Neuroscience and Biobehavioral Reviews 132 (2022) 679–690

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Hormones and neuroplasticity: A lifetime of adaptive responses

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ARTICLE INFO

Keywords:
Social investigation
Parental
Maternal
Paternal
Aging
Estradiol
Progesterone
Testosterone
Glucocorticoids
Brain
Behavior

ABSTRACT

Major life transitions often co-occur with significant fluctuations in hormones that modulate the central nervous system. These hormones enact neuroplastic mechanisms that prepare an organism to respond to novel environmental conditions and/or previously unencountered cognitive, emotional, and/or behavioral demands. In this review, we will explore several examples of how hormones mediate neuroplastic changes in order to produce adaptive responses, particularly during transitions in life stages. First, we will explore hormonal influences on social recognition in both males and females as they transition to sexual maturity. Next, we will probe the role of hormones in mediating the transitions to motherhood and fatherhood, respectively. Finally, we will survey the long-term impact of reproductive experience on neuroplasticity in females, including potential protective effects and risk factors associated with reproductive experience in mid-life and beyond. Ultimately, a more complete understanding of how hormones influence neuroplasticity throughout the lifespan, beyond development, is necessary for understanding how individuals respond to life changes in adaptive ways.

1. Introduction

In order to produce adaptive behavior, an individual must integrate information about their internal state with information about their external environment, and then select and enact the appropriate cognitive, emotional, and/or behavioral responses. As individuals enter new life stages, both their internal state and the demands of their external environment may change, sometimes dramatically and with relatively short notice. How then does the brain adapt to these changing internal and external conditions in order to maximize the likelihood of producing adaptive responses? Hormones are potent modulators of the central nervous system that have profound effects on physiology and behavior. Indeed, significant hormonal shifts often accompany major life transitions and frequently enact neuroplastic mechanisms that may prepare an organism to respond to novel environmental conditions and/or previously unencountered cognitive and behavioral demands. What is more, new environmental stimuli can quickly and reciprocally impact hormone conditions, providing a mechanism for the dynamic regulation of internal hormonal status. In this way, tightly-regulated hormone-mediated neuroplasticity allows organisms to better meet the demands of their environment as they move through life stages.

In this review, we will explore several examples of how hormones mediate neuroplastic changes in order to produce adaptive responses, particularly during transitions across life stages. First, we will explore hormonal influences on social recognition in both males and females, emphasizing the role of steroid hormones in promoting social recognition mechanisms required for successful social and sociosexual encounters. Next, we will examine the role of hormones in mediating the transition to motherhood in females, focusing on the role of peripartum fluctuations in estrogens and progesterone in enacting neuroplasticity required for maternal and maternal-associated behaviors. Third, we will probe the role of hormones in mediating the transition to fatherhood in males, considering data from paternal laboratory rodents to understand the influence of gonadal steroids and glucocorticoids on neural and behavioral plasticity. Finally, we will survey the long-term impact of reproductive experience on neuroplasticity, including potential protective effects and risk factors associated with reproductive experience as an individual ages.

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https://doi.org/10.1016/j.neubiorev.2021.11.029
Received 7 July 2021; Received in revised form 15 October 2021; Accepted 8 November 2021
Available online 20 November 2021

1.1. From males to females: sex differences and hormonal influences in social recognition

Social recognition – the ability to recognize a conspecific or distinguish between conspecifics – is essential for adaptive social behaviors in most social species. Social bonds (e.g. pair bonds, mother-offspring, etc.; Carter and Perkeybile, 2018; Choleris et al., 2004) and social hierarchical organizations (Wang et al., 2014) fail when an animal cannot discriminate mate from mother, buddy from bully, friend from foe, or kin from intruder and use this information to display situationally relevant and appropriate behavior. The period of young adulthood and sexual maturity brings with it a particular need for social recognition to drive adaptive social and sociosexual behaviors leading to survival and reproductive success. Information gathered from a conspecific in service of social recognition includes, but is not limited to, sex, reproductive state and status, relatedness, health, affect, familiarity, place in social hierarchy, and individual identity (Choleris et al., 2012, 2009). While the distinctions of these levels may seem pedantic, they are important in disambiguating the likely partially, but not fully, overlapping neural mechanisms that underlie social behavior.

Sex differences exist in many social behaviors, including social recognition. Male rats investigate juvenile conspecifics significantly more than female rats (Bluthé and Dantzer, 1990; Markham and Juraska, 2007; Thor, 1980), with this sex difference reducing with age (Markham and Juraska, 2007) as males show age-related declines in social investigation (Guan and Dluzen, 1994; Prediger et al., 2006, 2005; Terranova et al., 1994; but see also Hlinák and Krejcí, 1991). Despite this, young adult female rats retain the derived social memory for a greater duration than young adult male rats (Bluthé and Dantzer, 1990; Markham and Juraska, 2007). Social recognition in males is highly dependent upon vasopressin (Dantzer et al., 1988, 1987), with the effects of vasopressin being dependent upon sex steroids (Bluthe et al., 1990; Bluthé et al., 1993). Sex steroids also play a role in social recognition in female rats. Following surgical removal of the ovaries (ovariectomy or OVX), female rats showed reduced recognition of a male juvenile conspecific (Hlinák, 1993). This effect was reversed by estradiol dipropionate treatment, with these treatment effects disappearing following washout (Hlinák, 1993). Combined, these sex differences and effects of sex steroid treatment led to further investigations into sex steroid influence on social recognition behavior.

Estrogens influence social recognition (reviewed in Sheppard et al., 2020). Early studies found that performance on social recognition tasks varies across the estrous cycle, with proestrus – the highest 17β-estradiol (E2) phase of the cycle – being associated with enhanced social recognition (Sánchez-Andrade et al., 2005; Sánchez-Andrade and Kendrick, 2011; but see also Markham and Juraska, 2007, in which social investigation, but not recognition memory, was influenced by estrous phase). Estrogen receptors α (ERα) and β (ERβ) are differently involved in the effects of estrogens on social recognition. ERα is particularly important to social recognition, as both male (Imwalle et al., 2002) and female (Choleris et al., 2006, 2003) ERα knock-out (ERαKO) mice (i.e. mice with the ERα gene rendered nonfunctional) are completely impaired on social recognition tasks. Female ERβ knock-out (ERβKO) mice show abnormal habituation to familiar social stimuli (i.e. no significant reduction in social investigation over repeated exposures), but still show intact, albeit reduced, preference for novel social stimuli in a social discrimination task (Choleris et al., 2006, 2003), suggesting that, while involved in social recognition, ERβ plays a lesser role than ERα. Further suggesting a role in social behaviour, male mice lacking ERβ in the nervous system, but not in peripheral tissues, exhibit normal sociability but reduced social investigation and aggression, alongside increases in anxiety and despair-like behaviours (Dombret et al., 2020). These mice further show reductions in vasopressin and oxytocin mRNA expression in the bed nucleus of the stria terminalis (BNST; Dombret et al., 2020). Retention of social memory is impaired in male and female ERαKO mice (females are also impaired in acquisition), whereas ERβKO mice show no deficits (Sánchez-Andrade and Kendrick, 2011). Interestingly, while ERβ may not be necessary for social recognition memory, pharmacological agonism of it, or ERα, 48 h prior to training is sufficient to improve social recognition (Choleris et al., 2009). Furthermore, there exist region-by-receptor interactions, as ERα knock-down in the medial nucleus of the amygdala (MeA) impairs social recognition, but ERα knock-down in the ventromedial nucleus of the hypothalamus does not (Spiteri et al., 2010). This suggests that estrogen actions are required in some brain regions involved in social behaviours but not in others.

It bears mentioning that sex hormones are uniquely situated to rapidly modify social behaviors for use in situations that require dynamic responses "in the now", such as in social and socio-sexual encounters. Recently, investigations into the rapid effects of estrogens (<1 h, as opposed to the classical, genomic effects) have revealed ERs, brain regions, and cellular mechanisms involved in estrogenic facilitation of short-term social recognition memory, at least in OVX female mice. Short-term social recognition memory is facilitated following systemic E2 or ERα, ERβ, or G protein-coupled estrogen receptor (GPER1) agonist administration (Gabor et al., 2015; Phan et al., 2012, 2011). The dorsal hippocampus contributes to this as intrahippocampal E2, ERα agonism, or GPER1 agonism similarly facilitates social recognition (Lymer et al., 2017; Phan et al., 2015). Modulation of dendritic spines in the dorsal hippocampus appears to play a role in these affects as E2 rapidly increases dendritic spine density in the region (Phan et al., 2015, 2012; Tuscher et al., 2016), with E2-facilitated social recognition being blocked when actin polymerization is inhibited, thus blocking increases in dendritic spine density (Sheppard et al., 2021). The disparity between systemic and intrahippocampal results with regards to ERβ led to investigations uncovering that ER agonism in the MeA (by E2 as well as ERα, ERβ, and GPER1 agonists; Lymer et al., 2018) and the paraventricular nucleus (PVN) of the hypothalamus (by E2; Paletta et al., 2018) also facilitates social recognition. These are likely not the only regions involved in the processing of social information into memory as the social behavior network involves numerous brain regions, including, in addition to the aforementioned regions, the lateral septum, supraoptic nucleus of the hypothalamus, and BNST (Newman, 1999; Sheppard et al., 2018).

Androgens (e.g. testosterone) also play a role in social recognition. Castrated male rats show greater social recognition memory retention compared to gonadally-intact males despite showing lower investigation during initial encounters (Bluthé et al., 1993). Timing of testing and post-castration duration appear to be factors in the direction and magnitude of effects of castration (reviewed in Choleris et al., 2009). Testosterone may exert effects on social recognition through its conversion to estradiol. Gonadally-intact male mice lacking the gene for aromatase – the enzyme responsible for the conversion of testosterone to estradiol – show impaired social recognition (Pierman et al., 2008). Treatment of castrated aromatase knock-out mice with testosterone metabolites (estradiol benzoate and dihydrotestosterone propionate) restores social recognition (Pierman et al., 2008). It is important to note that aromatase knock-out mice have increased levels of testosterone (Fisher et al., 1998), further suggesting that the effects of testosterone on social recognition are through secondary, estrogenic mechanisms. However, the direct effects of testosterone on androgen receptors (ARs) may play a role in social recognition. In mice lacking androgen receptors in the nervous system, males show normal sociability, but are impaired in their recognition of male, but not female, conspecifics (Karlsson et al., 2016a). This suggests involvement of ARs in social recognition, at least with regards to male-male social interactions. While beyond the scope of this review, it is important to note that many effects of sex steroid hormones on social recognition occur through regulation of oxytocin and vasopressin systems. For reviews on these interactions and systems, we suggest Bredewold and Veenema, 2018; Choleris et al., 2009; Paletta et al., 2018.

Given the complexity of human social interaction (see commentary and review in Lockwood et al., 2020), social recognition is often parsed

into more specific cognitive processes, such as face or emotion recognition (e.g. Keightley et al., 2011; Lopatina et al., 2018; Skuse et al., 2014; Zink et al., 2011). Interestingly, women perform better at many of these tasks than do men (Lewin and Herlitz, 2002; Rehnman and Herlitz, 2007), with ER polymorphisms affecting performance in women (Karlsson et al., 2016b). What is evident in the comparison of human and animal (primarily rodent) studies, is that, while sensory modality of social information processing may differ (e.g. rodents using predominantly olfaction, humans using vision, both species using audition), a number of brain regions and systems are shared. For instance, social reward processing in rodents and humans shares a number of regions (e.g. amygdala, PVN, striatal subregions), shows functional homology in others (e.g. medial prefrontal cortex in humans and infralimbic, prelimbic, and cingulate regions in rodents), and has distinct species differences in still others (e.g. regions involved in sensory input to the "social brain"; Grimm et al., 2020). Furthermore, much has been made of oxytocin and vasopressin systems in social behaviors, including social recognition, and evidence suggests that these systems, as well as others (reviewed in Grimm et al., 2020), are conserved between mammalian species with regards to many social behaviors (Althammer et al., 2018; Caldwell, 2017; Goodson, 2008; Kompier et al., 2019). These systems are heavily influenced by sex steroid hormones, but the actions of sex steroid hormones on these nonapeptide systems in service of social behaviour are poorly characterized in humans, whereas they are an ongoing area of research in animal models (Bredewold and Veenema, 2018; Choleris et al., 2009; Paletta et al., 2018).

A recent review by Prounis and Ophir (2020) highlighted the division between human and rodent studies of the social brain, calling the two conceptual "social brains" distinct but complementary and calling for improved collaboration for the mutual benefit of both fields (Prounis and Ophir, 2020). Whereas much is now known regarding the influences of sex steroids in rodent models of social cognition, understanding of the contributions of steroid hormones to human social recognition is lacking. Improved collaboration between researchers of animal and human social behaviour may facilitate or catalyze investigations synthesizing the two bodies of knowledge and provide a more thorough and holistic understanding of the social brain across species.

1.2. From non-maternal to maternal: steroid hormone regulation of neural plasticity in the transition to motherhood

The transition to parenthood requires animals to enact specific, complex, and energetically-expensive patterns of behavior. For first-time parents, many of these behaviors are completely novel, but also required for the survival and wellbeing of their offspring. In females, it has been hypothesized that endocrine fluctuations during the peripartum period may open an additional sensitive period for neuroplasticity in adulthood (Champagne and Curley, 2016), similar to the effects of hormonal fluctuations during the neonatal and pubertal periods (Phoenix et al., 1959; Wallen, 2009). Although it is clear that many hormones (e.g., beta-endorphins, prolactin, oxytocin, corticosterones) act on the brain during the peripartum period (Lévy, 2016), here we will focus on the impact of ovarian hormone fluctuations during the peripartum period on neuroplastic changes that facilitate maternal behaviors, as well as changes in cognition, mood/affect, and sensation/perception.

In placental mammals, including humans, levels of estradiol and progesterone fluctuate dramatically during the peripartum period. Plasma levels of estradiol are low during the first part of pregnancy, but rise precipitously and remain elevated through the day of parturition (Hendrick et al., 1998). Following birth and the expulsion of the placenta, however, estradiol levels quickly drop to pre-partum levels and remain suppressed for days to months, depending on the species (McNeilly, 2001). In contrast, progesterone levels are high during the first part of pregnancy, but then slowly decline prior to parturition (Rosenblatt, 1988; Vannuccini et al., 2016). Although it is clear that the human brain undergoes significant structural plasticity during the peripartum period (e.g., Hoekzema et al., 2017), the precise contribution of peripartum hormonal fluctuations to these neuroplastic changes is more difficult to test in human subjects. There is a rich literature, however, in rodent models establishing that peripartum fluctuations in ovarian hormones are critical for the onset of maternal behaviors, while simultaneously suppressing aversive or aggressive behavior towards neonates. Perhaps most convincingly, exogenous administration of estradiol and progesterone in a pattern that approximates the peripartum hormonal fluctuations has been shown to reliably induce maternal behavior in ovariectomized nulliparous female rats, who typically would show aversive rather than maternal behaviors (Mayer et al., 1990; Rosenblatt, 1988; Siegel and Rosenblatt, 1975).

How then do these hormones promote the onset of maternal behavior? Because of their lipid-like nature, steroid hormones such as estradiol and progesterone can passively cross the blood-brain barrier, allowing them to bind to estrogen and progesterone receptors in the brain. These steroids act on a network of hormone-sensitive brain regions that have been identified as a "maternal caregiving network" (Bridges, 2015). In particular, it has been well-established that hormone action in the MPOA and the adjoining ventral BNST (BNSTv) is critical for the onset of maternal behavior in rodents (Kohl et al., 2018, 2017; Lonstein et al., 2015; Numan, 1988). Here, estradiol seems to play a facilitatory role, whereas progesterone plays an inhibitory role (Fahrbach and Pfaff, 1986; Sheehan and Numan, 2002). During late pregnancy, ERα concentrations are increased in the MPOA, whereas there is no change in ERβ expression, and a decrease in progesterone receptors. Individual differences in estrogen receptor expression are also linked with differences in maternal care quality, with higher ERα expression being linked to better maternal care (Champagne et al., 2003). What's more, structural plasticity in the MPOA during the peripartum period is linked to changes in steroid hormone levels. MPOA soma size is increased in late-pregnant and lactating rats, as well as rats given pregnancy-like steroid treatment, compared to nulliparous females (Keyser-Marcus et al., 2001). Finally, late-pregnant, lactating, and pregnancy hormone-treated females have increased GFAP-immunoreactivity and astrocytic complexity in the MPOA than nulliparous females (Kinsley and Lambert, 2008).

The MPOA/vBNST complex projects directly to the ventral tegmental area (VTA). These projections from estrogen-sensitive neurons (Morrell et al., 1984) may confer the salience and reinforcing properties of pups or pup-related cues via the mesolimbic dopamine pathway (Afonso et al., 2013, 2009). Electrophysiological recordings from the VTA in postpartum female rats show lower numbers of spontaneously active DA cells than nulliparous females (Rincón-Cortés and Grace, 2020). Further, female rats who are withdrawn from estrogen following treatment with pregnancy-like hormones show decreased intracranial self-stimulation of the medial forebrain bundle (Schiller et al., 2013), an additional measure of motivation that depends on dopaminergic fibers emanating from the VTA. Although these data suggest that peripartum fluctuations in steroid hormones may impact VTA dopamine projections, this has not been directly tested. The nucleus accumbens (NAc) is the primary target of VTA dopamine projections. In the NAc, baseline dopamine levels are significantly lower in postpartum female rats and in females following treatment with pregnancy-like hormones compared to cycling females (Afonso et al., 2013). However, both postpartum and hormone-primed females show a facilitated dopamine response to distal pup cues compared to cycling females (Afonso et al., 2013, 2009), suggesting that changes in peripartum hormones result in a decrease in basal dopamine tone that may impact other behaviors, but do not appear to decrease the saliency of pup-associated cues.

While steroid action in the MPOA and mesolimbic pathway is important for the onset of maternal behavior, peripartum fluctuations in estradiol and progesterone also act outside of this maternal network of brain regions to impact behaviors that, although not part of the classical suite of maternal behaviors, are relevant for the transition to

motherhood. The somatosensory cortex (Xerri et al., 1994) and auditory cortex (Schiavo et al., 2020) undergo plasticity in response to the onset of maternal behavior, although the exact contribution of steroid hormone fluctuations to these changes is unclear. Peripartum changes in the hippocampus and associated circuitry have been well-studied for their impact on cognitive and affective functions. For example, multiparous female rats have higher brain-derived neurotrophic factor (BDNF) levels in both the CA1 region of the hippocampus and the septum compared to nulliparous females (Macbeth et al., 2008). These increases in BDNF may be related to enhanced cognition, as multiparous females also perform better on novel object recognition, a non-spatial memory task. It is plausible that these behavioral and brain changes are due at least in part to fluctuations in steroid hormones, as female rats treated with pregnancy-like hormones have increased dendritic spine density in the hippocampus, which is associated with increased BDNF levels, and may reflect the increased need for resource-gathering behaviors during motherhood (Kinsley and Lambert, 2008).

Interestingly, in experiments where nulliparous female rodents are treated with pregnancy-like hormones and subsequently withdrawn from estradiol, a model that isolates and emphasizes the rapid decline of estradiol at parturition and may lead to an "estrogen withdrawal" state, several measures of hippocampal plasticity decrease rather than increase. For example, in estrogen-withdrawn female rats, cell proliferation (Green et al., 2009), dendritic spine density (Baka et al., 2017), and BDNF levels (Suda et al., 2008) all decrease in the hippocampus rather than increase. In mice, estrogen withdrawal also decreases the survival and growth of newborn neurons in the hippocampus via the down-regulation of NMDA receptors (Zhang et al., 2016). Likewise, estrogen withdrawal decreases the induction of long-term depression in the basolateral amygdala (BLA) in mice (Yang et al., 2017). Notably, estrogen-withdrawn animals show a behavioral phenotype that may be indicative of increased stress-susceptibility, anxiety-like behavior, or some core features of depression. Specifically, estrogen withdrawal following a hormone-simulated pregnancy increases immobility in the forced swim test (Green et al., 2009; Schiller et al., 2013; Stoffel and Craft, 2004), decreases sucrose preference (Green et al., 2009; Navarre et al., 2010), decreases escape performance following inescapable shock (Baka et al., 2017; Suda et al., 2008), and decreases the time spent in the open arms of an elevated plus (Suda et al., 2008) in female rats. Many of these behavioral results have been replicated in mice (Yang et al., 2017; Zhang et al., 2016) and Syrian hamsters (Hedges et al., 2021), suggesting it is a highly reproducible way to model the impact of postpartum estrogen withdrawal on behavior across multiple species. When taken together with data from females that are either pregnant or treated with pregnancy-like hormones, these data suggest that high levels of estrogen during late pregnancy may confer resilience, whereas rapid withdrawal from estrogen may confer susceptibility to disruptions in mood/affect.

The complete mechanism by which estrogen withdrawal confers this susceptibility is not completely understood, but recent evidence points to the midbrain dorsal raphe nucleus (DRN) as an important site. This estradiol-sensitive brain region (Alves et al., 1998) is the primary source of serotonin in the brain (Abrams et al., 2004), and is known to regulate affective behaviors. Recent work has demonstrated that parturient female rats have higher levels of oxytocin receptor (OTR) binding in the DRN than nulliparous or early pregnant females, and that this increase in OTR binding returns to baseline levels by postpartum day 7 (Grieb and Lonstein, 2021). Further, knocking down OTR levels in the DRN decreased maternal behaviors, increased aggression, and increased measures of anxiety-like and depression-like behaviors (Grieb et al., 2021). Recent data in Syrian hamsters suggests that these changes may be mediated, at least in part, by the rapid decrease in estrogen during the postpartum period. Like in parturient female rats, estrogen withdrawal following treatment with pregnancy-like hormones increases OTR receptor density in the DRN. What's more, pharmacological blockade of OTRs during estrogen withdrawal prevents the characteristic increase in anxiety-like behaviors in the elevated plus and open field (Hedges et al., 2021), also matching the findings in parturient female rats. Interestingly, these changes are accompanied by an increase in oxytocin immunoreactivity in the PVN, suggesting that increased OTR binding in the DRN may be a postsynaptic consequence of increased oxytocin transmission from the PVH (Hedges et al., 2021).

Although there is abundant evidence that fluctuations in steroid hormones during the peripartum period promote structural and functional plasticity in the brain, it is not well-characterized which of these hormone-mediated neuroplastic changes persist past the early postpartum period, and if so, for how long. Notably, the onset of maternal behavior requires a pregnancy-like hormonal environment, but the maintenance of maternal behavior is less dependent on these hormonal changes (Keller et al., 2019). Returning to the analogy of the peripartum period as an additional sensitive period for brain organization in adulthood, one can imagine that maternal experience continually activates this brain circuitry in order to maintain these changes in the absence of the peripartum hormonal environment. The long-term neural and behavioral repercussions of reproductive neuroplasticity will be explored in more depth in section 1.4.

1.3. From non-paternal to paternal: the role of steroid hormones and neural mechanisms in emotional and cognitive behaviors

In many mammalian species, one of the most important life transitions occurs at the time of parenthood (Saxbe et al., 2018) – one that requires significant learning and regulation of emotions (Glasper et al., 2019; Kim, 2016; Leuner et al., 2010; Pereira, 2016; Rutherford et al., 2015). While maternal care is commonly displayed in mammalian species, paternal care is rarely exhibited and is typically synonymous with monogamy (Kleiman, 1977); therefore, the endocrine and neurobiological correlates of this transition from non-paternal male to paternal male, in rodents, is limited to the study of a few lab-tolerant species, like *Octodon degus*, California mice (*Peromyscus californicus*), prairie voles (*Microtus ochragaster*), Djungarian hamsters (*Phodopus campbelli),* mandarin voles (*Lasiopodomys mandarinus),* and Mongolian gerbils (*Meriones unguiculatus)*. Given the usefulness of these species, we will focus on evidence that suggests gonadal steroid hormone expression, in key brain regions, may mediate the initiation, development, and maintenance of paternal behavior in rodents. Though not traditionally paternal in the wild, the neuroendocrine mechanisms of paternal care have been elucidated using male house mice. A relationship between paternal behaviors and ER immunoreactivity has been observed in the BNST, hippocampus, lateral septal nuclei, subiculum, medial preoptic nucleus (MPOA), the entorhinal and piriform cortices, and the arcuate nucleus of the hypothalamus (ARH) (Ehret et al., 1993). Using non-monogamous common laboratory mice, data suggest that aromatization of T into E2 is important for the initiation, development, and maintenance of paternal behavior in a number of brain regions involved in paternal care, including the nucleus accumbens, MPOA, ventral pallidum, hippocampus, amygdala, and prefrontal cortex (Akther et al., 2015).In addition to these rodent models, we also highlight studies utilizing human fathers, as this work has greatly contributed to our understanding of region-specific activation of neural regions before and after the birth of offspring.

Much like maternal mammals mentioned above, paternal mammalian species undergo fluctuations in peripheral hormone levels in response to offspring, despite not undergoing pregnancy, parturition, or lactation. Prevailing evidence suggests that these alterations in hormone levels are necessary to maintain paternal care in these species (Saltzman et al., 2017). As will be demonstrated below, there is not overwhelming consistency as to what specific hormones are necessary or sufficient to promote and maintain paternal care. This is likely due to the various reasons why paternal care evolved (Saltzman and Ziegler, 2014; Wynne-Edwards and Timonin, 2007).

There is now mounting evidence from rodents demonstrating the

role of the gonadal steroid hormones, testosterone (T), estradiol (E2), and progesterone (P), in the initiation and/or maintenance of paternal behavior. The strongest evidence can be observed in studies that pay attention to the temporal effects of T (and/or its metabolites) in rodent species that naturally exhibit paternal care in the wild (i.e., biparental species). For example, T levels in plasma of Djungarian hamsters increase before the birth of offspring but decrease shortly after the birth of pups (Wynne-Edwards and Reburn, 2000). In Mongolian gerbils, more huddling of pups is associated with lower levels of circulating T (Clark and Galef, 2000). Together, these two studies suggest that pup presence influences T concentrations in these biparental species. Additional support for the temporal nature of gonadal steroid hormones on paternal behavior is demonstrated in first-time California mouse fathers. High concentrations of E2 gradually return to baseline as pups approach weaning age (Hyer et al., 2017). It is possible that the reduction in T and increase in E2 observed following offspring birth may be a result of the aromatization process of T into E2. This is further discussed below. Rodent models, like the California mouse and prairie vole, have been used to demonstrate the relationship between T and caregiving behavior in males. Following castration, paternal care is reduced (Wang and De Vries, 1993; Trainor and Marler, 2002, 2001), however, T and E2, but not dihydrotestosterone, restores pup grooming and huddling behaviors in California mice (Trainor and Marler, 2001). These data suggest that the effects of T on paternal behavior are a result of T's aromatization to E2. This relationship between T (and its metabolite E2, but not dihydrotestosterone) and caregiving behavior in males is further supported by evidence suggesting castration impairs such behaviors. This has been demonstrated in prairie voles (Wang and De Vries, 1993) and California mice (Trainor and Marler, 2002, 2001). While the relationship between T and paternal behavior has become well-defined, E2's role is less clear. For example, in Djungarian hamsters, E2 levels do not rise close to birth and return to baseline following the birth of offspring (Schum and Wynne-Edwards, 2005). Additionally, while castration reduces E2 concentrations in the periphery of this species, it does not reduce paternal behavior (Hume and Wynne-Edwards, 2006, 2005). Data suggesting a role of P in paternal behavior in rodents is less congruent than data supporting T and E2. For example, progesterone levels are higher near the birth of offspring in Djungarian hamsters (Schum and Wynne-Edwards, 2005) but lower in California mouse fathers (Trainor et al., 2003). While these data are discrepant at first glance, it may have less to do with the number of conflicting studies and more to do with the need for further investigation into other paternal rodent species.

More convincing evidence is observed in human males, which suggests that T levels decrease during the transition to fatherhood. Following the birth of a child, T levels decline (Alvergne et al., 2009; Berg and Wynne-Edwards, 2001; Gray et al., 2006; Perini et al., 2012b, 2012a); however, active engagement in their child's life is required for T levels to remain low (Gray and Anderson, 2010). For example, human fathers with lower levels of circulating T gazed at and spent more time in physical contact with their young (Weisman et al., 2014). Additionally, lower T levels in fathers predicted greater child involvement (Kuo et al., 2018). Fathers with lower T levels are also more sympathetic to the sound of an infant crying (Fleming et al., 2002), and in fact, concentrations of T have actually been reported to decrease in response to infant crying, particularly when fathers are able to behaviorally respond to infant distress (Fleming et al., 2002; van Anders et al., 2012). In response to infant distress, the reduction in T concentrations is correlated with paternal sensitivity in assays of father-young infant interaction (Kuo et al., 2016). Lastly, lower T levels are observed in fathers who participate in more instrumental caregiving activities (Mascaro et al., 2013). Collectively, these studies suggest that reductions in T following the birth of offspring may be indicative of sensitive caregiving.

Support for the role of glucocorticoids in paternal behavior is relatively weak in rodent species (Wynne-Edwards and Timonin, 2007), with many of the reported effects being species-specific. Seminal evidence from male *P. campbelli* and *P. sungorus,* two species of voles, demonstrated a reduction in corticosterone (CORT) levels following the birth of their offspring (Reburn and Wynne-Edwards, 1999). However, this effect is not observed in *Microtus ochrogaster*, the prairie vole, following the birth of offspring. In the biparental California mouse, acute CORT administration does not alter male caregiving behavior; however, chronic stress can temporarily disrupt paternal behavior (Harris et al., 2013). However, at baseline, CORT concentrations are similar among virgin males, non-fathers, and fathers (Harris and Saltzman, 2013). These data from the California mouse suggest that multiple, and sustained, activation of the hypothalamic-pituitary-adrenal (HPA) axis are necessary to affect paternal behavior. Furthermore, the species-specific effects of paternal experience on CORT highlight the need to consider social structure and specific paternal behaviors within and not across species.

In human fathers, despite wide cultural variations in paternal care (reviewed in Konner, 2018), a stronger relationship exists between basal and reactive cortisol and paternal involvement in offspring. In response to interaction with newborn and older children, higher basal cortisol is observed following childcare and play (Kuo et al., 2018). Modulations in cortisol reactivity do not act independently of other steroid hormones, as a negative relationship between caregiving quality and cortisol concentrations is observed in fathers with high levels of testosterone (Bos et al., 2018), suggesting that an interplay between the HPA and the hypothalamic-pituitary-gonadal axes are important and warrant further investigation. Despite a stronger relationship, studies are limited and additional studies exploring the functional relevance of these changes in cortisol should be performed.

The relationship between the expression of gonadal steroid hormone receptors in key neural regions and paternal care has been explored and consistent support for the role of estrogens has been demonstrated in the biparental California mouse and mandarin vole. In highly-responsive mandarin vole fathers, the BNST, ARH, and medial amygdaloid nucleus express more ERα immunoreactive cells than low responsivity males (Li et al., 2015). Similarly, increased ERβ expression is observed in the hippocampus of California mouse fathers following the birth of offspring (Hyer et al., 2017). Aromatase, an enzyme necessary for the biosynthesis of estrogens, is observed in increased levels in the MPOA of California mice (Trainor et al., 2003) and may contribute to the presentation of paternal behaviors.

While hormone receptor expression can be ascertained using laboratory rodent species, this is not possible in studies of human paternal care. Therefore, associations between circulating T concentrations and the activation of neural systems involved in paternal care are examined. Correlations between T and brain activation are region-specific, and involve areas related to motivated behaviors and emotion. For example, in response to interactions between the father and infant, T is positively correlated with the activation of the left caudate nucleus (Kuo et al., 2012). However, a negative correlation is observed between neural activation in the mid frontal gyrus, a brain region important for face emotion processing, and T concentration in fathers (Mascaro et al., 2014). These region-specific activations in new fathers as a result of T may serve to enhance empathy for the child and increase the likelihood of sustained interaction.

Understanding changes in steroid hormone concentrations in the periphery, alterations to hormone receptor expression in key neural regions, and differential activation of neural circuits is critically important to understanding mechanisms that may contribute to behavioral change during, and following, the transition to fatherhood. Many of the same behaviors modified by maternal experience are also altered with paternal experience, including learning and memory, anxiety-like behaviors, and stress-coping behaviors. Much like the neuroendocrine regulation of paternal care, the data are species-specific. Also, it appears that the amount of paternal care experience (i.e., age of offspring) is important to understand behavioral outcomes.

Very few studies have examined the effects of paternal experience on learning and memory. In male C57BL/6 mice, paternal experience

increases social memory for offspring (Mak and Weiss, 2010), yet this enhancement in social memory for offspring is not enhanced in prairie vole fathers (Lieberwirth et al., 2013). In mice that are not traditionally paternal in the wild, this increase in social recognition may be necessary to prevent inbreeding. Similar to the lack of benefit of fatherhood in prairie voles, first-time California mouse fathers do not demonstrate enhanced object recognition at the time of weaning (Glasper et al., 2011). Given the reduced interaction of the paternal male with his offspring late in the rearing period (Bester-Meredith et al., 1999), the lack of effects of offspring on cognition in the paternal male is not surprising. However, California mouse males housed with the maternal female and pups for 7 days showed enhancements in spatial memory on the dry land version of the Morris Water Maze (Franssen et al., 2011). Additionally, periods of increased pup interaction are associated with improvements in other behaviors, such as anxiety-like behavior in this species (Glasper et al., 2015; Hyer et al., 2016). Collectively, these data suggest that offspring interaction, and not simply paternal experience, is important for enhancing learning and memory in males.

Compelling data from the California mouse suggests that the transition from non-paternal to actively engaged in offspring care comes with considerable changes to anxiety-like behavior. During early offspring care in first-time fathers, California mice do not observe changes in open arm exploration during the elevated plus maze task (Chauke et al., 2012; Hyer et al., 2017); similar findings are observed at the time of weaning (Glasper et al., 2011). However, during a time of increased offspring interaction, California mouse fathers experience reduced anxiety-like behavior on the elevated plus maze (Glasper et al., 2015; Hyer et al., 2016). However, more experienced California mouse fathers exhibit earlier reductions in anxiety-like behaviors within the open field (Bardi et al., 2011). The generalizability of the effects of multiparity on anxiety-like behavior across a host of tests is unknown but suggests that paternal experience, across many litters, may increase emotional regulation.

Pre-clinical studies, although few in number, on the effects of paternal experience on stress-coping behaviors suggest that fathers exhibit behavioral despair (i.e., increased floating during the Porsolt forced swim task) following separation from offspring. Specifically, permanent or repeated separation of offspring from paternal males results in increased floating time (Hyer and Glasper, 2017; Kong et al., 2015). While these data suggest that a disruption of the bond between the father and offspring may be detrimental to the emotional health of the father, this major transition into fatherhood can also induce distress and the recurrence of some psychiatric disorders, like depression, in human males (Bruno et al., 2020). While perinatal depression (PND) is recognized in the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) (American Psychological Society, 2013) as a subtype of a major depressive disorder, paternal perinatal depression (PPND) is not widely acknowledged or well-researched; therefore, it is not recognized as an official psychiatric disorder. Nevertheless, prevalence rates of PPND in first-time fathers range from 1% to 26 % (reviewed in Wang et al., 2021) and up to 50 % when partners experience depression (Goodman, 2004). This wide range in prevalence rates is likely a result of numerous intrinsic and extrinsic factors, such as sociodemographic factors (e.g., age, socioeconomic status, marital status), history of psychological factors (e.g., depression history), pregnancy-related factors (e.g., infertility), and history of substance use (reviewed in Wang et al., 2021). Biological mechanisms, like fluctuations in T, PRL, and CORT may also increase the risk for paternal depression (reviewed in Glasser and Lerner-Geva, 2019). Given the multitude of variables impacting PPND, pinpointing the mediating factors will require additional studies, as well as larger sample sizes in order to perform the necessary statistical analyses. Of note, the appearance of depression in fathers appears later in the postpartum period (Paulson and Bazemore, 2010), as opposed to earlier in females, and may speak to etiology. Further investigation of this transition period in a males life may elucidate the neurobiological and endocrine underpinnings of PPND, which may differ from what is observed in females, and highlight possible mechanisms to prevent and treat this disorder.

1.4. From the peripartum period to aging: the long-term impact of reproductive experience on neuroplasticity

It is clear from the previous sections that the transition to parenthood is a time of great behavioral and neural plasticity – to be sure, anyone who has gone through parenthood understands a life-altering event has occurred, so it should not be shocking to discover that this is a time of great plasticity in the parents. Pregnancy in particular is an impressive physical feat that requires significant maternal adaptation to a variety of physiological systems (cardiovascular, pulmonary, immune) to ensure the successful development of the fetus. As noted above, the placenta drives the extraordinarily high levels of steroid and peptide hormones throughout the 38 weeks of a normal pregnancy (Napso et al., 2018). At parturition, with the ejection of the placenta, these hormones are reduced dramatically and the individual becomes hypogonadal during the postpartum. Lactation comes with its own set of metabolic demands and is associated with a different endocrine profile than that during pregnancy (Napso et al., 2018). Coordinated along with these dramatic endocrine profiles and physiological demands during the peripartum period a significant amount of neuroplasticity needs to occur to allow the expression of maternal behaviors to ensure the survival of the offspring. Given these physiological demands both during and after pregnancy, it should not come as a huge surprise that these adaptations may have long-term repercussions to the maternal brain.

Indeed, evidence suggests that there are several changes in the short and long-term to a variety of brain regions with motherhood in both humans and rodents (de Lange et al., 2019; Hoekzema et al., 2017; for review: Duarte-Guterman et al., 2019). Together the body of evidence that is emerging from studies is that pregnancy alters the trajectory of brain aging both structurally and functionally. In the short term, Hoeksema et al. (2017) found that a variety of brain regions in the cortex and in the hippocampus exhibited dramatic reductions in gray matter volume that manifested two months after the postpartum and were still evident two years later. It would be a mistake to interpret these changes as impairments in function, as the group found no evidence for changes in a variety of cognitive tasks. Furthermore, the group found that reductions in gray matter were associated with better maternal-infant attachment, indicating that these reductions were beneficial for the organism. Although this is counterintuitive it is important to consider that most of the research in the past that links structure to function has used exclusively male subjects. As always, it is an empirical question as to whether changes in gray matter or plasticity are associated with differences in performance. There are a few examples of reduced neuropil or neurogenesis in the hippocampus being associated with better performance in female rodents. Indeed, chronic stress reduces dendritic complexity in the CA3 region of the hippocampus in male and female rodents which is associated with impaired spatial learning in males but enhanced spatial learning in females (Galea et al., 1997; Luine et al., 2017). In the rodent, hippocampal neurogenesis is reduced mid-gestation to the late postpartum (Eid et al., 2019; Workman et al., 2015). However, intriguingly in the late postpartum at the time when pups have been weaned (postnatal day 30), there is commensurate enhancement in spatial working and reference memory in the dam (Love et al., 2005; Pawluski et al., 2006b). Curiously, the reductions in neurogenesis in the short term have been attributed to pregnancy alone and not to experience with pups (Pawluski and Galea, 2007), whereas the improvements to learning and memory in the late postpartum are attributed to both pregnancy and mothering (Pawluski et al., 2006a). These findings remind us to consider that plasticity that results in reductions in neurogenesis, dendritic complexity, and gray matter volume need not be detrimental to the organism.

Several studies have noted reductions in hippocampal neurogenesis in the early postpartum (Darnaudéry et al., 2007; Leuner et al., 2007;

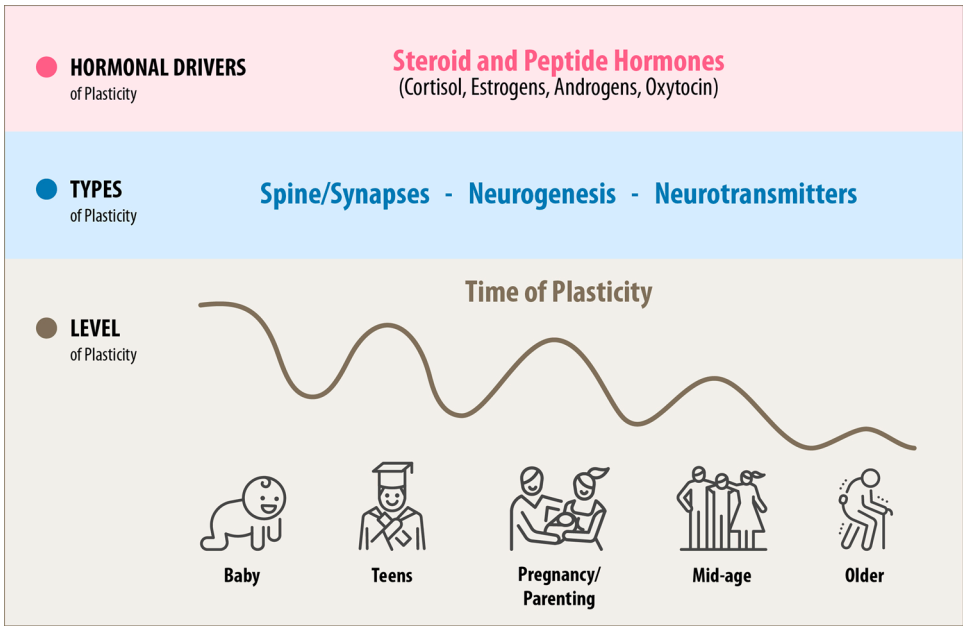

Fig. 1. Hormones drive neuroplasticity across the lifespan. As an individual ages, steroid and peptide hormones act on hormone-sensitive neural targets to drive structural and functional plasticity. Although early life and adolescence are well-known critical periods for hormones to exert neuroplastic effects, hormone-driven neuroplasticity continues throughout the lifespan. In particular, during pregnancy/parenthood, in middle-age, and to a lesser extent in older adults, there is evidence that hormone-driven neuroplasticity drives adaptive behavioral responses to new physiological and environmental demands. This plasticity can be modified during these periods with other factors, such as enrichment, exercise and stress, that also affect hormone levels.

Pawluski and Galea, 2007). However, this time is also associated with increases in other forms of dendritic spines and electrophysiology including increased CA1 spine density in primiparous rats (Kinsley et al., 2006) and enhanced late long-term potentiation (L-LTP) in biparous rats in the early postpartum (Tomizawa et al., 2003). These findings suggest that many forms of plasticity are altered in the early and late postpartum in the hippocampus. But how long do these changes in neuroplasticity last? In terms of both enhanced CA1 spine density and reduced neurogenesis in the dentate gyrus, these changes are still evident as late as postnatal day 30 (Brusco et al., 2008; Workman et al., 2015). In humans, work by Ann Marie de Lange (de Lange et al., 2019, 2020) found that previous parity reduced the amount of evident "brain aging" using a large dataset from the UK Biobank. They showed that the effects of previous pregnancy, without regard to the number of births, were associated with less brain aging across middle age (ages 40–70). Several brain regions were more strongly related to the reductions in brain aging including the nucleus accumbens and the hippocampus (de Lange et al., 2020). These findings are intriguing as they follow what has been seen with neurogenesis in the dentate gyrus in laboratory rats (Eid et al., 2019). In middle-age, previously parous rats have enhanced neurogenesis levels compared to nulliparous rats (Barha and Galea, 2011; Eid et al., 2019; Galea et al., 2018b). These changes are accompanied by slight enhancements in performance in spatial tasks compared to nulliparous age matched controls (Barha and Galea, 2011; Galea et al., 2018b; Love et al., 2005). Perhaps more strikingly, previous parity alters the neurogenic and cognitive response to estrogens in middle age (Barha et al., 2015; Barha and Galea, 2011; Galea et al., 2018b). Indeed, in responding to a variety of estrogens, multiparous middle-aged rats respond similarly to young adult rats by rapidly upregulating cell proliferation in the dentate gyrus, an effect that is not seen in nulliparous middle-aged rats (Barha and Galea, 2011). These effects are not limited to rapid effects on cell proliferation but similar effects are seen with middle-aged primiparous rats as primiparous rats showed a very different response to a hormone therapy than nulliparous rats in middle age. Indeed, Premarin, a hormone therapy, made of mainly estrone, impaired acquisition of a spatial task in primiparous but not nulliparous rats (Galea et al., 2018b), and similar impairments in performance with Premarin are seen in young adult female rats (Barha and Galea, 2013). These findings collectively suggest that previous reproductive experience renders the middle-aged brain more "youthful".

The fact that parity increases plasticity in the long-term flies in the face of reports that past parity is associated with increased risk to develop Alzheimer's Disease (AD) (Colucci et al., 2006; Jang et al., 2018; Ptok et al., 2002). However, there are equivocal findings in the literature, with those finding that grandparity (more than five births) is associate with increased risk to develop AD (Jang et al., 2018) and others finding a reduced risk to develop AD that differs based on geographical location (Bae et al., 2020). Inconsistencies within the literature may be explained in part to the 'Healthy Cell Bias'. Roberta Brinton has suggested that estrogens may be beneficial in healthy women but not in women with disease (Brinton, 2008). Indeed, evidence exists that the beneficial effects of previous parity on AD-related factors are affected by genotype, such that parity is beneficial only in genotypes that are not associated with increased risk for AD (Corbo et al., 2007; Cui et al., 2014). Rena Li and her colleagues found that multiparity enhanced performance in middle-aged wild-type mice but not in a mouse model of AD (APP23). Furthermore, they found that plaques, a neuropathological feature of AD, were increased in previously parous APP23 mice compared to nulliparous controls (Cui et al., 2014). Differences in findings between studies also may be due to differences in disorders of pregnancy like hypertension or gestational diabetes which led to increased risk for cardiovascular disease later in life (Parikh et al., 2021). In any case, it is clear that reproductive experience influences the health of the females later in life, which may include brain health.

It is not currently known what the long-term changes in plasticity with parity may be attributed to but there are a number of changes in the female physiology that occur long term with parity. These changes include, but are not limited to, changes in hormones, inflammation and metabolism (reviewed in Barth and de Lange, 2020; Galea et al., 2018a). Hormones, inflammation and metabolism are all factors that mediate changes in neuroplasticity and brain aging (for review see Mahmoud et al., 2016; Mattson and Arumugam, 2018). After pregnancy there are dramatic reductions in gonadal hormones in the short term that result in a suppression of the menstrual cycle. But what is less well known is that there are long-lasting changes to a variety of hormones across the menstrual cycle after giving birth as estradiol and estrone are permanently reduced across the different phases of the menstrual cycle (Bernstein et al., 1985; Dorgan et al., 1995). Complicated changes in inflammation are seen not only across pregnancy and the early postpartum but these can also extend into middle age (Barth and de Lange, 2020). Intriguingly, the number of sons is associated with greater increases in inflammatory signaling later in life (Galbarczyk et al., 2021),

indicating the fetal sex plays a role. New research also suggests that parity negatively influences DNA methylation patterns contributing to increased epigenetic age in people with impaired glucose tolerance during pregnancy (Kresovich et al., 2019). The effects of previous reproductive experience to influence disease risk for certain cancers and for cardiovascular disease under conditions of pregnancy disorders such as hypertension, preeclampsia, or gestational diabetes is known (Garovic et al., 2020; Okoth et al., 2020). For example, preeclampsia, hypertension and gestational diabetes during pregnancy increases the risk for cardiovascular disease by approximately two-fold (Okoth et al., 2020), but importantly other factors such as age of pregnancy and breastfeeding length can have a protective effect. For breast, endometrial and ovarian cancer parity is associated with a reduced risk of disease but this again is moderated by factors such as type of cancer and older age at first or last birth (Troisi et al., 2018). However, it is important to consider the impact of previous parity on the brain and how changes in neuroplasticity in the short and long term may not only be adaptive but also carry with them changes in risk for common diseases in aging.

2. Conclusion

It is clear that hormones influence neuroplasticity in order to produce adaptive behavioral responses at several key life transitions, including at sexual maturity and the transition to parenthood in both males and females. What is more, at least in females, neuroplasticity that occurs during the transition to motherhood has long-term consequences that extend well beyond the postpartum period and have important implications for health during mid-life and beyond (Fig. 1). The exact contribution of hormones to these longer-term changes, as well as if similar longer-term changes occur following the transition to fatherhood, are open questions. Ultimately, a more complete understanding of the mechanisms by which hormones influence neuroplasticity is necessary for understanding how individuals respond to life changes in adaptive ways, and is important for creating effective interventions in cases where adaptive responding is hindered.

Acknowledgements

Some of the work reported in this review was supported by Canadian Institutes for Health Research project grant to LAMG (PJT148662), the Brain and Behavior Initiative, the College of Behavioral and Social Sciences, and the Department of Psychology at the University of Maryland (ERG), and a Haverford College Faculty Research Grant (LEB).

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