998. Characterization of mice deficient in aromatase (ArKO) because of targeted disruption of the cyp19 gene. Proc. Natl. Acad. Sci. U. S. A. 95, 6965–6970.
Fisher, M., Feuerstein, G., Howells, D.W., Hurn, P.D., Kent, T.A., Savitz, S.I., Lo, E.H., Group, S., 2009. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke J. Cereb. Circ. 40 (6), 2244–2250.
Fleming, A.S., Kuchera, C., Lee, A., Winocur, G., 1994. Olfactory-based social learning varies as a function of parity in female rats. Psychobiology 22, 37–43.
Fortress, A.M., Fan, L., Orr, P.T., Zhao, Z., Frick, K.M., 2013. Estradiol-induced object recognition memory consolidation is dependent on activation on mTOR signaling in the dorsal hippocampus. Learn. Mem. 20, 147–155.
Fortress, A.M., Kim, J., Poole, R.L., Gould, T.J., Frick, K.M., 2014. 17β-Estradiol regulates histone alterations associated with memory consolidation and increases Bdnf promoter acetylation in middle-aged female mice. Learn. Mem. 21, 457–467.
Fortress, A.M., Heisler, J.D., Frick, K.M., 2015. The mTOR and canonical Wnt signaling pathways mediate the mnemonic effects of progesterone in the dorsal hippocampus. Hippocampus 25, 616–629.
Frick, K.M., Gresack, J.E., 2003. Sex differences in the behavioral response to spatial and object novelty in adult C57BL/6 mice. Behav. Neurosci. 117, 1283–1291.
Frick, K.M., Fernandez, S.M., Harburger, L.L., 2010. A new approach to understanding the molecular mechanisms through which estrogens affect cognition. Biochim. Biophys. Acta Gen. Subj. 1800, 1045–1055.
Frick, K.M., 2015. Sex steroid hormones matter for learning and memory: estrogenic regulation of hippocampal function in male and female rodents. Learn. Mem. 22, 472–493.
Frye, C.A., Duffy, C.K., Walf, 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.
Fuxjager, M.J., Knaebe, B., Marler, C.A., 2015. A single testosterone pulse rapidly reduces urinary marking behaviour in subordinate, but not dominant, white-footed mice. Anim. Behav. 100, 8–14.
Gabor, C.S., Phan, A., Clipperton-Allen, A.E., Kavaliers, M., Choleris, E., 2012. Interplay of oxytocin, vasopressin and sex hormones in the regulation of social recognition. Behav. Neurosci. 126, 97–109.
Gabor, C.S., Lymer, J.M., Phan, A., Choleris, E., 2015. Rapid effects of the G-Protein Coupled Estrogen Receptor (GPER) on learning and dorsal hippocampus dendritic spines in female mice. Physiol. Behav. 149, 53–60.
Galea, L.A., Kavaliers, M., Ossenkopp, K.P., Innes, D., Hargreaves, E.L., 1994. Sexually dimorphic spatial learning varies seasonally in two populations of deer mice. Brain Res. 635 (1-2 (Jan 28)), 18–26.
Galea, L.A., Kavaliers, M., Ossenkopp, K.P., 1995. Gonadal hormone levels and spatial learning performance in the Morris water maze in male and female meadow voles, Microtus pennsylvanicus. Horm. Behav. 29, 106–125.
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.A.M., Frick, K.M., Hampson, E., Sohrabji, F., Choleris, E., 2016. Why estrogens matter for behavior and brain health. Neurosci. Biobehav. Revs. http://dx.doi.org/10.1016/j.neubiorev.2016.03.024.
Galef, B.G., Kennett, D.J., Wigmore, S.W., 1984. Transfer of information concerning distant foods in rats. A robust phenomenon. Anim. Learn. Behav. 12, 292–296.
Galef Jr., B.G., 1988. Imitation in animals: history, definitions and interpretation of the data from the psychological laboratory. In: Zentall, T., Galef, B.J. (Eds.), Social Learning: Psychological and Biological Perspectives. Erlbaum, Hillsdale, NJ, pp. 3–28.
Gaulin, S.J.C., Fitzgerald, R.W., 1986. Sex differences in spatial ability: an evolutionary hypothesis and test. Am. Nat. 127, 74–88.
Gaulin, S.J., FitzGerald, R.W., Wartell, M.S., 1990. Sex differences in spatial ability and activity in two vole species (Microtus ochrogaster and M. pennsylvanicus). J. Comp. Psychol. 104, 88–93.
Geary, D.C., 2010. Male, Female: The Evolution of Human Sex Differences, 2nd ed. American Psychological Association, Washington, DC.
Geary, D.C., 2016. Evolution of sex differences in trait- and age-Specific vulnerabilities. Persp. Psychol. Sci. 11, 855–876.
Georgiadis, J.R., Kringelbach, M.L., Pfaus, J.G., 2012. Sex for fun: a synthesis of human and animal neurobiology. Nat. Rev. Urol. 9, 486–498.
Gibson, C.L., Attwood, L., 2016. The impact of gender on stroke pathology and treatment. Neurosci. Biobehav. Rev. 67, 119–124.
Gibson, C.L., 2013. Cerebral ischemic stroke: is gender important? J. Cerebr. Blood Flow Metabol. Off. J. Int. Soc. Cereb.Blood Flow Metab. 33 (9), 1355–1361.
Gilks, W.P., Abbott, J.K., Morrow, E.H., 2014. Sex differences in disease genetics: evidence, evolution, and detection. Trends. Genet. 30, 453–463.
Gillies, G.E., McArthur, S., 2010. Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. Pharmacol. Rev. 62, 155–198.

Goldstein, L.B., 2008. Minocycline treatment in acute stroke. Curr. Atheroscler. Rep. 10 (4), 286–287.
Good, M., Day, M., Muir, J.L., 1999. Cyclical changes in endogenous levels of oestrogen modulate the induction of LTD and LTP in the hippocampal CA1 region. Eur. J. Neurosci. 11, 4476–4480.
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.
Haast, R.A., Gustafson, D.R., Kiliaan, A.J., 2012. Sex differences in stroke. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 32 (12), 2100–2107.
Hagberg, H., Wilson, M.A., Matsushita, H., Zhu, C., Lange, M., Gustavsson, M., Poitras, M.F., Dawson, T.M., Dawson, V.L., Northington, F., Johnston, M.V., 2004. PARP-1 gene disruption in mice preferentially protects males from perinatal brain injury. J. Neurochem. 90 (5), 1068–1075.
Hajszan, T., Milner, T.A., Leranth, C., 2007. Sex steroids and the dentate gyrus. Prog. Brain Res. 163, 399–415.
Hamilton, W.D., Zuk, M., 1982. Heritable true fitness and bright birds: a role for parasites? Science 218, 384–387.
Hamson, D.K., Roes, M.M., Galea, L.A., 2016. Sex hormones and cognition: neuroendocrine influences on memory and learning. Compr. Physiol. 6 (3), 1295–1337.
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.
Hart, D., Nilges, M., Pollard, K., Lynn, T., Patsos, O., Shiel, C., Clark, S.M., Vasudevan, N., 2014. Activation of the G-protein coupled receptor 30 (GPR30) has different effects on anxiety in male and female mice. Steroids 81, 49–56.
Hasegawa, Y., Hojo, Y., Kojima, H., Ikeda, M., Hotta, K., Sato, R., Ooishi, Y., Yoshiya, M., Chung, B.-C., Yamazaki, T., Kawato, S., 2015. Estradiol rapidly modulates synaptic plasticity of hippocampal neurons: involvement of kinase networks. Brain Res. 1621, 147–161.
Hatanaka, Y., Hojo, Y., Mukai, H., Murakami, G., Komatsuzaki, Y., Kim, J., Ikeda, M., Hiragushi, A., Kimoto, T., Kawato, S., 2014. Rapid increase of spines by dihydrotestosterone and testosterone in hippocampal neurons: dependence on synaptic androgen receptor and kinase networks. Brain Res. 1621, 121–132.
Hayden-Hixson, D.M., Ferris, C.F., 1991. Steroid-specific regulation of agonistic responding in the anterior hypothalamus of male hamsters. Physiol. Behav. 50, 793–799.
Hazell, G., Yao, S., Roper, J., Prossnitz, E., O'Carroll, A., Lolait, S., 2009. Localisation of GPR30 a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. J. Endocrinol. 202, 223–236.
Heyes, C.M., 1994. Social learning in animals: categories and mechanism. Biol. Rev. 69, 207–231.
Hill, M.D., Kent, D.M., Hinchey, J., Rowley, H., Buchan, A.M., Wechsler, L.R., Higashida, R.T., Fischbein, N.J., Dillon, W.P., Gent, M., Firszt, C.M., Schulz, G.A., Furlan, A.J., Investigators obotP-, 2006. Sex-based differences in the effect of intra-Arterial treatment of stroke analysis of the PROACT-2 study. Stroke J. Cereb. Circ. 37, 2322–2325.
Hlinák, Z., 1993. Social recognition in ovariectomized and estradiol-treated female rats. Horm. Behav. 27, 159–166.
Ho, M.L., Lee, J.N., 1992. Ovarian and circulating levels of oxytocin and arginine vasopressin during the estrous cycle in the rat. Acta Endocrinol. 126, 530–534.
Howland, J.G., Wang, Y.T., 2008. Synaptic plasticity in learning and memory: stress effects in the hippocampus. Prog. Brain Res. 169, 145–158.
Huang, Z., Huang, P.L., Panahian, N., Dalkara, T., Fishman, M.C., Moskowitz, M.A., 1994. Effects of cerebral ischemia in mice deficient in neuronal nitric oxide synthase. Science 265, 1883–1885.
Hyde, J.S., 2016. Sex and cognition: gender and cognitive functions. Curr. Opin. Neurobiol. 38, 53–56.
Imwalle, D.B., Scordalakales, E.M., Rissman, E.F., 2002. Estrogen receptor α influences socially motivated behaviors. Horm. Behav. 42, 484–491.
Inagaki, T., Gautreaux, C., Luine, V., 2010. Acute estrogen treatment facilitates recognition memory consolidation and alters monoamine levels in memory-related brain areas. Horm. Behav. 58, 415–426.
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 (9), 989–998.
Jackson, D., Kirkbride, J., Croudace, T., Morgan, C., Boydell, J., Errazuriz, A., Murray, R.M., Jones, P.B., 2013. Meta-analytic approaches to determine gender differences in the age-incidence characteristics of schizophrenia and related psychoses. Int. J. Methods. Psychiatr. Res. 22 (1), 36–45.
Jacobs, L.F., Gaulin, S.J.C., Sherry, D., Hoffman, G.E., 1990. Evolution of spatial cognition: sex-specific patterns of spatial behavior predict hippocampal size. Proc. Natl. Acad. Sci. U. S. A. 87, 6349–6352.
Jennions, M.D., Petrie, M., 1997. Variation in mate choice and mating preferences: a review of causes and consequences. Biol. Rev. 72, 283–327.
Jeyaseelan, K., Lim, K.Y., Armugam, A., 2008. MicroRNA expression in the blood and brain of rats subjected to transient focal ischemia by middle cerebral artery occlusion. Stroke J. Cereb. Circ. 39 (3), 959–966.
Joel, D., Yankelevitch-Yahav, R., 2014. Reconceptualizing sex, brain and psychopathology: interaction, interaction, interaction. Br. J. Pharmacol. 171 (20), 4620–4635.
Joel, D., Berman, Z., Tavor, I., Wexler, N., Gaber, O., Stein, Y., Shefi, N., Pool, J., Urchs, S., Margulies, D.S., Liem, F., Hänggi, J., Jäncke, L., Assaf, Y., 2015. Sex beyond the genitalia: the human brain mosaic. Proc. Natl. Acad. Sci. U. S. A. 112 (50), 15468–15473.
Jolles, J.W., Boogert, N.J., van den Bos, R., 2015. Sex differences in risk-taking and associative learning in rats. R. Soc. Open Sci. 2, 150485.
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 (8), 811–825.
Kapral, M.K., Fang, J., Hill, M.D., Silver, F., Richards, J., Jaigobin, C., Cheung, A.M., Investigators of the Registry of the Canadian Stroke, N., 2005. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. Stroke J. Cereb. Circ. 36 (4), 809–814.
Kassis, H., Shehadah, A., Li, C., Zhang, Y., Cui, Y., Roberts, C., Sadry, N., Liu, X., Chopp, M., Zhang, Z.G., 2016. Class IIa histone deacetylases affect neuronal remodeling and functional outcome after stroke. Neurochem. Int. 96, 24–31.
Kent, D.M., Price, L.L., Ringleb, P., Hill, M.D., Selker, H.P., 2005. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke a pooled analysis of randomized clinical trials. Stroke J. Cereb. Circ. 36, 62–65.
Kent, D.M., Buchan, A.M., Hill, M.D., 2008. The gender effect in stroke thrombolysis: of CASES, controls, and treatment-effect modification. Neurology 71, 1080–1083.
Kim, J.J., Rison, R.A., Fanselow, M.S., 1993. Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. Behav. Neurosci. 107, 1093–1098.
Kim, J.M., Jung, K.H., Chu, K., Lee, S.T., Ban, J., Moon, J., Kim, M., Lee, S.K., Roh, J.K., 2015. Atherosclerosis-Related circulating MicroRNAs as a predictor of stroke recurrence. Transl. Stroke Res. 6 (3), 191–197.
Kim, J., Szinte, J.S., Boulware, M.I., Frick, K.M., 2016. 17β-estradiol and agonism of G-protein Coupled Estrogen Receptor (GPER) enhance hippocampal memory via different cell-signaling mechanisms. J. Neurosci. 36, 3309–3321.
Klabunde, M., Weems, C.F., Raman, M., Carrion, V.G., 2016. The moderating effects of sex on insula subdivision structure in youth with posttraumatic stress symptoms. Depress. Anxiety. http://dx.doi.org/10.1002/da.22577.
Kodali, S., Williams, M.R., Doshi, D., Hahn, R.T., Humphries, K.H., Nkomo, V.T., Cohen, D.J., Douglas, P.S., Mack, M., Xu, K., Svensson, L., Thourani, V.H., Tuzcu, E.M., Weissman, N.J., Leon, M., 2016. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. Ann. Int. Med. 164 (6), 377–384.
Kohler, E., Prentice, D.A., Bates, T.R., Hankey, G.J., Claxton, A., van Heerden, J., Blacker, D., 2013. Intravenous minocycline in acute stroke: a randomized, controlled pilot study and meta-analysis. Stroke J. Cereb. Circ. 44 (9), 2493–2499.
Koss, W.A., Frick, K.M., 2016. Memory-enhancing effects of 17β-estradiol in male and female mice. Soc. Neurosci. Abstr, Poster 179, 106.
Koss, W.A., Frick, K.M., 2017. Sex differences in hippocampal function. J. Neurosci. Res. 95, 539–562.
Kow, L.M., Pfaff, D.W., 2016. Rapid estrogen actions on ion channels: a survey in search for mechanisms. Steroids 11, 46–53. http://dx.doi.org/10.1016/j.steroids.2016.02.018.
Kramár, E.A., Chen, L.Y., Brandon, N.J., Rex, C.S., Liu, F., Gall, C.M., Lynch, G., 2009. Cytoskeletal changes underlie estrogen's acute effects on synaptic transmission and plasticity. J. Neurosci. 29, 12982–12993.
Krause, D.N., Duckles, S.P., Pelligrino, D.A., 2006. Influence of sex steroid hormones on cerebrovascular function. J. Appl. Physiol. 101 (4), 1252–1261.
Krek, A., Grun, D., Poy, M.N., Wolf, R., Rosenberg, L., Epstein, E.J., MacMenamin, P., da Piedade, I., Gunsalus, K.C., Stoffel, M., Rajewsky, N., 2005. Combinatorial microRNA target predictions. Nat. Genet. 37 (5), 495–500.
Kruger, D.J., Nesse, R.M., 2006. An evolutionary life history understanding of sex differences in human mortality rates. Hum. Nat. 74, 74–97.
Kumar, A., Bean, L.A., Rani, A., Jackson, T., Foster, T.C., 2015. Contribution of estrogen receptor subtypes, ERα, ERβ, and GPER1 in rapid estradiol-mediated enhancement of hippocampal synaptic transmission in mice. Hippocampus. http://dx.doi.org/10.1002/hipo.22475.
Lai, S.M., Duncan, P.W., Dew, P., Keighley, J., 2005. Sex differences in stroke recovery. Prevent. Chronic Dis. 2 (3), A13.
Lai, M.C., Lombardo, M.V., Suckling, J., Ruigrok, A.N., Chakrabarti, B., Ecker, C., Deoni, S.C., Craig, M.C., Murphy, D.G., Bullmore, E.T., AIMS Consortium, M.R.C., Baron-Cohen, S., 2013. Biological sex affects the neurobiology of autism. Brain 136, 2799–2815.
Lampl, Y., Boaz, M., Gilad, R., Lorberboym, M., Dabby, R., Rapoport, A., Anca-Hershkowitz, M., Sadeh, M., 2007. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. Neurology 69 (14), 1404–1410.
Lande, R., 1980. Sexual dimorphism sexual selection, and adaptation in polygenic characters. Evolution 34, 292–305.
Landgraf, R., Frank, E., Aldag, J.M., Neumann, I.D., Sharer, C.A., Ren, X., Terwilliger, E.F., Niwa, M., Wigger, A., Young, L.J., 2003. Viral vector-mediated gene transfer of the vole V1a vasopressin receptor in the rat septum: improved social discrimination and active social behaviour. Eur. J. Neurosci. 18, 403–411.
Lang, J.T., McCullough, L.D., 2008. Pathways to ischemic neuronal cell death: are sex differences relevant? J. Transl. Med. 6, 33.
Langley, B., Brochier, C., Rivieccio, M.A., 2009. Targeting histone deacetylases as a multifaceted approach to treat the diverse outcomes of stroke. Stroke J. Cereb. Circ. 40 (8), 2899–2905.
Laredo, S.A., Landeros, R.V., Trainor, B.C., 2014. Rapid effects of estrogens on behavior: environmental modulation and molecular mechanisms. Front. Neuroendocrinol. 35, 447–458.
Launer, L.J., Andersen, K., Dewey, M.E., Letenneur, L., Ott, A., Amaducci, L.A., Brayne, C., Copeland, J.R.M., Dartigues, J.-F., Kragh-Sorensen, P., Lobo, A., Martinez-Lage, J.M., Stijnen, T., Hofman, A., 1999. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. Neurology 52, 78–84.
Leal, S.L., Yassa, M.A., 2013. Perturbations of neural circuitry in aging, mild cognitive impairment, and Alzheimer's disease. Ageing Res. Rev. 12, 823–831.

Leranth, C., Petnehazy, O., MacLusky, N.J., 2003. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J. Neurosci. 23, 1588–1592.
Leuner, B., Gould, E., 2010. Structural plasticity and hippocampal function. Ann. Rev. Psychol. 61 (111-140), C1–C3.
Lewis, M.C., Kerr, K.M., Orr, P.T., Frick, K.M., 2008. Estradiol-induced enhancement of object memory consolidation involves NMDA receptors and protein kinase A in the dorsal hippocampus of female C57BL/6 mice. Behav. Neurosci. 122, 716–721.
Li, J., McCullough, L.D., 2009. Sex differences in minocycline-induced neuroprotection after experimental stroke. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 29 (4), 670–674.
Lim, L.P., Lau, N.C., Garrett-Engele, P., Grimson, A., Schelter, J.M., Castle, J., Bartel, D.P., Linsley, P.S., Johnson, J.M., 2005. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature 433 (7027), 769–773.
Liu da, Z., Jickling, G.C., Ander, B.P., Hull, H., Zhan, X., Cox, C., Shroff, N., Dykstra-Aiello, C., Stamova, B., Sharp, F.R., 2016. Elevating microRNA-122 in blood improves outcomes after temporary middle cerebral artery occlusion in rats. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 36 (8), 1374–1383.
Liu, F., Li, Z., Li, J., Siegel, C., Yuan, R., McCullough, L.D., 2009. Sex differences in caspase activation after stroke. Stroke J. Cereb. Circ. 40 (5), 1842–1848.
Liu, F., Lang, J., Li, J., Benashski, S.E., Siegel, M., Xu, Y., McCullough, L.D., 2011. Sex differences in the response to poly(ADP-ribose) polymerase-1 deletion and caspase inhibition after stroke. Stroke J. Cereb. Circ. 42 (4), 1090–1096.
Locklear, M.N., Kritzer, M.F., 2014. Assessment of the effects of sex and sex hormones on spatial cognition in adult rats using the Barnes maze. Horm. Behav. 66 (2), 298–308.
Luine, V.N., Jacome, L.F., MacLusky, N.J., 2003. Rapid enhancement of visual and place memory by estrogens in rats. Endocrinology 144, 2836–2844.
Lymer, J.M., Robinson, A., Winters, B.D., Choleris, E., 2017. The rapid effects of the G-protein coupled estrogen receptor in the dorsal hippocampus on learning in female mice. Pychoneuroendocrinology 77, 131–140.
Mabley, J.G., Horvath, E.M., Murthy, K.G., Zsengeller, Z., Vaslin, A., Benko, R., Kollai, M., Szabo, C., 2005. Gender differences in the endotoxin-induced inflammatory and vascular responses: potential role of poly(ADP-ribose) polymerase activation. J. Pharmacol. Exp. Ther. 315 (2), 812–820.
Machado, L.S., Kozak, A., Ergul, A., Hess, D.C., Borlongan, C.V., Fagan, S.C., 2006. Delayed minocycline inhibits ischemia-activated matrix metalloproteinases 2 and 9 after experimental stroke. BMC Neurosci. 7, 56.
Machado, L.S., Sazonova, I.Y., Kozak, A., Wiley, D.C., El-Remessy, A.B., Ergul, A., Hess, D.C., Waller, J.L., Fagan, S.C., 2009. Minocycline and tissue-type plasminogen activator for stroke: assessment of interaction potential. Stroke J. Cereb. Circ. 40 (9), 3028–3033.
Madsen, T.E., Khoury, J.C., Alwell, K.A., Moomaw, C.J., Kissela, B.M., Los Rios La Rosa, F., Woo, D., Adeoye, O., Flaherty, M.L., Khatri, P., Ferioli, S., Kleindorfer, D., 2015. Analysis of tissue plasminogen activator eligibility by sex in the Greater Cincinnati/Northern Kentucky Stroke Study. Stroke J. Cereb. Circ. 46 (3), 717–721.
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.
Maner, J.K., Richey, J.A., Cromer, K., Mallott, M., Lejuez, C.W., Joiner, T.E., Schmidt, N.B., 2007. Dispositional anxiety and risk-avoidant decision-making. Personal. Indiv. Diff. 42, 665–675.
Maney, D.L., 2016. Perils and pitfalls of reporting sex differences: philos. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371 (1688), 20150119.
Mannella, P., Brinton, R.D., 2006. Estrogen receptor protein interaction with phosphatidylinositol 3-kinase leads to activation of phosphorylated Akt and extracellular signal-regulated kinase 1/2 in the same population of cortical neurons: a unified mechanism of estrogen action. J. Neurosci. 26, 9439–9447.
Manwani, B., Liu, F., Xu, Y., Persky, R., Li, J., McCullough, L.D., 2011. Functional recovery in aging mice after experimental stroke. Brain Behav. Immun. 25 (8), 1689–1700.
Marlowe, F.W., 2005. Hunter-gatherers and human evolution. Evol. Anthropol. 14, 54–67.
Matsukawa, N., Yasuhara, T., Hara, K., Xu, L., Maki, M., Yu, G., Kaneko, Y., Ojika, K., Hess, D.C., Borlongan, C.V., 2009. Therapeutic targets and limits of minocycline neuroprotection in experimental ischemic stroke. BMC Neurosci. 10, 126.
Matsuura, S., Egi, Y., Yuki, S., Horikawa, T., Satoh, H., Akira, T., 2011. MP-124, a novel poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor, ameliorates ischemic brain damage in a non-human primate model. Brain Res. 1410, 122–131.
Matta, R., Ervin, S.J.K., Choleris, E., 2016. The neurobiology of social learning. Chpt 8. In: Mary Olmstead, C. (Ed.), Animal Cognition: Principles, Evolution, and Development. Nova Science Publishers.
Matta, R., Tiessen, A.N., Choleris, E., 2017. The role of dorsal hippocampal dopamine D1-type receptors in social learning social interactions and food Intake in male and female mice. Neuropsychopharmacology (under revision).
May, M., 2016. Sex on the brain: unraveling the differences between women and men in neurodegenerative disease. Nat. Med. 22 (12), 1370–1372.
McCarrey, A.C., Resnick, S.M., 2015. Postmenopausal hormone therapy and cognition. Horm. Behav. 74, 167–172.
McCarthy, M.M., Nugent, B.M., 2013. Epigenetic contributions to hormonally-mediated sexual differentiation of the brain. J. Neuroendocrinol. 25, 1133–1140.
McCarthy, M.M., 2016. Sex differences in the developing brain as a source of inherent risk. Dialogues Clin. Neurosci. 18, 361–372.
McCullough, L.D., Alkayed, N.J., Traystman, R.J., Williams, M.J., Hurn, P.D., 2001. Postischemic estrogen reduces hypoperfusion and secondary ischemia after experimental stroke. Stroke 32 (3), 796–802.
McCullough, L.D., Zeng, Z., Blizzard, K.K., Debchoudhury, I., Hurn, P.D., 2005. Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 25 (4), 502–512.
McIntyre, L., Bono, L., Genissel, A., Westerman, R., Junk, D., Telonis-Scott, M., Harshman, L., Wayne, M.L., Kopp, A., Nuzhdin, S.V., 2006. Sex-specific expression of alternative transcripts in Drosophila. Genome Biol. 7, R79.
Mendrek, A., Mancini-Marïe, A., 2016. Sex/gender differences in the brain and cognition in schizophrenia. Neurosci. Biobehav. Rev. 67, 57–78.
Mitra, S.W., Hoskin, E., Yudkovitz, J., Pear, L., Wilkinson, H.A., Hayashi, S., Pfaff, D.W., Ogawa, S., Rohrer, S.P., Schaeffer, J.M., McEwen, B.S., Alves, S.E., 2003. Immunolocalization of estrogen receptor beta in the mouse brain: comparison with estrogen receptor alpha. Endocrinology 144, 2055–2067.
Mitterling, K.L., Spencer, J.L., Dziedzic, N., Shenoy, S., McCarthy, K., Waters, E.M., McEwen, B.S., Milner, T.A., 2010. Cellular and subcellular localization of estrogen and progestin receptor immunoreactivities in the mouse hippocampus. J. Comp. Neurol. 518, 2729–2743.
Montano, M., Long, K., 2011. RNA surveillance-an emerging role for RNA regulatory networks in aging. Age. Res. Rev. 10 (2), 216–224.
Morris, R.G.M., Garrud, P., Rawlins, J.N.P., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297, 681–683.
Morrow, E.H., 2015. The evolution of sex differences in disease. Biol. Sex Diff. 6, 5–12.
Motta-Mena, N.V., Puts, D.A., 2017. Endocrinology of human female sexuality, mating, and reproductive behavior. Horm. Behav. 91, 19–35. http://dx.doi.org/10.1016/j.yhbeh.2016.11.012.
Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., de Ferranti, S., Despres, J.-P., Fullerton, H.J., Howard, V.J., 2015. Heart disease and stroke statistics-2015 update: a report from the american heart association. Circulation 131 (4), e29.
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.
Murray, H.E., Pillai, A.V., McArthur, S.R., Razvi, N., Datla, K.P., Dexter, D.T., Gillies, G.E., 2003. Dose- and sex-dependent effects of the neurotoxin 6-hydroxydopamine on the nigrostriatal dopaminergic pathway of adult rats: differential actions of estrogen in males and females. Neuroscience 116, 213–222.
Naumova, A.K., Tuwaijri, A.A., Morin, A., Vaillancout, V.T., Madore, A.-M., Berlivet, S., Kohan-Ghadr, H.R., Moussette, S., Laprise, C., 2013. Sex- and age-dependent DNA methylation at the 17q12-q21 locus associated with childhood asthma. Hum. Genet. 132, 811–822.
Nemoto, E.M., 2000. A complex role for nitric oxide in ischemic stroke. Crit. Care Med. 28 (1), 280–281.
Nesse, R.M., Williams, G.C., 1996. Why We Get Sick: The New Science of Darwinian Medicine. Vintage Books Piblisher, New York.
Nesse, R.M., Bergstrom, C.T., Ellison, P.T., Flier, J.S., Gluckman, P., Govindaraju, D.R., Niethammer, D., Omenn, G.S., Perlman, R.L., Schwartz, M.D., Thomas, M.G., Stearns, S.C., Valle, D., 2010. Evolution in health and medicine Sackler colloquium: making evolutionary biology a basic science for medicine. Proc. Natl. Acad. Sci. U. S. A. 107 (Suppl 1), 1800–1807.
Nomura, M., McKenna, E., Korach, K.S., Pfaff, D.W., Ogawa, S., 2002. Estrogen receptor β regulates the gene expression of oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. Mol. Brain Res. 109, 84–94.
Oberlander, J.G., Woolley, C.S., 2016. 17β-estradiol acutely potentiates glutamatergic synaptic transmission in the hippocampus through distinct mechanisms in males and females. J. Neurosci. 36, 2677–2690.
Ogawa, S., 2004. Differential roles of two types of estrogen receptors in the regulation of neuroendocrine functions and socio-sexual behaviors. Jpn. J. Anim. Psychol. 54, 49–58.
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.
Orr, P.T., Rubin, A.J., Fan, L., Kent, B.A., Frick, K.M., 2012. The progesterone-induced enhancement of object recognition memory consolidation involves activation of the extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) pathways in the dorsal hippocampus. Horm. Behav. 61, 487–495.
Padma Srivastava, M.V., Bhasin, A., Bhatia, R., Garg, A., Gaikwad, S., Prasad, K., Singh, M.B., Tripathi, M., 2012. Efficacy of minocycline in acute ischemic stroke: a single-blinded, placebo-controlled trial. Neurol. India 60 (1), 23–28.
Palanza, P., 2001. Animal models of anxiety and depression: how are females different? Neurosci. Biobehav. Rev. 25, 219–233.
Park, M.J., Sohrabji, F., 2016. The histone deacetylase inhibitor, sodium butyrate, exhibits neuroprotective effects for ischemic stroke in middle-aged female rats. J. Neuroinflam. 13 (1), 300.
Parmigiani, S., Ferrari, P.F., Palanza, P., 1998. An evolutionary approach to behavioral pharmacology: using drugs to understand proximate and ultimate mechanisms of different forms of aggression in mice. Neurosci. Biobehav. Rev. 23, 143–153.
Patisaul, H.B., Scordalakes, E.M., Young, L.J., Rissman, E.F., 2003. Oxytocin, but not oxytocin receptor, is regulated by oestrogen receptor beta in the female mouse hypothalamus. J. Neuroendocrinol. 15, 787–793.
Peng, X., Li, W., Zhang, W., 2012. Poly(ADP-ribose) polymerase 1 inhibition protects human aortic endothelial cells against LPS-induced inflammation response. Acta Biochim. Biophys. Sin. (Shanghai) 44 (11), 911–917.
Pereira, L.M., Bastos, C.P., de Souza, J.M., Ribeiro, F.M., Pereira, G.S., 2014. Estradiol enhances object recognition memory in Swiss female mice by activating hippocampal estrogen receptor α. Neurobiol. Learn. Mem. 114, 1–9.

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 (6), 1309–1320.
Petrea, R.E., Beiser, A.S., Seshadri, S., Kelly-Hayes, M., Kase, C.S., Wolf, P.A., 2009. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. Stroke J. Cereb. Circ. 40 (4), 1032–1037.
Phan, A., Lancaster, K.E., Armstrong, J.N., MacLusky, N.J., Choleris, E., 2011. Rapid effects of estrogen receptor α and β 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 17β-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.C., 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.
Pierman, S., Sica, M., Allieri, F., Viglietti-Panzica, C., Panzica, G.C., Bakker, J., 2008. Activational effects of estradiol and dihydrotestosterone on social recognition and the arginine–vasopressin immunoreactive system in male mice lacking a functional aromatase gene. Horm. Behav. 54, 98–106.
Reeves, M.J., Bushnell, C.D., Howard, G., Gargano, J.W., Duncan, P.W., Lynch, G., Khatiwoda, A., Lisabeth, L., 2008. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol. 7 (10), 915–926.
Renolleau, S., Fau, S., Goyenvalle, C., Joly, L.M., Chauvier, D., Jacotot, E., Mariani, J., Charriaut-Marlangue, C., 2007. Specific caspase inhibitor Q-VD-OPh prevents neonatal stroke in P7 rat: a role for gender. J. Neurochem. 100 (4), 1062–1071.
Resnick, S., Espeland, M., An, Y., Maki, P., Coker, L., Jackson, R., Stefanick, M., Wallace, R., Rapp, S., 2009. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J. Clin. Endocrinol. Metab. 94, 4152–4161.
Rice, T.R., 2015. Violence among young men: the importance of a gender-specific developmental approach to adolescent male suicide and homicide. Int. J. Adolesc. Med. Health. 27, 177–181.
Rink, C., Khanna, S., 2011. MicroRNA in ischemic stroke etiology and pathology. Physiol. Genom. 43 (10), 521–528.
Rocca, W.A., Bower, J.H., Maraganore, D.M., Ahlskog, J.E., Grossardt, B.R., de Andrade, M., Melton 3rd, L.J., 2008. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology 70, 200–209.
Roved, J., Westerdahl, H., Hasselquist, D., 2017. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm. Behav. 88, 95–105. http://dx.doi.org/10.1016/j.yhbeh.2016.11.017.
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.
Russon, A.E., 1997. Exploiting the expertise of others. In: Whiten, A., Byrne, R.W. (Eds.), Machiavellian Intelligence II Extension and Evaluations. Cambridge University Press, New York, pp. 174–231.
Rutter, M., Caspi, A., Moffitt, T.E., 2003. Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. J. Child Psychol. Psychiatr. 44, 1092–1115.
Sánchez-Andrade, G., Kendrick, K.M., 2011. Role of alpha- and beta-estrogen receptor receptors in mouse social recognition memory: effects of gender and estrous cycle. Horm. Behav. 59, 114–122.
Sánchez-Andrade, G., James, B.M., Kendrick, K.M., 2005. Neural encoding of olfactory recognition memory. J. Reprod. Dev. 51, 547–558.
Sano, K., Tsuda, M.C., Musatov, S., Sakamoto, T., Ogawa, S., 2013. Differential effects of site specific knockdown of estrogen receptor α in the medial amygdala, medial preoptic area, and ventromedial nucleus of the hypothalamus on sexual and aggressive behavior of male mice. Eur. J. Neurol. 37, 1308–1319.
Sarkar, D.K., Frautschy, S.A., Mitsugi, N., 1992. Pituitary portal plasma levels of oxytocin during the estrous cycle, lactation, and hyperprolactinemia. Ann. N. Y. Acad. Sci. 652, 397–410.
Schulz, K.M., Sisk, C.L., 2016. The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neurosci. Biobehav. Rev. 70, 148–158.
Schwartz, N., Verma, A., Bivens, C.B., Schwartz, Z., Boyan, B.D., 2016. Rapid steroid hormone actions via membrane receptors. Biochim. Biophys. Acta 1863, 2289–2298.
Scordalakes, E.M., Rissman, E.F., 2004. Aggression and arginine vasopressin immunoreactivity regulation by androgen receptor and estrogen receptor α. Genes Brain Behav. 3, 20–26.
Selvamani, A., Sohrabji, F., 2010. The neurotoxic effects of estrogen on ischemic stroke in older female rats is associated with age-dependent loss of insulin-like growth factor-1. J. Neurosci. 30 (20), 6852–6861.
Selvamani, A., Sohrabji, F., 2016. Mir363-3p improves ischemic stroke outcomes in female but not male rats. Neurochem. Int. http://dx.doi.org/10.1016/j.neuint.2016.10.008.
Selvamani, A., Sathyan, P., Miranda, R.C., Sohrabji, F., 2012. An antagomir to microRNA Let7f promotes neuroprotection in an ischemic stroke model. PLoS One 7 (2), e32662.
Selvamani, A., Williams, M.H., Miranda, R.C., Sohrabji, F., 2014. Circulating miRNA profiles provide a biomarker for severity of stroke outcomes associated with age and sex in a rat model. Clin. Sci. (Lond. Engl. 1979) 127 (2), 77–89.
Shansky, R.M., Woolley, C.S., 2016. Considering sex as a biological variable will be valuable for neuroscience research. J. Neurosci. 36 (47), 11817–11822.
Shepherd, A.M., Laurens, K.R., Matheson, S.L., Carr, V.J., Green, M.J., 2012. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci. Biobehav. Rev. 36, 1342–1356.
Shobha, N., Sylaja, P., Kapral, M., Fang, J., Hill, M., Network IotRotCS, 2010. Differences in stroke outcome based on sex. Neurology 74 (9), 767–771.
Shors, T.J., Chua, C., Falduto, J., 2001a. 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., 2001b. Neurogenesis in the adult is involved in the formation of trace memories. Nature 410 (6826), 372–376.
Shors, T.J., 2016. A trip down memory lane about sex differences in the brain. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371, 20150124.
Siegel, C., Turtzo, C., McCullough, L.D., 2010. Sex differences in cerebral ischemia: possible molecular mechanisms. J. Neurosci. Res. 88 (13), 2765–2774.
Silva, G.S., Lima, F.O., Camargo, E.C., Smith, W.S., Lev, M.H., Harris, G.J., Halpern, E.F., Koroshetz, W., Furie, K.L., 2010. Gender differences in outcomes after ischemic stroke: role of ischemic lesion volume and intracranial large-artery occlusion. Cerebrovasc. Dis. 30 (5), 470–475.
Simon, N.G., Whalen, R.E., 1986. Hormonal regulation of aggression: evidence for a relationship among genotype, receptor binding, and behavioral sensitivity to androgen and estrogen. Aggress. Behav. 12, 255–266.
Simpkins, J., Rajakumar, G., Zhang, Y.-Q., Simpkins, C., Greenwald, D., Yu, C., Bodor, N., Day, A., 1997. Estrogens may reduce mortality and ischemic damage caused by middle cerebral artery occlusion in the female rat. J. Neurosurg. 87, 724–730.
Sinchak, K., Roselli, C.E., Clemens, L.G., 1996. Levels of serum steroids, aromatase activity, and estrogen receptors in preoptic area, hypothalamus, and amygdala of B6D2F1 male house mice that differ in the display of copulatory behavior after castration. Behav. Neurosci. 110 (3), 593–602.
Snyder, J.S., Hong, N.S., McDonald, R.J., Wojtowicz, J.M., 2005. A role for adult neurogenesis in spatial long-term memory. Neuroscience 130, 843–852.
Snyder, H.M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D.B., Espeland, M.A., Gatz, M., Mielke, M.M., Raber, J., Rapp, P.R., Yaffe, K., Carrillo, M.C., 2016. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's Research Initiative. Alzheimers Dement. 12, 1186–1196.
Sohrabji, F., 2015. Estrogen-IGF-1 interactions in neuroprotection: ischemic stroke as a case study. Front. Neuroendocrinol. 36, 1–14.
Song, Z.F., Chen, D.Y., Du, B., Ji, X.P., 2013. Poly (ADP-ribose) polymerase inhibitor reduces heart ischaemia/reperfusion injury via inflammation and Akt signalling in rats. Chin. Med. J. 126 (10), 1913–1917.
Spalding, K.L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H.B., Boström, E., Westerlund, I., Vial, C., Buchholz, B.A., Possnert, G., Mash, D.C., Druid, H., Frisén, J., 2013. Dynamics of hippocampal neurogenesis in adult humans. Cell 153 (6), 1219–1227.
Spiteri, T., Ågmo, A., 2009. Ovarian hormones modulate social recognition in female rats. Physiol. Behav. 98, 247–250.
Spiteri, T., Musatov, S., Ogawa, S., Ribeiro, A., Pfaff, D.W., Ågmo, A., 2010. The role of the estrogen receptor alpha in the medial amygdala and ventromedial nucleus of the hypothalamus in social recognition, anxiety and aggression. Behav. Brain Res. 210, 211–220.
Spritzer, M.D., Solomon, N.G., Meikle, D.B., 2005. Influence of scramble competition for mates upon the spatial ability of male meadow voles. Anim. Behav. 69, 425–436.
Stagliano, N.E., Dietrich, W.D., Prado, R., Green, E.J., Busto, R., 1997. The role of nitric oxide in the pathophysiology of thromboembolic stroke in the rat. Brain Res. 759 (1), 32–40.
Stary, C.M., Xu, L., Sun, X., Ouyang, Y.B., White, R.E., Leong, J., Li, J., Xiong, X., Giffard, R.G., 2015. MicroRNA-200c contributes to injury from transient focal cerebral ischemia by targeting Reelin. Stroke J. Cereb. Circ. 46 (2), 551–556.
Sun, Y., Zhou, L., Lv, D., Liu, H., He, T., Wang, X., 2015. Poly(ADP-ribose) polymerase 1 inhibition prevents interleukin-1beta-induced inflammation in human osteoarthritic chondrocytes. Acta Biochim. Biophys. Sin. (Shanghai) 47 (6), 422–430.
Suzuki, S., Brown, C.M., Wise, P.M., 2009. Neuroprotective effects of estrogens following ischemic stroke. Front. Neuroendocrinol. 30 (2), 201–211.
Swan, A.A., Clutton, J.E., Chary, P.K., Cook, S.G., Liu, G.G., Drew, M.R., 2014. Characterization of the role of adult neurogenesis in touch-screen discrimination learning. Hippocampus 24 (12), 1581–1591.
Switzer, J.A., Hess, D.C., Ergul, A., Waller, J.L., Machado, L.S., Portik-Dobos, V., Pettigrew, L.C., Clark, W.M., Fagan, S.C., 2011. Matrix metalloproteinase-9 in an exploratory trial of intravenous minocycline for acute ischemic stroke. Stroke J. Cereb. Circ. 42 (9), 2633–2635.
Switzer, J.A., Sikora, A., Ergul, A., Waller, J.L., Hess, D.C., Fagan, S.C., 2012. Minocycline prevents IL-6 increase after acute ischemic stroke. Transl. Stroke Res. 3 (3), 363–368.
Szot, P., Dorsa, D.M., 1993. Differential timing and sexual dimorphism in the expression of the vasopressin gene in the developing rat brain. Brain Res. Dev. Brain Res. 73, 177–183.
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. 19, 5792–5801.
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 (Pt A), 350–366.
Terranova, J.I., Song, Z., Larkin, T.E., Hardcastle, N., Norvelle, A., Riaz, A., Albers, H.E., 2016. Serotonin and arginine-vasopressin mediate sex differences in the regulation of dominance and aggression by the social brain. Proc. Natl. Acad. Sci. U. S. A. 113 (46), 13233–13238.
Thor, D.H., 1980. Testosterone and persistence of social investigation in laboratory rats. J. Comp. Physiol. Psychol. 94, 970–976.
Tirilizad Steering Committee, 2000. Tirilazad mesylate in acute ischemic stroke. Syst. Rev. 31, 2257–2265.

Toung, T.K., Hurn, P.D., Traystman, R.J., Sieber, F.E., 2000. Estrogen decreases infarct size after temporary focal ischemia in a genetic model of type 1 diabetes mellitus. Stroke 31 (11), 2701–2706.
Towfighi, A., Markovic, D., Ovbiagele, B., 2013. Sex differences in revascularization interventions after acute ischemic stroke. J. Stroke Cerebrovasc. Dis. 22 (8), e347–353.
Trainor, B.C., Lin, S., Finy, M.S., Rowland, M.R., Nelson, R.J., 2007. Photoperiod reverses the effects of estrogens on male aggression via genomic and nongenomic pathways. Proc. Natl. Acad. Sci. U. S. A. 104, 9840–9845.
Trainor, B.C., Finy, M.S., Nelson, R.J., 2008. Rapid effects of estradiol on male aggression depend on photoperiod in reproductively non-responsive mice. Horm. Behav. 53, 192–199.
Tuscher, J.J., Fortress, A.M., Kim, J., Frick, K.M., 2015. Regulation of object recognition and object placement by ovarian sex steroid hormones. Behav. Brain Res. 285, 140–157.
Tuscher, J.J., Luine, V.N., 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.
Valsecchi, P., Galef, B.G.J., 1989. Social influences on the food preferences of house mice (*Mus musculus*). Int. J. Comp. Psychol. 2, 245–256.
van der Worp, H.B., de Haan, P., Morrema, E., Kalkman, C.J., 2005. Methodological quality of animal studies on neuroprotection in focal cerebral ischaemia. J. Neurol. 252 (9), 1108–1114.
vom Saal, F.S., 1979. Prenatal exposure to androgen influences morphology and aggressive behavior of male and female mice. Horm. Behav. 12, 1–11.
Voyer, D., Voyer, S.D., Saint-Aubin, J., 2016. Sex differences in visual-spatial working memory: a meta-analysis. Psychon. Bull. Rev. http://dx.doi.org/10.3758/s13423-016-1085-7.
Wade, C.B., Dorsa, D.M., 2003. Estrogen activation of cyclic adenosine 5'-monophosphate response element-mediated transcription requires the extracellularly regulated kinase/mitogen-activated protein kinase pathway. Endocrinology 144, 832–838.
Wade, C.B., Robinson, S., Shapiro, R.A., Dorsa, D.M., 2001. Estrogen receptor (ER)α and ERß exhibit unique pharmacologic properties when coupled to activation of the mitogen-activated protein kinase pathway. Endocrinology 142, 2336–2342.
Walf, A.A., Rhodes, M.E., Frye, C.A., 2006. Ovarian steroids enhance object recognition in naturally cycling and ovariectomized, hormone-primed rats. Neurobiol. Learn. Mem. 86, 35–46.
Walmer, D.K., Wrona, M.A., Hughes, C.A., Nelson, K.G., 1992. Lactoferrin expression in the mouse reproductive tract during the natural estrous cycle: correlation with circulating estradiol and progesterone. Endocrinology 131, 1458–1466.
Wang, Z.X., Bullock, N.A., Devries, G.J., 1993. Sexual differentiation of vasopressin projections of the bed nucleus of the stria terminals and medial amygdaloid nucleus in rats. Endocrinology 132, 2299–2306.
Wang, T., Han, W., Wang, B., Jiang, Q., Solberg-Woods, L.C., Palmer, A.A., Chen, H., 2014a. Propensity for social interaction predicts nicotine-reinforced behaviors in outbred rats. Genes Brain Behav. 13, 202–212.
Wang, Y., Zhao, S., Liu, X., Fu, Q., 2014b. Effects of the medial or basolateral amygdala upon social anxiety and social recognition in mice. Turk. J. Med. Sci. 44, 353–359.
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.
Waters, E.M., Yildirim, M., Janssen, W.G., Lou, W.Y., McEwen, B.S., Morrison, J.H., Milner, T.A., 2011. Estrogen and aging affect the synaptic distribution of estrogen receptor beta-immunoreactivity in the CA1 region of female rat hippocampus. Brain Res. 1379, 86–97.
Waters, E.M., Thompson, L.I., Patel, P., Gonzales, A.D., Ye, H.Z., Filardo, E.J., Clegg, D.J., Gorecka, J., Akama, K.T., McEwen, B.S., Milner, T.A., 2015. G-protein-coupled estrogen receptor 1 is anatomically positioned to modulate synaptic plasticity in the mouse hippocampus. J. Neurosci. 35, 2384–2397.
Watters, J.J., Campbell, J.S., Cunningham, M.J., Krebs, E.G., Dorsa, D.M., 1997. Rapid membrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene transcription. Endocrinology 138, 4030–4033.
Wilson, M., Daly, M., 1985. Competitiveness, risk taking, and violence: the young male syndrome. Ethol. Sociobiol. 6, 59–73.
Winocur, G., 1990. Anterograde and retrograde amnesia in rats with dorsal hippocampal or dorsomedial thalamic lesions. Behav. Brain Res. 38, 145–154.
Wood, G.E., Shors, T.J., 1998. Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones. Proc. Natl. Acad. Sci. U. S. A. 95 (7), 4066–4071.
Wooten, G.F., Currie, L.J., Bovbjerg, V.E., Lee, J.K., Patrie, J., 2004. Are men at greater risk for Parkinson's disease than women? J. Neurol. Neurosurg. Psychiatry 75, 637–639.
Workman, J.L., Chan, M.Y., Galea, L.A., 2015. Prior high corticosterone exposure reduces activation of immature neurons in the ventral hippocampus in response to spatial and nonspatial memory. Hippocampus 25 (3), 329–344.
Wyman, M.J., Cutter, A.D., Rowe, L., 2012. Gene duplication in the evolution of sexual dimorphism. Evol. Int. J. Org. Evol. 66, 1556–1566.
Xu, L.J., Ouyang, Y.B., Xiong, X., Stary, C.M., Giffard, R.G., 2015. Post-stroke treatment with miR-181 antagomir reduces injury and improves long-term behavioral recovery in mice after focal cerebral ischemia. Exp. Neurol. 264, 1–7.
Yagi, S., Chow, C., Lieblich, S.E., Galea, L.A., 2016. Sex and strategy use matters for pattern separation, adult neurogenesis, and immediate early gene expression in the hippocampus. Hippocampus 26 (1), 87–101.
Yagi, S., Drewczynski, D., Wainwright, S.R., Barha, C.K., Hershorn, O., Galea, L.A., 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.
Yang, S.H., Perez, E., Cutright, J., Liu, R., He, Z., Day, A.L., Simpkins, J.W., 2002. Testosterone increases neurotoxicity of glutamate in vitro and ischemia-reperfusion injury in an animal model. J. Appl. Physiol. 92 (1), 195–201.
Yang, D.W., Pan, B., Han, T.Z., Xie, W., 2004. Sexual dimorphism in the induction of LTP: critical role of tetanizing stimulation. Life Sci. 75, 119–127.
Yang, C.F., Chiang, M.C., Gray, D.C., Prabhakaran, M., Alvarado, M., Juntti, S.A., Unger, E.K., Wells, J.A., Shah, N.M., 2013. Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males. Cell 153, 896–909.
Yang, Y., Salayandia, V.M., Thompson, J.F., Yang, L.Y., Estrada, E.Y., Yang, Y., 2015. Attenuation of acute stroke injury in rat brain by minocycline promotes blood-brain barrier remodeling and alternative microglia/macrophage activation during recovery. J. Neuroinflammation 12, 26.
Yokomaku, D., Numakawa, T., Numakawa, Y., Suzuki, S., Matsumoto, T., Adachi, N., Nishio, C., Taguchi, T., Hatanaka, H., 2003. Estrogen enhances depolarization-induced glutamate release through activation of phosphatidylinositol 3-kinase and mitogen-activated protein kinase in cultured hippocampal neurons. Mol. Endocrinol. 17, 831–844.
Yoshida, T., Limmroth, V., Irikura, K., Moskowitz, M.A., 1994. The NOS inhibitor, 7-nitroindazole, decreases focal infarct volume but not the response to topical acetylcholine in pial vessels. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 14, 924–929.
Young, L.J., Wang, Z., Donaldson, R., Rissman, E.F., 1998. Estrogen receptor α is essential for induction of oxytocin receptor by estrogen. Neuroreport 9, 933–936.
Yrjanheikki, J., Tikka, T., Keinanen, R., Goldsteins, G., Chan, P.H., Koistinaho, J., 1999. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc. Natl. Acad. Sci. U. S. A. 96 (23), 13496–13500.
Yuan, M., Siegel, C., Zeng, Z., Li, J., Liu, F., McCullough, L.D., 2009. Sex differences in the response to activation of the poly (ADP-ribose) polymerase pathway after experimental stroke. Exp. Neurol. 217 (1), 210–218.
Zandi, P.P., Carlson, M.C., Plassman, B.L., Welsh-Bohmer, K.A., Mayer, L.S., Steffens, D.C., Breitner, J.C.S., 2002. Hormone replacement therapy and incidence of Alzheimer disease in older women. JAMA 288, 2123–2129.
Zeng, L., Liu, J., Wang, Y., Wang, L., Weng, S., Tang, Y., Zheng, C., Cheng, Q., Chen, S., Yang, G.Y., 2011. MicroRNA-210 as a novel blood biomarker in acute cerebral ischemia. Front. Biosci. (Elite Ed.) 3, 1265–1272.
Zhang, Q.G., Han, D., Wang, R.M., Dong, Y., Yang, F., Vadlamudi, R.K., Brann, D.W., 2011. C terminus of Hsc70-interacting protein (CHIP)-mediated degradation of hippocampal estrogen receptor-alpha and the critical period hypothesis of estrogen neuroprotection. Proc. Natl. Acad. Sci. U. S. A. 108, E617–624.
Zhang, R.L., Zhang, Z.G., Chopp, M., 2013. Targeting nitric oxide in the subacute restorative treatment of ischemic stroke. Expert. Opin. Investig. Drugs 22 (7), 843–851.
Zhang, X.Y., Chen, D.C., Tan, Y.L., Tan, S.P., Wang, Z.R., Yang, F.D., Xiu, M.H., Hui, L., Lv, M.H., Zunta-Soares, G.B., Soares, J.C., 2014. Gender difference in association of cognition with BDNF in chronic schizophrenia. Psychoneuroendocrinology 48, 136–146.
Zhang, B.H., Han, M., Zhang, X.Y., Hui, L., Jiang, S.R., Yang, F.D., Tan, Y.L., Wang, Z.R., Li, J., Huang, X.F., 2015. Gender differences in cognitive deficits in schizophrenia with and without diabetes. Compr. Psychiatry 63, 1–9.
Zhao, Z., Fan, L., Frick, K.M., 2010. Epigenetic alterations regulate the estradiol-induced enhancement of memory consolidation. Proc. Natl. Acad. Sci. U. S. A. 107, 5605–5610.