Social behavior, hormones and adult neurogenesis

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ABSTRACT

A variety of experiences have been shown to affect the production of neurons in the adult hippocampus. These effects may be mediated by experience-driven hormonal changes, which, in turn, interact with factors such as sex, age and life history to alter brain plasticity. Although the effects of physical experience and stress have been extensively characterized, various types of social experience across the lifespan trigger profound neuroendocrine changes in parallel with changes in adult neurogenesis. This review article focuses on the influence of specific social experiences on adult neurogenesis in the dentate gyrus and the potential role of hormones in these effects.

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1. Introduction

Adult neurogenesis in the dentate gyrus is sensitive to a large number of internal and external cues. The production and survival of new neurons (Fig. 1) can be modulated by growth factors, neurotransmitters and hormones, as well as by environmental conditions and specific experiences (see Song et al., 2012; Shors et al., 2012; Cameron and Glover, 2015 for reviews). While the regulation of adult neurogenesis by physical activity and stress has been extensively examined (Opendak and Gould, 2015), a smaller but emerging body of evidence has focused on social experience, particularly in the context of understanding the function of adult-generated neurons. Several studies have examined a variety of social experiences, including mating, social stress and parenting, on the production and survival of new neurons, with a particular emphasis on the functional consequences of such experience-induced changes. Social experiences have a strong influence on endocrine factors known to affect adult neurogenesis, suggesting several interesting potential connections. Additional findings have linked new neurons to social behavior itself. Taken together, these findings suggest that social experience may modulate adult neurogenesis through changes in hormones in order to shape the hippocampus so that it produces appropriate social behavior. This review article will consider studies that have explored the influence of specific social experiences on adult neurogenesis in the dentate gyrus, the potential role of hormones

in these effects, as well as the impact such changes may have on behaviors associated with the hippocampus.

2. Sexual experience effects on adult neurogenesis

Social interactions can be stressful, rewarding, or a combination of the two. At least for some species, sexual experience may provide a straightforward example of a rewarding social interaction. Female hamsters form conditioned place preferences following sexual encounters (Meisel and Joppa, 1994), and male rats will readily form such preferences and learn to bar-press to gain access to a sexually receptive female (Everitt and Stacey, 1987; Tenk et al., 2009). For nonhuman primates as well, male and female rhesus monkeys will learn operant tasks to gain access to a receptive mate (Keverne, 1976; Michael and Keverne, 1968). In line with these results, sexual experience has been associated with activation of reward circuitry in the brain (Paredes, 2009). However, sexual experience is far from simple in terms of its effects on the brain and body, engaging an array of neural and hormonal systems. This complex and contingent behavior can exert profound effects on structural plasticity in the adult brain. For instance, transitioning from a reproductively suppressed subordinate to a dominant breeder in a hierarchy of naked mole rats produces robust changes in brain structure, including increased neurons in brain nuclei related to sexual behavior (Holmes et al., 2007). Sexual experience has been shown to increase the rate of adult neurogenesis in the hippocampus of young adult (Leuner et al., 2010b) and middle aged male rats (Glasper and Gould, 2013), as well as the number of dendritic spines on granule cells of the dentate gyrus (DG)

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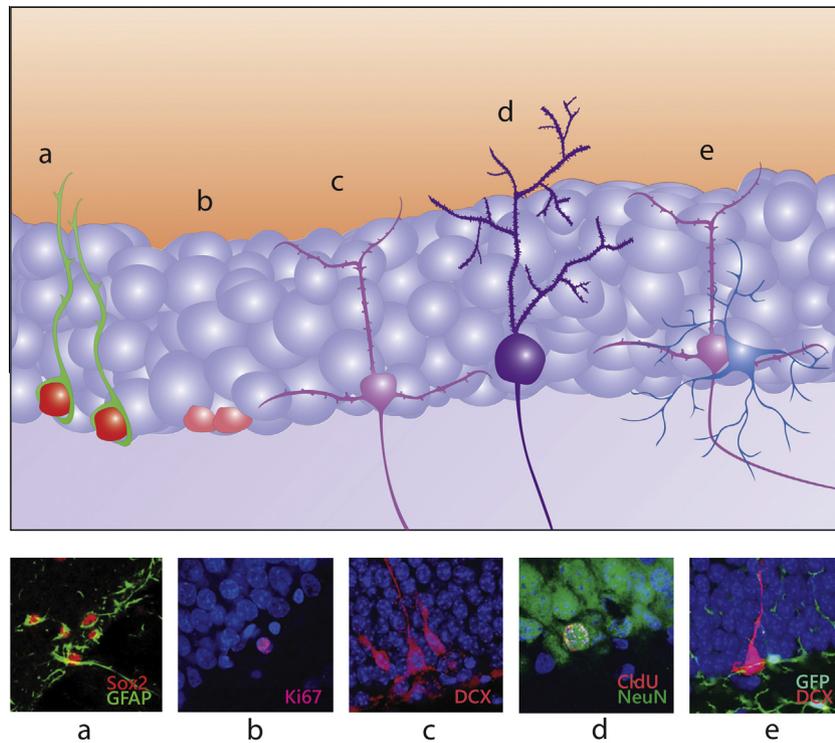E-mail address: goulde@princeton.edu (E. Gould).

Fig. 1. Stages of adult neurogenesis in the dentate gyrus. Social interaction can affect the production of new neurons at one or multiple stages in their development. Top panel: Schematic diagram of adult neurogenesis in the granule cell layer of the dentate gyrus showing relevant cell types at different stages in the process. First, new neurons originate from precursor cells that have glial-like characteristics (A). These cells proliferate (B) and produce daughter cells that differentiate into immature neurons (C). Some of these immature neurons will survive and differentiate into mature neurons (D), while others will degenerate and their debris will be cleared by microglial phagocytosis (E). Bottom panel: confocal microscopic images of different cell types in the process of adult neurogenesis: (A) Glia-like precursor cells; Sox2 (red), Glial fibrillary acidic protein (GFAP) (green). (B) Proliferating precursor cells; Ki67 (red), Hoechst 33342 (blue). (C) Immature granule cells labeled with doublecortin (DCX) (red), Hoechst 33342 (blue). (D) Mature granule cells labeled with NeuN (green), CldU, a thymidine analog taken up by proliferating cells (red), Hoechst 33342 (blue). (E) Immature neuron near microglial cell, labeled with green fluorescent protein (GFP). DCX (red), GFP (green), Hoechst 33342 (blue).

of adult male rats (Glasper et al., 2015; Leuner et al., 2010b) (Fig. 1). Although the exact mechanisms through which these effects occur are unknown, several lines of evidence suggest the involvement of hormonal signals. The hippocampus is enriched with receptors for gonadal hormones, oxytocin, luteinizing hormone (LH), and prolactin, which may contribute to the effects of sexual experience on adult neurogenesis and dendritic spines in this brain region (Galea et al., 2013; Gimpl and Fahrenholz, 2001; Mak and Weiss, 2010).

Sexual experience provides a particularly useful paradigm through which to study experiential regulation of adult neurogenesis, as it can be reproduced readily in the laboratory and engages a variety of hormonal mechanisms that differ between sexes and across the lifespan. In young adult male rats, merely one sexual encounter is sufficient to stimulate cell proliferation in the hippocampus (Leuner et al., 2010a,b). Despite many possible candidates, a straightforward mechanistic description of this phenomenon remains elusive. Indeed, sexual experience is not defined by a unidimensional experience but rather comprises a complex combination of environmental, social and physiological cues and behaviors. Furthermore, the effects of reproductive hormones on adult neurogenesis may depend on species, sex differences, hormonal status, life history and social status. Indeed, even environmental cues associated with sexual experience, independently of mating itself, may induce changes in brain plasticity. Understanding the endocrinology underlying sexual experience may provide clues to the growth-promoting nature of this behavior.

2.1. Baseline differences in hormone levels

The effects of sexual experience on adult neurogenesis may depend on an animal's baseline endocrine status, which varies between males and females, as well as across species. Since endocrine systems are highly intertwined, a complete understanding of the role of hormones in the effects of sexual experience on adult neurogenesis requires a comprehensive view of multiple endocrine systems. However, in order to begin to understand the effects of hormones on adult neurogenesis in a naturalistic social context, it may be instructive to begin by examining what is known about individual hormone effects on adult neurogenesis.

Although no studies to date have examined the effects of sexual experience on adult neurogenesis in female rats, evidence exists that exposure to male pheromones stimulates adult neurogenesis in the dentate gyrus, as well as in the olfactory bulb of female mice (Mak et al., 2007). These findings strongly suggest that sexual contact, which naturally involves olfactory cues, would do the same. It is particularly interesting to note that stimulation of adult neurogenesis did not occur with exposure to pheromones of subordinate males, raising the possibility that while olfactory cues are sufficient to induce the effect when the male is dominant, actual mating behavior may be necessary to stimulate neuron growth when the male is subordinate (Mak et al., 2007). As will be discussed later in this review, social status appears to be a salient mediator of experience-dependent effects on adult neurogenesis.

It is likely that the hormonal state of the female is important for eliciting the stimulatory effects of sexual experience on adult

neurogenesis. In females of many species, the estrous cycle is a potent modulator of sexual behavior through periodic fluctuations in the levels of reproductive hormones. It has been demonstrated that female rats have higher baseline rates of cell proliferation in the hippocampus than males, but only when female rats are in proestrus (Tanapat et al., 1999). However, species differences in estrous cycle changes appear to exist; similar fluctuations in cell production in the dentate gyrus of adult mice have not been detected (Lagace et al., 2007; Overall et al., 2013; Tzeng et al., 2014).

Another important variable to consider in the effects of sexual experience on adult neurogenesis may be the receptivity of the female, e.g., differences in forced mating versus controllable conditions. As mentioned previously, we are not aware of a direct measure of the effects of sexual experience on adult neurogenesis in female rats. However, lordosis can only occur if females are sexually receptive; although this can be experimentally induced, mating is not possible with a female that is not receptive (Yamanouchi, 1980). Therefore, known measures of the effects of sexual experience in males can only be from conditions where a female was receptive. Even female odors, which are sufficient to induce hormonal changes in male rats, must be sampled while females are in a receptive state in order to produce these effects (Bonilla-Jaime et al., 2006). On the other hand, sexually experienced males that attempted to mount an unreceptive female showed increases in LH, prolactin, and testosterone (Kamel et al., 1977) – hormones that are known to stimulate adult neurogenesis (see Sections 2.3 and 2.5 for more detail). These findings suggest that even if the female is not willing, additional cues related to sexual experience may lead to anticipatory increases in hormone levels that can affect adult neurogenesis (See Section 2.7 for further discussion).

2.2. Estrogen, sexual experience, and adult neurogenesis

Studies in the wild and in the laboratory have shown a link between sexual experience, estrogen levels and the production of new neurons. Of the three principal forms of estrogen, estrone, estradiol and estriol, estradiol (E_2) is the most potent and, for this reason, is typically used in laboratory paradigms (McClure et al., 2013; Rannevik et al., 1995). E_2 confers dose-dependent neurotrophic and neuroprotective effects throughout the brain, including in the hippocampus (Lee and McEwen, 2001), but its effects on adult neurogenesis in this region vary with species, animal sex and treatment duration (see Table 1). These effects can alter one or multiple aspects of new neuron production, altering cell proliferation and/or the survival (including differentiation and maturation) of these new cells (Fig. 1). As mentioned above, female rats in proestrus have slightly higher baseline rates of cell proliferation than males. This suggests that acute increases in estrogen may simulate these changes; indeed, acute estrogen administration stimulates cell proliferation within 2–4 h. However, this effect is reversed after 48 h and abolished after an exposure of 3 days, suggesting that the effects of estrogen are highly dependent on dosage and timing (Banasr et al., 2001; Ormerod et al., 2003).

In order to interpret the effects of exogenous E_2 on stages of adult neurogenesis in the hippocampus, it is important to consider how E_2 levels following administration to ovariectomized (OVX) females compare to endogenous estrogen levels in cycling females. A single injection of 10 μg E_2 in OVX females results in proestrus levels of circulating E_2 (Sohrabji et al., 1994; Viau and Meaney, 1991) and rescues OVX-induced decreases in cell proliferation to sham levels one week after OVX, but not four weeks after OVX (Tanapat et al., 1999, 2005). This suggests that, over time, OVX may suppress the ability of proliferating cells to respond to estrogen, perhaps through changes in estrogen receptor densities. Furthermore, extragonadal sources of estrogen (Zhao et al., 2005)

may increase endogenous estrogen levels following OVX to restore cell proliferation. Acute injection of 0.3 μg of E_2 restores estrogen levels to the diestrus range (Viau and Meaney, 1991) yet also produces increases in cell proliferation (Barha et al., 2009). On the other hand, acute administration of 1.0 μg and 50 μg E_2 failed to produce increases in cell proliferation (Barha et al., 2009; Tanapat et al., 2005). Although these dose-dependent effects of E_2 are complex, a clear picture emerges regarding chronic E_2 administration, which fails to stimulate adult neurogenesis at any dose (see Pawluski et al., 2009 for review). These effects may be related to down-regulation of receptors or changes in levels of other hormones, such as adrenal steroids (see Section 2.9 for further discussion).

Long-lasting changes in E_2 levels in seasonal breeding animals reveal the importance of species and baseline hormone levels in the link between sexual experience and adult neurogenesis (see Table 1). Female meadow voles caught during their breeding season exhibit high levels of E_2 and low levels of cell proliferation, compared with OVX rats or reproductively inactive voles; the opposite pattern is observed when these females are caught during the non-breeding season (Galea and McEwen, 1999). Furthermore, differences in social strategies between species can determine the effects of hormone levels on adult neurogenesis: E_2 administration increased cell proliferation in the DG of the promiscuous meadow vole, but did not produce changes in the pair-bonding prairie vole species (Fowler et al., 2005). These effects appear to also depend on the age of an animal, as will be discussed below (Section 2.8).

The effects of exogenous E_2 appear to depend on whether the species in question is typically exposed to high levels of gonadal steroids. Exogenous E_2 administration to female meadow voles enhances cell survival while chronic E_2 injections suppress adult neurogenesis in female rats (Barker and Galea, 2009; Ormerod et al., 2003). Unlike rats, with a 4 day estrous cycle with highly fluctuating estrogen and progesterone levels, voles exhibit inducible ovulation with consistently high levels of circulating estrogen over 20–30 days (Carter et al., 1989; Ormerod and Galea, 2001; Ormerod et al., 2003). Consequently, chronic exogenous estrogen administration to a vole is less likely to create a highly unnatural hormonal milieu than the same hormone regimen for a rat. As will be discussed in Section 2.9, the suppressive effects of chronic estrogen appear to be mediated by glucocorticoid levels (Ormerod et al., 2003). It is interesting to note that while E_2 injections at all stages of cell maturation increase cell survival in female voles, the survival of new neurons was only enhanced in castrated males if E_2 was administered on day 4–10 after cell birthdating with bromodeoxyuridine (BrdU) during the axon extension phase of new neurons (Hastings and Gould, 1999; Ormerod and Galea, 2001; Ormerod et al., 2004).

Evidence suggests that estrogen may work directly in the hippocampus to affect adult neurogenesis. There are two estrogen receptor (ER) subtypes (ERα and ERβ), both of which are expressed in the dentate gyrus, on neurons and astrocytes (ERβ only) (Azcoitia et al., 1999). ERα mediates both male and female sexual behavior (Kudwa et al., 2006). Studies have shown co-localization of DNA synthesis markers and ERα/ERβ mRNA and protein (Mazzucco et al., 2006). Co-localization of ERβ with the immature neuron marker doublecortin (DCX) suggests that E_2 may act directly on neurons in the hippocampus to impact cell survival. Administration of an ERβ antagonist to adult females prevented increases in cell proliferation related to levels of insulin-like growth factor-1 (IGF-1) (Perez-Martin et al., 2003), a growth factor that has been linked to changes in adult neurogenesis with physical exercise (Glasper et al., 2010).

Serotonin may be involved in the effects of estrogen on adult neurogenesis, as blockade of serotonin receptors with an antagonist prevents estrogen-induced increases in cell proliferation

Table 1

Summary of effects of social experience on adult neurogenesis and putative hormonal substrates. Social experience can alter one or multiple aspects of new neuron production, through effects of cell proliferation and/or the survival (including differentiation and maturation) of these new cells (see Fig. 1). Neuroendocrine changes associated with these specific experiences are suggested as putative mechanisms for changes in adult neurogenesis.

Social experience	Species/sex	Adult neurogenesis	References	Potential hormonal involvement
Acute sexual encounter	Rat ♂	↑ Neurogenesis ↑ Cell proliferation	Leuner et al. (2010b)	OT, T, Prl, LH
Repeated sexual encounter	Rat ♂	↑ Neurogenesis	Glasper and Gould (2013) and Leuner et al. (2010b)	OT, T, Prl, LH
Breeding season	Meadow vole ♀ (wild-caught)	↓ Cell proliferation ↑ Cell survival	Galea and McEwen (1999) and Ormerod and Galea (2001)	E$_2$, CORT E$_2$
	Meadow vole ♂ (wild-caught)	↔ Cell proliferation	Ormerod et al. (2003, 2004)	E$_2$, OT, T, DHT
Exposure to dominant male pheromones	Mouse ♀	↑ Cell proliferation	Mak et al. (2007) and Mak and Weiss (2010)	T, Prl, LH
	Sheep ♀	↑ Cell proliferation	Hawken et al. (2009) and Smith et al. (2001)	E$_2$, LH
Acute social defeat	Rodent ♂, tree shrew ♂, marmoset ♂ (subordinates)	↓ Neurogenesis ↓ Cell proliferation	Lagace et al. (2007) and Schoenfeld and Gould (2011)	CORT
Chronic social defeat	Rat ♂ (subordinate)	↓ Cell proliferation/survival	Van Bokhoven et al. (2011)	CORT, T
	Mouse ♂ (subordinate)	↓ Neurogenesis ↓ Cell proliferation	Czéh et al. (2007) and Ferragud et al. (2010)	CORT
Social isolation	Rat ♂♀ (adolescent)	↓ Neurogenesis ↓ Cell proliferation/survival	Lu et al. (2003) and McCormick et al. (2005)	CORT ♀
	Guinea pig ♂ (adolescent)	↓ Cell proliferation/survival	Rizzi et al. (2007)	CORT
	Mouse ♂ (adolescent)	↔ Cell proliferation	Heine et al. (2004) and Ibi et al. (2008)	CORT
	Mouse ♂	↓ Neurogenesis	Dranovsky et al. (2011)	CORT
Maternal separation	Rat ♂ (adolescent)	↓ Cell proliferation[a]/survival ↓ Cell differentiation	Greisen et al. (2005a) and Mirescu et al. (2004)	CORT
	Rat ♂	↓ Neurogenesis ↓ Cell proliferation	Oomen et al. (2010)	CORT
Dominance hierarchy	Rat ♂ (dominant)	↑ Neurogenesis	Kozorovitskiy and Gould (2004)	T, LH, OT T
	Rat ♂ (subordinate)	↔ Neurogenesis		
	Baboon ♂ (dominant)	↑ Neurogenesis	Wu et al. (2014)	CORT
	Baboon ♂ (subordinate)	↓ Neurogenesis		CORT
Disrupted social hierarchy	Rat ♂	↓ Neurogenesis	Opendak et al. (2015)	CORT, OT
Parenting	Rat ♀	↓ Neurogenesis	Leuner et al. (2007) and Pawluski and Galea (2007)	CORT
	California mouse ♂♀	↓ Neurogenesis	Glasper et al. (2011)	CORT

CORT, corticosterone; E$_2$, estradiol; HPA, hypothalamic-pituitary-adrenal axis; LH, luteinizing hormone; OT, oxytocin; Prl, prolactin; T, testosterone.

[a] Contradictory evidence.

in the hippocampus (Banasr et al., 2001). Furthermore, polymorphism in the serotonin transporter interacts with female macaque dominance status to mediate the effects of estrogen administration on sexual motivation (Michopoulos et al., 2011; Toufexis et al., 2014). E$_2$ synthesis in the early postnatal hippocampus also appears to play a role in plasticity in this region; blocking *de novo* E$_2$ synthesis in cultured hippocampal neurons from PN5 female rats decreased cell proliferation and increased apoptosis (Fester et al., 2006). Taken together, these findings present intriguing clues about the role of reproductive hormones in adult neurogenesis in females, as well as some suggestive evidence for natural circumstances that impact brain plasticity.

2.3. Androgens

Unlike females, male rodents typically have relatively stable baseline levels of gonadal hormones. As such, sexual experience likely interacts with these levels to affect adult neurogenesis in a sex-specific manner. Increases in the rate of new neuron formation in male rats following sexual experience may involve androgens, including testosterone and its metabolite dihydrotestosterone (DHT), although it appears these effects are specific to increasing cell survival, not proliferation. Testosterone levels are increased following sexual contact in male rats (Bonilla-Jaime et al., 2006). Seasonal variation in androgen levels has been correlated with levels of adult neurogenesis in wild meadow voles (Galea and McEwen, 1999; Ormerod and Galea, 2001), with higher numbers of surviving new cells in males that were reproductively active when testosterone levels were high, compared to when levels were low in males without reproductive activity. A causal link has been established through studies showing that castration of male rats reduces cell survival, and that injections of testosterone and DHT can increase survival of newborn neurons in the castrated adult male rat in the laboratory (Spritzer and Galea, 2007). These manipulations, like naturally occurring testosterone variations, failed to induce changes in cell proliferation. Effects of androgens may also depend on species, as gonadectomy has been shown to *increase* cell survival in the hippocampus of adolescent macaques (Allen et al., 2014). These manipulations were performed in pre-pubertal animals, whereas most rodent studies typically involve gonadectomy in adulthood; as such, age is an important consideration in comparing these effects. However, species differences are likely to be as important in interpretation of results as gonadectomy in adolescent male rats appears to have no effect on cell proliferation or neuronal survival (Ho et al., 2012; Allen et al., 2015).

Although testosterone can be converted to E$_2$ via the aromatase enzyme, E$_2$ administration failed to mimic the effects of testosterone in males, suggesting that these neuroprotective effects work through an androgen receptor-dependent mechanism (Spritzer and Galea, 2007). Androgen receptors are expressed in the CA1 and CA3 regions of the rat hippocampus (Tabori et al., 2005), although the Wistar rat strain appears to express these receptors in the DG (Brännvall et al., 2005; Hamson et al., 2013). It is important to note that although these effects are typically highlighted in males, an animal's breeding status can trump sex differences in the expression of androgen receptors in the adult brain (Holmes et al., 2007, 2008). Administration of flutamide, an androgen receptor antagonist, prevented increases in adult neurogenesis in the hippocampus of adult male rats, and males lacking androgen receptors did not show an increase in neuronal survival following androgen treatment. There were no differences in the survival of new neurons in rats lacking androgen receptors that received either androgen or vehicle treatments; androgen treatment only increased survival in wild-type males (Hamson et al., 2013).

Treatment duration is an important factor in these effects, as testosterone treatments shorter than 30 days either suppressed new neuron survival or had no effect (Brännvall et al., 2005; Carrier and Kabbaj, 2012; Hamson et al., 2013; Spritzer and Galea, 2007; Spritzer et al., 2011). It is important to note that this contrasts with a single bout of sexual experience, which causes an acute increase in testosterone and an increase in cell proliferation (Bonilla-Jaime et al., 2006; Kamel et al., 1977; Leuner et al., 2010b). Repeated exposure to sexually receptive females did not produce persistently elevated levels of testosterone; instead, testosterone peaked after the first sexual contact and returned to baseline thereafter (Shulman and Spritzer, 2014). These results, in combination with the report of increased neurogenesis after two weeks of daily sexual contact (Leuner et al., 2010b), support a dissociation between the amount of sexual activity a male rat engages in and circulating testosterone levels (Damassa et al., 1977; Smith et al., 1977).

It is difficult to explore the necessity of testosterone in sexual experience-induced increases in adult neurogenesis, given the necessity of the hormone for sexual behavior. However, available evidence is consistent with the possibility that testosterone itself drives not only sexual behavior, but may be involved in the effect of this experience on adult neurogenesis.

2.4. Progesterone

Progesterone modulates many of the behavioral and physiological effects of estrogen and regulates testosterone in the control of sexual behavior in males (Butcher et al., 1974). This hormone is a crucial mediator of the reproductive system and appears to be important for normal reproductive function and arousal in both sexes. Progesterone knockout males show fewer sexual advances and females lacking progesterone receptors are infertile (Conneely et al., 2003; Phelps et al., 1998). Estrogen and progesterone have highly contingent effects on the brain, as progesterone receptor levels in the subgranular zone of the DG have been shown to increase after E$_2$ treatment, and alternatively decrease after progesterone treatment (Guerra Araiza et al., 2003). Furthermore, elevation in progesterone levels following E$_2$ elevation eliminates or reduces E$_2$-related increases in adult neurogenesis in the adult female rat (Tanapat et al., 2005). Progesterone treatment alone increased cell proliferation in adult male rats and, somewhat paradoxically, progesterone reverses increased cell proliferation in male rats following traumatic brain injury (Barha et al., 2011). In addition, progesterone metabolite administration has been shown to enhance cell proliferation *in vitro* (Wang et al., 2005). There is also some evidence that administration of progesterone in male mice doubles the survival rate of adult born neurons when administered 5–7 days post incorporation of BrdU (Zhang et al., 2010). It may be that, as a whole, the effects of progesterone induce a net positive increase in adult neurogenesis in males and a decrease in females. However, it remains unknown whether these effects are dominant in animals having species-typical experiences that involve changes in multiple relevant hormones.

2.5. Oxytocin, prolactin and luteinizing hormone

Beyond estrogen and androgen release, sexual experience and related cues can induce profound changes in peptide hormones that may, in turn, affect adult brain plasticity. Among these, oxytocin, prolactin and LH have been shown to stimulate adult neurogenesis in the hippocampus (Leuner et al., 2012; Mak and Weiss, 2010).

Oxytocin is a peptide that is released from the pituitary gland, as well as throughout the brain, during sexual activity and is involved in affiliative behavior and mating across a variety of species (Mooney et al., 2014; Numan and Young, 2015). This is an attractive candidate mechanism for mating-induced changes in adult neurogenesis, as the hippocampus is dense with oxytocin

receptors (Gimpl and Fahrenholz, 2001). An acute dose of oxytocin administered to male rats either centrally or peripherally increases cell proliferation in the ventral DG, but not in the subventricular zone (SVZ), and chronic administration for seven days increases the number of adult-born neurons in the hippocampus (Leuner et al., 2012). The closely related peptide vasopressin fails to reproduce these effects. It is likely that oxytocin is working directly in the hippocampus to stimulate cell proliferation, possibly via oxytocin receptors expressed by proliferating precursor cells (Opendak et al., 2015). As oxytocin effectively mimics sexual experience effects on adult neurogenesis in terms of time course, region-specific actions and its ability to buffer elevated glucocorticoid levels, this neurohormone likely plays a role in the mechanism by which sexual experience increases adult neurogenesis.

Sexual experience may affect adult neurogenesis through changes in levels of prolactin, which is elevated in response to sexual activity, in both appetitive aspects, such as lordosis posture in females, and consummatory aspects, such as intromission and ejaculation in males (Exton et al., 2001). Mak and Weiss (2010) showed that exogenous infusion of prolactin increases adult neurogenesis in both the DG and SVZ. Furthermore, exogenous administration of prolactin has been shown reverse stress-induced decreases in neurogenesis (Torner et al., 2009). Although sexual activity induces prolactin release in both sexes, females, but not males, lacking prolactin receptors exhibit reproductive irregularities (Binart et al., 2010; Snowdon and Ziegler, 2015). In females, pregnancy-induced increases in adult SVZ neurogenesis are mediated by prolactin (Shingo et al., 2003). This stimulation of adult neurogenesis can also result after a virgin female is mated with a vasectomized male, resulting in "pseudopregnancy," or infertile mating. In this scenario, sexual stimulation results in the generation of a functional corpus luteum that secretes estrogen and progesterone; as mentioned above, both of these hormones may be sufficient to impact adult neurogenesis (Smith et al., 1975).

The gonadotropin LH is a potent modulator of sexual maturation, gestation and reproductive behavior that also exerts profound effects on plasticity in the adult brain. In adult males, LH is released from the anterior pituitary under the control of gonadotropin-releasing hormone to stimulate testosterone production in the testes; during sexual arousal, pulses of LH occur in concert with increases in plasma testosterone. Interestingly, males that were unable to initiate sexual behavior due to medial preoptic area lesions showed LH increases when exposed to a receptive female (Kamel and Frankel, 1978), suggesting that sexual motivation, rather than consummation, is sufficient to engage this hormone. LH administration increases adult neurogenesis in both the SVZ and DG, independently of the effects of prolactin (Mak and Weiss, 2010). The effects of this hormone are difficult to separate from those of testosterone; an open question remains whether LH retains the ability to increase cell proliferation in gonadectomized males.

LH may be a primary substrate for pheromone-dependent increases in hippocampal neurogenesis in females. As mentioned above, Mak and Weiss (2010) observed increases in DCX-labeled immature neurons and BrdU labeled cells that express the neuronal marker NeuN in the DG of females exposed to male pheromones; these increases were not the result of suppressed apoptosis. Unlike the prolactin receptor, which is only expressed in the SVZ in females, LH receptors are present in both the SVZ and DG of female rats, and exogenous administration of LH increased neurogenesis in the DG by over 50%. During proestrus in females, LH levels influence the production of estrogen in the ovaries and administration of LH-releasing factor to OVX-hypophysectomized females induces the appetitive lordosis reflex (Daane and Parlow, 1971; Pfaff, 1973). As LH administration can increase cell proliferation in both intact and OVX females, it is

likely that LH engages the hippocampus directly to increase neurogenesis, independently of estrogen, through action on hippocampal LH receptors (Mak et al., 2007).

2.6. External cues related to sexual experience

Although copulation itself produces profound hormonal changes, external cues related to mating are also major effectors of changes in adult brain plasticity. Pheromones, non-tactile exposure, and environmental cues can not only potentiate appetitive sexual behaviors, but evidence also suggests that these cues can induce changes in adult brain plasticity through anticipatory increases in hormones related to sexual experience.

Whereas sexually experienced male rats exhibit increases in LH, follicle stimulating hormone, prolactin and testosterone after a single mating encounter, testosterone, prolactin and LH levels can be increased by estrus female odor alone, as well as attempting to mate with an unreceptive female (Kamel et al., 1977; Kamel and Frankel, 1978; Bonilla-Jaime et al., 2006). As described above, this anticipatory surge in LH may be sufficient to induce changes in adult neurogenesis. This was also observed in female mice, as exposure to pheromones from a dominant male increases cell proliferation in the neurogenic regions via a prolactin-dependent mechanism in the SVZ and via LH in the DG (Mak and Weiss, 2010). This effect specifically required an intact main olfactory system, rather than an intact vomeronasal organ, as destruction of the olfactory epithelium through $ZnSO_4$ application prevented increases in cell proliferation following pheromone exposure. The presence of testosterone was also crucial for these effects, as using odor from gonadectomized males precluded increases in cell proliferation in females.

Unlike mice and rats with a continuously fluctuating estrous cycle, voles have an inducible proestrus state, which can be triggered by exposure to male pheromones (Cohen-Parsons and Carter, 1987). In prairie voles, this male (or male pheromone)-induced proestrus increases estrogen levels and ERs in the brain (Hnatczuk and Morrell, 1995; Smith et al., 2001). This is also the case in sheep: exposure of ewes to novel males in a surge of peripheral LH and E_2 (Hawken et al., 2009). A single exposure to a novel male, in the absence of physical contact, produces an increase in cell proliferation in the hippocampus within hours. In addition to estrogen, this effect is likely mediated by increases in levels of LH, which can cross the blood brain barrier (Lukacs et al., 1995) to act directly upon hippocampus LH receptors (Abtahi et al., 2013).

2.7. Experience-related effects

Prior sexual history is an important mediating factor in the effects of mating-induced hormonal changes on adult neurogenesis. For instance, mating produces an increase in testosterone levels in sexually-experienced males, but not naïve males (Bonilla-Jaime et al., 2006; Kamel et al., 1977, but see Shulman and Spritzer, 2014). Furthermore, testosterone and corticosterone increase in experienced males even in the absence of intromission or ejaculation (Bonilla-Jaime et al., 2006). Even environmental cues associated with a prior sexual experience are sufficient to increase testosterone and LH in sexually experienced males (Graham and Desjardins, 1980). Oxytocin-related brain changes can also depend on prior sexual experience. Oxytocinergic neurons in the paraventricular nucleus and medial preoptic area in sexually experienced, but not naïve, males preferentially express c-Fos immunoreactivity following exposure to female estrus odor (Nishitani et al., 2004; Witt and Insel, 1994).

Experience-dependent effects may relate to differences between acute and chronic exposure to sexual experience and

related stimuli. Indeed, a single sexual encounter in a naive animal likely interacts with a very different baseline hormonal milieu than a single sexual encounter in an animal with a history, even if recent, of similar experiences. A single sexual experience increases cell proliferation in the hippocampus in male rats, while daily sexual encounters for two weeks increase the survival of new neurons. (Leuner et al., 2010b). These findings parallel data showing that acute oxytocin administration in naive animals increases cell proliferation in the absence of sexual contact, while daily injections over seven days increases adult neurogenesis (Leuner et al., 2012). Effects of chronic sexual experience may also reflect changes due to persistently elevated levels of prolactin, which has been shown to remain high after multiple ejaculations in male rats (Phillips-Farfán and Fernández-Guasti, 2009). As mentioned previously, testosterone levels are unlikely to mediate the effects of chronic sexual experience on adult neurogenesis (Shulman and Spritzer, 2014).

Familiarity with a partner also can mediate the effects of sexual experience on adult neurogenesis. While one study showed survival of new neurons increased following repeated copulation with a mix of familiar and unfamiliar female partners (Leuner et al., 2010b), another group reported that repeated encounters with unfamiliar females suppressed adult neurogenesis (Spritzer et al., 2016). This discrepancy may also be related to the timing of BrdU administration, which occurred after sexual experience in the first study and before sexual experience in the second.

It appears that unless a sexual experience is stressful, most cues relevant to mating will trigger hormonal changes in experienced males, even including failed attempts at mounting a non-receptive female (Kamel et al., 1977). These findings have led some authors to conclude that some elevations in testosterone, LH, and prolactin measured after sexual experience may actually reflect anticipatory increases that precede sexual behavior, rather than result from it (Graham and Desjardins, 1980; Shulman and Spritzer, 2014). As such, the motivational and appetitive aspects of sexual experience may be a more salient variable than consummation in modulating adult neurogenesis in the hippocampus.

2.8. Sexual experience and adult neurogenesis across the lifespan

Adult neurogenesis in male rats has been shown to decrease with age (Glasper and Gould, 2013). Perhaps in a related manner, gonadal hormone levels have also been shown to decrease across the lifespan (Pawluski et al., 2009). Sexual experience can prevent these decreases; a single 30 min bout of sexual activity, as well as continuous exposure to a receptive female, increased cell proliferation and adult neurogenesis in retired breeding males (Glasper and Gould, 2013). Sexual activity may also restore hippocampal plasticity in females; middle-aged nulliparous females failed to show changes in adult neurogenesis following ovariectomy or E_2 treatment, while sexual contact prevented this effect (Barha et al., 2011). This may be related to changes in sensitivity of adult neurogenesis to E_2 treatment in old age, as chronic E_2 increases cell proliferation in female rats aged 22 months, without effects at younger ages (Perez-Martin et al., 2005). However, sensitivity to acute estrogen is also reversed in 12 month-old females, as acute E_2 in these older rats fails to replicate the stimulatory effect on cell proliferation seen at younger ages (Chiba et al., 2007).

2.9. Sexual experience and stress

Hormonal regulation of adult neurogenesis is not limited to a specific set of "reproductive hormones". Rather, there is a reciprocal interaction between the hypothalamic pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes (Carey et al., 1995; Mastorakos et al., 2006; Viau, 2002). In females, the release

of gonadal hormones modulates the HPA response to stress; E_2 increases corticocosterone levels in rodents, baboons and monkeys by preventing negative regulation of the HPA axis (Carey et al., 1995; Giussani et al., 2000). These effects may reflect combined effects of elevated progesterone and estrogen levels; an acute dose of E_2 was shown to suppress the HPA response to restraint and predator stress in rats and mice (Falconer and Galea, 2003; Young et al., 2001), In the wild, corticosterone and E_2 levels are both elevated during the breeding season and are negatively correlated with rates of cell proliferation in female meadow voles (Galea and McEwen, 1999). Ormerod et al. (2003) found that adrenal steroids mediate E_2-induced suppression of cell proliferation in the dentate gyrus, as 48 h of chronic E_2 fails to suppress cell proliferation in ADX and OVX females. In addition, female rats in proestrus exhibit longer lasting corticosterone elevations following stress, and higher levels of stress-induced adrenocorticotropic hormone (ACTH) (Viau and Meaney, 1991). Conversely, high corticosterone levels cause a temporary disruption of the estrous cycle of virgin females (Brummelte and Galea, 2010).

In contrast, testosterone in males decreases ACTH and corticosterone responses to stress, while gonadectomy increases these (Seale et al., 2004). It appears somewhat paradoxical, therefore, that sexual activity induces parallel increases in both testosterone and corticosterone in males (Bonilla-Jaime et al., 2006; Leuner et al., 2010b). Furthermore, the degree to which sex increases corticosterone levels can depend on prior mating history: in Wistar rats, this increase is highest in experienced males (Bonilla-Jaime et al., 2006). It is further unclear how a rewarding experience can robustly increase neurogenesis amid increased corticosterone levels, which are known to have the opposite effect on new neuron production (Opendak and Gould, 2015; Schoenfeld and Gould, 2012). The interaction between mating and stress on adult neurogenesis appears, therefore, to depend on a variety of factors, including sex, age and endocrine status.

Sexual experience increases adult neurogenesis despite an elevation in plasma glucocorticoids, which robustly suppress adult neurogenesis. A similar phenomenon has been observed in wheel running in rodents. This paradoxical outcome has been attributed to the hedonic value of this activities (Opendak et al., 2015; Schoenfeld and Gould, 2012). Sexual experience is a strong motivator in rodents, as males will bar press to gain access to a receptive female and learn place preferences to copulation (Paredes, 2009; Tenk et al., 2009). The voluntary nature of this activity likely plays a major role in its ability to buffer stress. Voluntary wheel running buffers the effects of stress hormones whereas forced running does not; animals in the wild will also run if provided a wheel, suggesting this activity is naturally rewarding (Holmes et al., 2004; Meijer and Robbers, 2014; Moraska et al., 2009).

The rewarding aspects of sexual experience provide clues to the mechanism by which it affects adult neurogenesis. The release of opioids, oxytocin, dopamine and serotonin can all accompany rewarding activities (Schoenfeld and Gould, 2011). Dopamine and serotonin have both been shown to have positive effects on adult neurogenesis (Klempin et al., 2013; Takamura et al., 2014). Furthermore, changes in dopamine metabolism that have been linked with sexual experience and serotonin have been shown to mediate the effects of voluntary wheel running on stress. As mentioned above, serotonin mediates the effects of estrogen on adult brain plasticity. In addition, socially rewarding experiences can induce oxytocin release, which may buffer the effects of stress through negative regulation of the HPA axis (Cohen et al., 2010; Windle et al., 2004). Indeed, oxytocin administration increased adult neurogenesis in the hippocampus even in the presence of elevated corticosterone levels and following exposure to a stressor (Leuner et al., 2012). Since increased androgen levels are known to be anxiolytic (Aikey et al., 2002; Frye and Seliga, 2001), it is

possible that release of androgens during sexual experience buffers the deleterious effects of stress hormones on adult neurogenesis. Social status may be a crucial mediator of such an effect, as there are parallel increases in androgen receptors and stress hormone-sensitive CRF$_1$ receptors in the brains of reproductively suppressed naked mole rats (Beery et al., 2016; Holmes et al., 2008).

Sexual activity reverses increases in plasma corticosterone and decreases in plasma testosterone due to chronic stress (Retana-Márquez et al., 2014). In line with these findings, the combination of stress and sexual experience produces control levels of adult neurogenesis (Kim et al., 2013). Spritzer et al. (2009) also showed that previous sexual experience reversed the deleterious effects of exposure to predator odor on adult neurogenesis and decreased risk assessment behavior, possibly by reducing anxiety. It is important to note that these authors did not observe an increase in cell proliferation following mating unless mating was accompanied with predator odor exposure. This additive process may involve BDNF, a neurotrophin that has been linked with increased adult neurogenesis following voluntary wheel running (Vivar et al., 2013; Yau et al., 2014). A single bout of sexual experience increases expression of BDNF and its receptor TrkB in the hippocampus and reverses the decrease in BDNF following restraint stress (Kim et al., 2013).

The voluntary nature and motivational aspects of sexual experience may produce sexually dimorphic effects. As discussed above, it remains to be seen whether non-receptive females would show an increase in adult neurogenesis following exposure to male odor (Mak and Weiss, 2010). Additional evidence for the importance of motivation is suggested by the fact that male rats which showed no interest in female rats also fail to show an increase in testosterone levels when exposed to female estrus odor (Bonilla-Jaime et al., 2006), although testosterone implants into the medial preoptic area were able to induce copulation in low-motivation males (Antonio-Cabrera and Paredes, 2014).

3. Social stress effects on adult neurogenesis

The social environment is complex, not only providing opportunities for mating and other affiliative behaviors, but also stressful scenarios involving competition, social rejection, isolation and fear. These social stressors are known to produce abnormal behaviors in mammals, such as increased anxiety (Huot et al., 2001), impaired fear response (Ladd et al., 2000), impaired learning in spatial navigation tasks (Huot et al., 2002) and compromised social behavior (Lovic et al., 2001), to name a few. Thus, understanding the molecular and cellular responsiveness to social stress will provide more insight into these depression-like behavioral phenotypes. Many studies have investigated the role of social stress using paradigms involving social defeat, social isolation and maternal separation. Although work using laboratory stress paradigms that do not include a social component has been informative, models of stressful social experience are necessary for understanding how the brains of social animals respond to such aversive situations.

3.1. Social defeat

Competition for resources and territory can engender agonistic behaviors in two otherwise docile animals. A male rat will establish territoriality when given sufficient living space, especially in the presence of female odors and after sexual experience (Albert et al., 1988; Barnett et al., 1968). This can be replicated in the lab through the use of the resident-intruder paradigm, in which an unfamiliar animal is placed in the cage of a territorial resident and subsequently attacked (see Fig. 2). Stress induced by social defeat has been shown to have suppressive effects on cell

proliferation and neurogenesis in the dentate gyrus of male tree shrews, rodents and marmosets (Schoenfeld and Gould, 2012). When a subordinate tree shrew is defeated by a comparatively dominant conspecific in an established dominant-subordinate relationship, the subordinate not only experiences physiological stress, but persistent psychosocial stress (von Holst, 1977) which induces a constant state of arousal in the presence of the dominant. This results in suppressive effects on the number of new cells generated in the dentate gyrus of the subordinate tree shrew (Gould et al., 1997). Studies have also shown that social defeat results in a loss of total granule cell layer volume, concomitant with increased levels of corticosterone after twenty-eight days of exposure to the dominant adult tree shrew (Fuchs et al., 1995). Similarly, in marmosets, a single exposure to the resident-intruder paradigm suppresses cell production in the dentate gyrus of the intruder (Gould et al., 1998). This resident-intruder paradigm has been shown to increase levels of circulating glucocorticoids through activation of the HPA axis.

Exposure to chronic social defeat has suppressive effects on cell proliferation and survival in the intact dentate gyrus of adult rodents. Adult male rat intruders were introduced to the home cage of another male rat, and intruders were subsequently attacked and defeated by the resident. After initial exposure, intruders were stationed in an enclosure within the resident's cage daily for five weeks. Chronic social defeat resulted in a decrease in number of proliferating and surviving new cells in the dentate gyrus of intruders (Czéh et al., 2007). Similarly, adult male mice underwent chronic social stress through repeated exposures to aggressive and dominant male counterparts. The number of proliferating cells and immature neurons were reduced in the dentate gyrus (see Fig. 1), along with impaired spatial navigation learning (Ferragud et al., 2010). Five days of exposure to social defeat and a subsequent three months of social isolation, all without significant changes in circulating corticosterone levels, produced a decrease in number of DCX-positive labeled cells in the intact dentate gyrus of adult male rats (Van Bokhoven et al., 2011). Collectively, these findings suggest that aggressive and threatening experiences between conspecifics suppress cell proliferation in the mammalian dentate gyrus.

3.2. Social isolation

Another type of stress that is known to suppress new neuron production is social isolation, in which animals are removed from group-housing and individually housed (see Fig. 2). Social isolation rearing paradigms allow for analysis of early life stress effects on brain development and organization. In adolescent male rats, four and eight weeks of social isolation during the weaning period significantly decreased cell proliferation and newborn cell survival compared to group-housed weaning counterparts (Lu et al., 2003). However, the decrease in cell proliferation and production after four weeks of social isolation was rescued by four subsequent weeks of group housing (Lu et al., 2003). Social isolation rearing in adolescent male guinea pigs affected cell proliferation, survival and differentiation in the intact dentate gyrus (Rizzi et al., 2007). Another study conducted on adolescent male mice replicated the effects of social isolation weaning on survival of newly dividing cells, but found no effect on cell proliferation in the intact dentate gyrus after social isolation (Ibi et al., 2008). A different social isolation paradigm examined a combination of chronic unpredictable stressors, one of which was social isolation (Heine et al., 2004). The chronic unpredictable stressors group showed a decrease in cell proliferation rate, but also showed suppression of apoptosis and recovery of cell proliferation rate after 3 weeks in adolescent male mice.
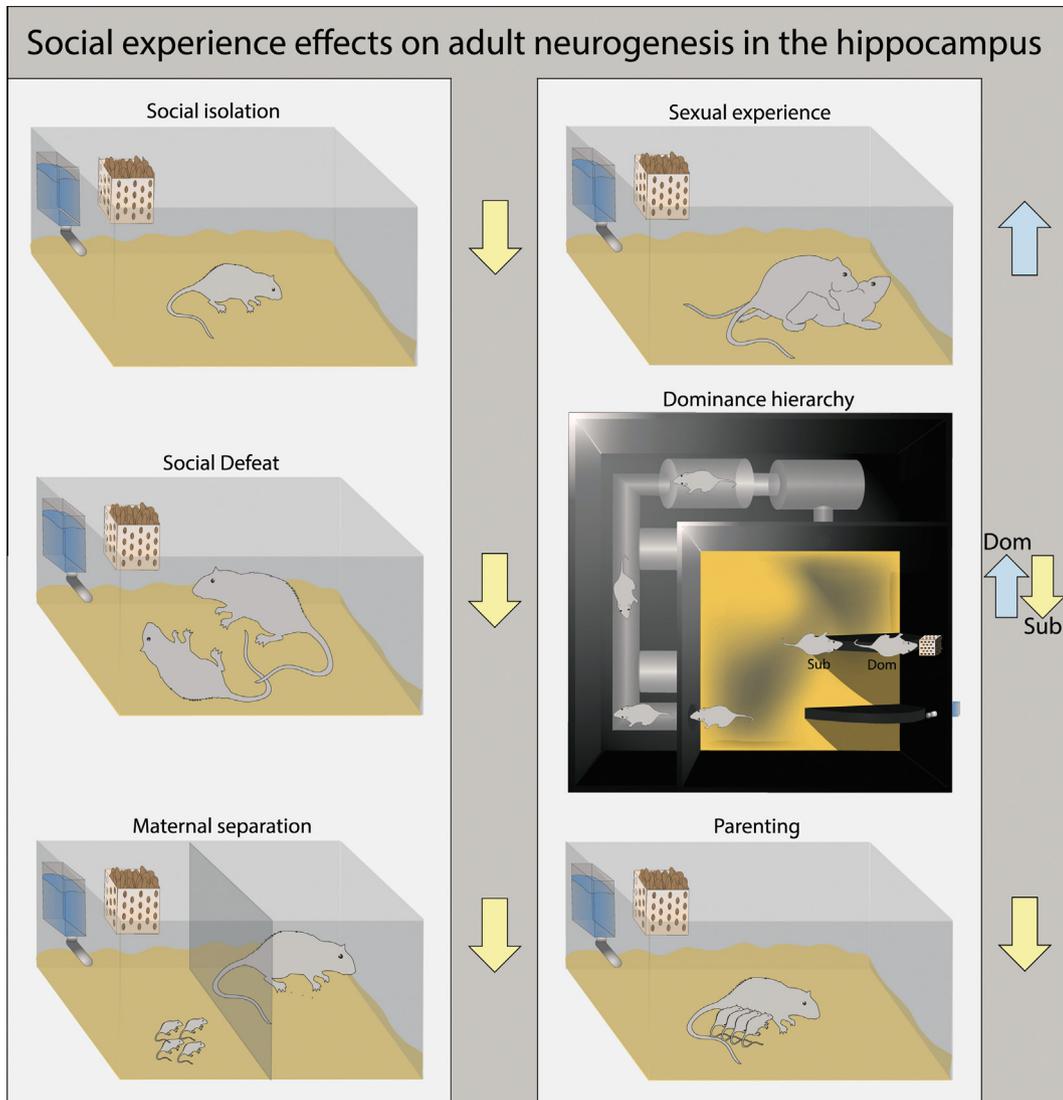
Fig. 2. Effects of typical social interactions on adult neurogenesis in the hippocampus in rodents. Interactions with a hedonic component, such as sexual experience and living as a dominant in a social hierarchy, stimulate adult neurogenesis, while a variety of social stressors, including social isolation, social defeat and maternal separation, inhibit adult neurogenesis. This suggests that activation of reward pathways is responsible for increases in cell proliferation and survival. However, an important exception to this claim can be observed with parenting, which has a strong hedonic component, but is associated with suppressed adult neurogenesis.

In contrast to early life social isolation, adult mice exposed to social isolation showed a decrease in DCX-positive cells (Dranovsky et al., 2011). This study further analyzed social isolation effects on adult mice neural stem cell (NSC) lineage in the intact dentate gyrus and found an increase in NSCs 1 month after tamoxifen administration. The significant increase was diminished by the 3 month time point, but provided further evidence of social relationship effects on cell proliferation. In adult rats, social isolation was shown to prevent the enhancement of new neuron production from positive regulators of neurogenesis. Physical exercise, such as running, is known to profoundly increase the number of new neurons in the dentate gyrus of adult mice (van Praag et al., 1999), but single-housed access compared to group-housed access to a running wheel altered these positive effects on adult neurogenesis in male rats (Stranahan et al., 2006), as well as females (Leasure and Decker, 2009). In males, the socially isolated running effects were rescued by decreasing corticosterone levels following adrenalectomy (Stranahan et al., 2006). While these studies are instructive in linking social environment to cell plasticity, for most species, social isolation is a relatively rare

occurrence, although it does have potential implications for solitary confinement in humans. Thus, it is unclear how to generalize these results to rodent behavior in animals living under natural circumstances.

3.3. Maternal separation

Similar to social isolation, maternal separation paradigms allow for the investigation of both the immediate and long-term effects of social deprivation stress on cell proliferation and adult neurogenesis. Maternal care effects on the hippocampus have been shown to be analogous to stress effects (Champagne et al., 2008; Lyons et al., 2009) by changing HPA axis function (Levine, 2000). It should be noted that maternal separation effects may be driven not necessarily by the absence of the mother, but by her behavior once the dam has been reunited with her pups.

The behavioral effects of maternal separation appear to be sexually dimorphic, leading to impairments in sexual reproductive behaviors in male but not female rodents (Greisen et al., 2005b; Rhees et al., 2001). Male rats subjected to maternal separation

for 24 h on postnatal day (PND) 3 showed reduced levels of cell proliferation, cell survival and neuronal differentiation in the dentate gyrus weeks later (Oomen et al., 2010). Moreover, adult rats showed a decrease in new cells in the intact dentate gyrus after experiencing 3 h of daily maternal separation beginning at PND1 for 2 weeks, compared to their counterparts experiencing only 15 min of maternal separation for the same period of time (Mirescu et al., 2004). Although these rats experienced persistent suppression of cell proliferation in adulthood, there were no observed changes in basal corticosterone levels, similarly to adult rats exhibiting learned helplessness (Malberg and Duman, 2003). This information holds the implication that early-life trauma is sufficient to induce long-term consequences in the ability of the adult brain to generate new neurons. However, contradictory evidence has shown stimulation of hippocampal brain-derived neurotrophic factor in rat pups maternally separated at 3 h intervals, along with maintained levels of adult neurogenesis compared to 15 min maternal separated counterparts, in adulthood (Greisen et al., 2005a). Thus it is unclear which aspect(s) of maternal separation affect behavior and adult neurogenesis, how or why compensatory responses are or are not triggered, and whether the effects are long-lasting.

3.4. Social stress: the involvement of hormones

Although much work has explored hormonal systems as substrates for the effects of stress on adult neurogenesis, understanding of these systems with respect to *social* stress remain incomplete. Neuromodulators, such as glutamate, and steroidal hormones, such as glucocorticoids and testosterone, have been implicated in the regulation of cell proliferation in response to social stress (see Table 1). Increased levels of glutamate and NMDA receptor activation in the hippocampus have been shown to suppress granule cell production and inhibit cell proliferation in an intact dentate gyrus during adolescent development and adulthood (Gould et al., 1997; Tanapat et al., 1998). This compensatory response to prolonged exposure to psychosocial stress leads to reduction in hippocampal volume, dendritic arborization and adult neurogenesis (McEwen, 2001). Social defeat decreases testosterone secretion in defeated male rats (Schuurman, 1980), but these testosterone effects, conceivably a product of increased levels of circulating corticosteroids, have not shown a direct effect on cell proliferation in the hippocampus (Buwalda et al., 2010) (see Section 2.3). In a social isolation study, adolescent male and female rats were exposed to novel cage mates after each social isolation trial for 48 days and then returned to their original cage mate. The same animals then underwent additional social isolation trials in adulthood. This chronic social isolation stress paradigm altered the HPA stress response in females, but not males (McCormick et al., 2005). Females showed increased corticosterone release in response to a novel stressor, suggesting that females are more vulnerable to the effects of early life stress due to potential differences of HPA axis regulation in adolescence. This difference may also be a product of naturally higher glucocorticoid levels in females than males in basal and stress-induced conditions (Kitay, 1961; Mevel et al., 1979). Sex differences in neural plasticity observed in response to social stress may be due, but not limited, to a combination of differences in regulation of the HPA axis and reproductive hormones. Overall, the suppressive effects of stressful social experiences on neurogenesis suggest that elevated glucocorticoid levels drive effects on cell proliferation. However, elevated glucocorticoid levels do not always result in suppressed neurogenesis within the hippocampus (see Sections 2.9 and 5), suggesting that other factors, including activation of specific neural pathways, are likely to play an important determining role. Many open questions remain regarding the mechanisms underlying changes to brain and behavior following exposure to complex social stressors.

4. Dominance hierarchies

The extent to which social experiences, such as fighting and mating, affect adult brain plasticity may be informed by an animal's position within a larger group. Dominance hierarchies provide one example of a complex social arrangement determined by individual differences. In the wild, rats are among a wide variety of species that naturally form dominance hierarchies as a result of competition for limited resources. This scenario can be replicated in the lab through the use of a visible burrow system (VBS), a semi-naturalistic enclosure made of Plexiglas and wood, with an open field and a network of chambers and tunnels. When mixed-sex rats are placed in a VBS, a brief period of fighting ensues until one male rat emerges as the dominant; this animal subsequently has preferential access to food, water, and receptive females (Blanchard et al., 1995). Through use of the VBS, researchers can observe the additive effects of multiple aspects of social life, including social stress and sexual experience. As a result, this paradigm can provide a useful lens through which to study ethologically relevant social behaviors and their effect on the brain. Previous studies have shown that dominant rats in a VBS produce more new neurons in the dentate gyrus than do subordinates (Kozorovitskiy and Gould, 2004). Although the exact mechanisms underlying this phenomenon remain unknown, hormonal changes involved in the formation and maintenance of social dominance hierarchies are likely to shed light on these processes.

4.1. Social position and adult neurogenesis

A rich literature has described the effects of life in a dominance hierarchy, including on measures of behavior, hormones and physiology (Blanchard et al., 1995; Hardy et al., 2002). These studies have focused on differences between dominants and subordinates within the aggressive Long Evans (LE) strain. When LE rats form a dominance hierarchy within a VBS, it has been shown that subordinate rats have elevated levels of corticosterone compared to dominants (Blanchard et al., 1995; Hardy et al., 2002). Subordinate rats show a decrease in aggression, overall activity, sexual and social behaviors, and an increase in a range of defensive responses to the dominant male (Blanchard et al., 1995, 2001). In addition, subordinates exhibit increases in the relative sizes of adrenal glands and spleen and decreases in the sizes of the thymus and testes than dominants.

Given the suppressive effect of corticosterone on adult neurogenesis, glucocorticoids are an attractive candidate mechanism to explain the difference between dominants and subordinates in new neuron production. However, the study in which dominants exhibited increased neurogenesis used the comparatively docile Sprague Dawley strain. This modification was intended to circumvent the highly stressful aspects of violent agonistic encounters observed with the LE strain. With additional slight modifications designed to simulate competition, Sprague Dawleys formed stable hierarchies, but there were no differences in stress reactivity, basal stress hormones, or in thymus, adrenal, or spleen weights. Despite a robust positive link between environmental complexity and adult neurogenesis, this aspect of the VBS was not responsible for increases in adult neurogenesis in dominant rats, as removal of complex burrows and tunnels failed to abolish differences between dominants and subordinates (Kozorovitskiy and Gould, 2004) (Fig. 2). Finally, subordinates did not differ from cage controls on measures of adult neurogenesis, indicating that a relative increase in dominants drove the difference, rather than a decrease in subordinates presumably following experience in a highly stressful social environment. This is in line with work showing that, in the absence of acute stress, defensive behavior

in subordinates is not sufficient to suppress adult neurogenesis (Falconer and Galea, 2003; Holmes and Galea, 2002). Therefore, a broader set of hormonal and neuroendocrine changes must be examined in order to understand the basis for these differences resulting from social status.

One benefit of social dominance in rats is preferential access to receptive females, which likely translates to increased opportunities for sexual experience. As described above, frequent sexual activity can result in elevated levels of gonadal hormones that can stimulate neurogenesis in the hippocampus, potentially resulting in increased production of new neurons in dominant rats. Support for this hypothesis is evident in a study of LE rats living in a VBS for two weeks; dominants exhibited persistently elevated levels of plasma testosterone and LH compared to subordinate rats (Hardy et al., 2002). As described above, both of these hormones can increase adult neurogenesis in male rodents, and testosterone levels may also increase amid agonistic encounters (Mak and Weiss, 2010; Spritzer and Galea, 2007). Although LH levels were not measured, testosterone levels did not differ between dominant and subordinate Sprague Dawley rats that exhibited differences in adult neurogenesis (Kozorovitskiy and Gould, 2004). This result may be expected, however, as testosterone appears to require a much longer course of treatment to produce changes in the production of new neurons (Spritzer and Galea, 2007).

It may be that dominants generate more new neurons as a result of increased levels of oxytocin and prolactin from frequent sexual experience. As mentioned above, both of these have been shown to increase during copulation and, separately, increase adult neurogenesis in the hippocampus (Exton et al., 2001; Leuner et al., 2012; Mak and Weiss, 2010). Oxytocin, LH and prolactin have not been directly measured in animals living in a dominance hierarchy, partially due to the difficulty in accurately capturing any sex-related increases in a timely manner. This may be irrelevant, however, as studies of social dominance in other species suggest that sexual experience may not be responsible for the differences observed in dominants. Within a social hierarchy of baboons, dominant males produce more new neurons than lower ranking males, with no evidence that dominants were more sexually experienced than subordinates (Wu et al., 2014). The authors also failed to observed changes in circulating glucocorticoid levels in subordinates, although testosterone levels were not reported. On the other hand, work using the hierarchical naked mole rat species shows that transitioning from a reproductively suppressed subordinate to a dominant breeder in a rigid reproductive hierarchy produces massive structural changes in the brains of subordinate males and females, in a manner that appears to depend on a combination of social cues and sexual experience itself (Holmes et al., 2007, 2008). Finally, it may be that the rewarding aspects of social dominance engage similar reward systems as do mating and voluntary wheel running to affect adult neurogenesis, such as the release of opioids, oxytocin, dopamine and serotonin.

4.2. Disrupting a social hierarchy

The VBS allows researchers to simulate the conditions that allow for the emergence of complex social arrangements, as well as for naturalistic perturbations of such arrangements. In the wild, an established hierarchy can be destabilized if a dominant dies or leaves the community. This change can be simulated in the laboratory by switching dominants between two parallel stable hierarchies, a manipulation that results in profound behavioral and physiological changes, including renewed fighting and reorganization of established social orders (Opendak et al., 2015). Disrupting an established dominance hierarchy decreases adult neurogenesis in all animals, regardless of social position, and prevents the increases observed in dominants living in a stable

hierarchy. Although the number of proliferating cells did not differ three days after disruption, neural progenitors and immature neurons were decreased in rats living in a disrupted dominance hierarchy. In addition, oxytocin receptor expression in the ventral hippocampus was increased in rats from a disrupted hierarchy, an effect observed previously following exposure to chronic, non-habituating stress (Liberzon and Young, 1997). The mechanisms for these changes remain unclear, as we failed to observe increases in corticosterone or testosterone levels in animals that had experience in disrupted hierarchies. Paradoxically, rats from a disrupted hierarchy exhibited a blunted corticosterone response compared to animals in stable hierarchies and cage controls. This may reflect the phenomenon of hypocortisolism, which can occur following repeated activation of the HPA axis (Heim et al., 2000; Rohleder et al., 2004). Overall, these results showed that certain experiences, such as social disruption, can trump the individual differences in the production of new neurons that result from living in a stable hierarchy.

4.3. Sex differences

For most rodent species, dominance hierarchies have typically been shown to occur among males, not females. Indeed, studies of enriched environment living effects on the brain often include primarily female mice to avoid the establishment of dominance hierarchies and related fighting. Dominance hierarchies among females, however, are relatively common in nonhuman primates.

Female macaques have a 28-day menstrual cycle which makes them a particularly useful model for studying the interaction between social status, psychosocial stress and the reproductive axis (Appt, 2004; Catchpole and van Wagenen, 1975; Wallen et al., 1984). Neurogenesis in adult females of different social status has not been evaluated, but some evidence suggests that social position mediates the effects of hormones known to alter the production of new neurons. Toufexis et al. (2014) showed that subordinate females constantly harassed both physically and psychologically by dominant females respond differently to estrogen treatment; E$_2$ reduced aggression and increased behaviors associated with sexual motivation and male affiliation in dominants, but not subordinates. As such, a full understanding of the effects of gonadal hormones on adult neurogenesis may require careful analysis of individual roles in complex social arrangements, such as dominance hierarchies.

5. Parenting

Parenting is a very complex social behavior that is marked by dramatic hormonal changes in caregivers (Gobinath et al., 2014; Leuner et al., 2010a). Here, it is relevant to note that typical parenting in females involves at least two aspects that affect hormone levels: pregnancy and infant contact, the latter of which includes lactation. Considerable evidence suggests that the majority of postpartum hormonal changes are driven by infant contact, as opposed to inherent hormonal changes that unfold as a consequence of parturition (Leuner et al., 2007, 2010a). Postpartum experience in mother rats has been shown to inhibit adult neurogenesis (Darnaudéry et al., 2007; Leuner et al., 2007; Pawluski and Galea, 2007; Hillerer et al., 2014), an effect that has been demonstrated in both first-time and experienced mothers (Fig. 2). The suppressive effects of maternal care on new neuron formation appear to be driven by lactation-induced increases in corticosterone levels as infant contact is necessary, as are fully responsive adrenal glands (Leuner et al., 2007). These findings are particularly intriguing because other studies have shown that maternal care has a growth-promoting action on dendritic spine

density in the hippocampus, as well as in the medial prefrontal cortex (Leuner and Gould, 2010). Furthermore, maternal experience has been shown to buffer the effects of stress on learning (Maeng and Shors, 2012) and stress has been shown to reverse the lactation-induced decrease in adult neurogenesis (Hillerer et al., 2014). These findings likely underscore the complex set of experiences that comprise parenting, as increased dendritic spine growth is highly reminiscent of the effects of enriched environment living in both the hippocampus and prefrontal cortex (Brown et al., 2003; Hirase and Shinohara, 2014). Consistent with this possibility, induced maternal behavior in nulliparous females through repeated infant contact stimulates proliferation and survival of new neurons (Pawluski and Galea, 2007), an effect that has also been observed with enriched environment living (Kempermann et al., 1997). Taken together, these findings suggest that parenting includes cues that may be interpreted as stressors, such as the increased energy demands necessary for lactation, as well as those that are likely enriching, such as the hedonic aspects of infant contact. The extent to which it is the enriching aspects of infant contact that buffer against the effects of stress, or even enable stress itself to promote growth, remains unknown.

Parenting behavior is very common among females of mammalian species and exceedingly rare among males. Among rodent species, California mice (*Peromyscus californicus*) are one of the few species that are truly biparental. California mouse fathers engage in all aspects of parenting that mothers do, including pup retrieval, licking/grooming, nest building and protection. The only parenting behavior California mouse fathers do not engage in is lactation and nursing of pups. Given this key difference, and the studies done to investigate the effects of lactation and nursing on adult neurogenesis in mother rats, it is perhaps surprising that California mouse fathers show a similar suppressive effect on adult neurogenesis during the postpartum period, as do California mouse mothers (Glasper et al., 2011). The extent to which these effects are also driven by increased levels of glucocorticoids in fathers, despite the lack of lactation, remains unknown, but it is likely relevant that studies have shown increased levels of glucocorticoids in fathers, as well as mothers, with infant contact (Leuner et al., 2010a). The suppressive influence of parenting on adult neurogenesis may reflect the increased energy demands necessary for engaging in caregiving behavior, regardless of whether lactation is involved. It is interesting to note that available evidence suggests that despite reductions in the number of new neurons in the dentate gyrus in both mothers and fathers, the emerging picture about potential functional consequences of these changes is unclear. Evidence suggests that shortly after parturition, hippocampus-dependent cognitive abilities are impaired (Darnaudéry et al., 2007) whereas at later time points, performance on tasks linked to the hippocampus is either enhanced (Darnaudéry et al., 2007; Gatewood et al., 2005; Kinsley et al., 1999, 2008) or is no different from controls (Glasper et al., 2011). The extent to which this dynamic profile of hippocampal function that emerges postpartum is causally linked to changes in adult neurogenesis remains unknown.

6. Concluding remarks

Numerous studies have shown that the production and survival of new neurons can be modulated by social experience in a positive or negative way. Sexual experience and living as a dominant in a social hierarchy stimulates adult neurogenesis, while a variety of social stressors, including social defeat, social isolation and maternal separation, inhibit adult neurogenesis. It is tempting to speculate that activation of reward pathways is an important mechanism underlying the effects of social experiences with

stimulatory effects on new neuron production. However, an important exception to this claim can be observed with parenting. Parenting has a very strong hedonic component, one that has been extensively documented for a wide range of mammalian species, notably rodents (Leuner et al., 2010a). Despite the rewarding component of parenting, both maternal and paternal care have been associated with suppressed adult neurogenesis in a manner that is similar to what is observed with more aversive experiences, such as social stress. These paradoxical effects likely highlight the complex interactions among the many hormones known to be modulated by different types of social experience and which are known to affect adult neurogenesis. A more extensive understanding of the mechanisms that underlie the effects of different types of social experience on adult neurogenesis will require additional investigation.

The sensitivity of new cell production and survival to multiple social experiences suggests a potential adaptive process whereby modulation of the number and organization of new neurons helps to sculpt the hippocampus so that it can more effectively cope with the environment. This possibility, which has been discussed with regard to general experience, including experiences that do not have a social component (Glasper et al., 2012), may also apply to specific social experiences. Modulation of new neuron production by social experience may set the stage for different social environments in the future. Some studies suggest that the hippocampus plays a role in certain types of social behavior (Hitti and Siegelbaum, 2014; Rubin et al., 2014; Tavares et al., 2015) although this link requires additional investigation. A few studies have pinpointed new neurons in the dentate gyrus as important mediators of social avoidance (Lagace et al., 2010), social recognition (Garrett et al., 2015) and social preference (Opendak et al., 2015), but the extent to which general principles exist about modulation of new neuron production by specific social experience and their functional consequences remains unknown.

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