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Plasticity of the Paternal Brain: Effects of Fatherhood on Neural Structure and Function

Running Title: Neuroplasticity in Fathers

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Abstract

Care of infants is a hallmark of mammals. Whereas parental care by mothers is obligatory for offspring survival in virtually all mammals, fathers provide care for their offspring in only an estimated 5-10% of genera. In these species, the transition into fatherhood is often accompanied by pronounced changes in males' behavioral responses to young, including a reduction in aggression toward infants and an increase in nurturant behavior. The onset of fatherhood can also be associated with sensory, affective, and cognitive changes. The neuroplasticity that mediates these changes is not well understood; however, fatherhood can alter production and survival of new neurons; function and structure of existing neurons; morphology of brain structures; and neuroendocrine signaling systems. Although these changes are thought to promote infant care by fathers, very little evidence exists to support this hypothesis; in most cases, neither the mechanisms underlying neuroplasticity in fathers nor its functional significance are known. In this paper we review the available data on the neuroplasticity that occurs during the transition into fatherhood. We highlight gaps in our knowledge and future directions that will provide key insights into how and why fatherhood alters the structure and functioning of the male brain.

Keywords: Fatherhood, Infant care, Neuroendocrine, Neurogenesis, Neuroplasticity, Paternal behavior,

1 INTRODUCTION

In female mammals, the onset of motherhood and successful rearing of offspring necessitate wholesale changes in behavior, as well as endocrine and physiological adjustments. Depending on the species, the need to nourish, warm, transport, and

protect her offspring can limit the amount of time a mother can spend foraging or hunting, alter her food intake and metabolism, decrease her mobility, and reduce her ability to thermoregulate (Kinsley et al., 2008; Olazabal et al., 2013a; Speakman, 2008). In addition, it may require cognitive and affective changes such that the mother becomes more attentive and attracted to infant-related sensory stimuli, such as cries and odors, more aggressive toward other conspecifics, and less easily perturbed by potentially threatening or distracting environmental stimuli (Lambert, 2012; Olazabal et al., 2013b; Slattery & Neumann, 2008). Not surprisingly, therefore, the onset of motherhood is associated with a multitude of changes in the maternal brain, both at the level of individual neurons and in properties of and connectivity among brain structures (González-Mariscal & Melo, 2017; Leuner & Sabihi, 2016; Leuner, Glasper, & Gould, 2010; Medina & Workman, 2020). This neural plasticity is likely mediated largely by the pronounced hormonal changes associated with pregnancy, parturition, and lactation, but can also be affected by interactions with infants or exposure to infant-related sensory stimuli (Medina & Workman, 2020).

In roughly 5-10% of mammalian genera, fathers, in addition to mothers, provide extensive care for their offspring and can have pronounced effects on offspring survival and development (Kleiman & Malcolm, 1981; Saltzman & Ziegler, 2014), including development of neuroendocrine, social, cognitive, and affective function (reviewed in Bales & Saltzman, 2016; Braun & Champagne, 2014). Although fathers do not experience the profound hormonal and physiological changes associated with pregnancy, parturition, and lactation, males in biparental species often undergo behavioral, endocrine, and physiological changes that allow them to meet the demands of parenthood. In recent years, researchers have begun to elucidate the neural plasticity that occurs as males become fathers and that might underlie these changes. Studies of rodents, nonhuman primates, and humans indicate that neuroplasticity in fathers, as in mothers, can be manifest in several processes, including changes in production and survival of neurons; functional and structural modifications in existing neurons; and larger-scale morphological changes of brain regions. In most cases, the mechanisms underlying such plasticity, including the effects of sensory cues from or experience with infants or females, and the roles of specific hormones and neuropeptides, have not

been elucidated. Moreover, the functional significance of fatherhood-induced neuroplasticity is almost entirely unknown.

In this review we aim to summarize and integrate findings on neuroplasticity in mammalian fathers, to highlight major gaps in our understanding of this plasticity, and to suggest promising directions for future research. We focus almost exclusively on rodents, because most of the work on neural plasticity has been performed in this taxon, but discuss findings from other mammalian taxa where possible. Importantly, almost all the data on plasticity of the paternal brain come from a small number of species in two rodent families (Cricetidae, Muridae), and therefore might not be representative of mammalian fathers in general. Moreover, although we believe that plasticity of the paternal brain is most relevant and most important in biparental species, in which fathers routinely provide care for their offspring, studies of uniparental or facultatively biparental house mice (*Mus musculus*) and rats (*Rattus norvegicus*) have yielded fascinating and detailed insights into plasticity of the male brain with respect to fatherhood and interactions with offspring; therefore, we include findings from these studies where relevant.

2 REVIEW OF FINDINGS

2.1 Plasticity in neurogenesis and cell survival

In rats, mice, and sheep (*Ovis aries*), the onset of motherhood is accompanied by changes in neurogenesis and cell survival in the maternal brain, especially in the subventricular zone and the dentate gyrus of the hippocampus (Table 1, Fig. 1; reviewed in González-Mariscal & Melo, 2017; Lambert, 2012; Leuner et al., 2010; Medina & Workman, 2018). Potential effects of fatherhood on birth and survival of neurons have been examined in several rodent species, with mixed results. The most common methods used in these studies are immunohistochemical staining for indicators of cell proliferation (e.g., bromodeoxyuridine [BrdU, an intercalating agent; Miller & Nowakowski, 1988] or Ki-67 [a protein associated with cell proliferation; Gerdes et al., 1984]) in combination with neuronal markers (e.g., TuJ1 [neuron-specific class III beta-tubulin, a component of neuronal microtubules; Lee et al., 1990], DCX [doublecortin, a protein involved in neuronal migration, strongly expressed in early stages of neuronal

development; Couillard-Despres et al., 2005], and/or NeuN [fox-3, a protein expressed in many neuronal nuclei and, to a lesser extent in some cell types, cytoplasm; Mullen et al., 1992]). The number and location of cells expressing these markers are measured in fathers and in males with varying amounts of interaction with females and/or pups to tease apart which aspects of the transition into fatherhood contribute to changes in neurogenesis and cell survival. While most research on neurogenesis focuses on the hippocampus (Anagnostou & Morales, 2019; Glasper et al., 2001; Hyer et al., 2016; Hyer et al., 2017; Lieberwirth et al., 2013; Mak & Weiss, 2010), some studies have investigated the olfactory bulbs (Mak & Weiss, 2010), amygdala (Lieberwirth et al., 2013), and hypothalamus (Lieberwirth et al., 2013), areas associated with memory, emotion, and detection of and response to stimuli from pups.

Mak and Weiss (2010) examined effects of fatherhood in the facultatively biparental house mouse, in which fathers do not provide infant care under natural conditions but do so when housed individually with pups or with their mate and pups in the laboratory (Gandelman et al., 1970; McCarthy & vom Saal, 1986). In an elegant study, Mak and Weiss (2010) compared neurogenesis (as indicated by BrdU-, Ki67-, and DCX-labeled cells) in the hippocampus and subventricular zone in groups of first-time fathers that had varying degrees of interaction with their own mate and pups or with an unfamiliar lactating female and pups for the first 2 days after birth of their offspring. Neurogenesis in the hippocampus and subventricular zone was highest in fathers housed with their own pups, either with or without their mate present, suggesting that interaction with one's own pups increases neurogenesis in this species. This increase continued through postnatal day 8, but by postnatal day 10, neurogenesis in both the hippocampus and subventricular zone had declined to baseline levels (i.e., levels observed in males on the day their pups were born) (Mak & Weiss, 2010).

Neurogenesis in the paternal brain has also been investigated in two obligately biparental rodents. One study of California mice (*Peromyscus californicus*) found that fathers exhibited increased neurogenesis (as indicated by BrdU and TuJ-1 colocalization) and increased survival of BrdU-labeled cells from postnatal day (PND) 9 to PND 16 in the dentate gyrus, compared to virgin males at comparable time points (Hyer et al., 2016). In a separate study by the same research group, however, California

mouse fathers that were housed with their mate and pups and tested when their pups were weaned (PND 28) showed decreased neurogenesis in the dentate gyrus compared to both age-matched virgin males and vasectomized males housed with a female (Glasper et al., 2011). The disparity between the results of these two studies likely reflects the difference in the time of testing: Hyer et al. (2016) examined fathers during their mates' mid-lactational period, whereas Glasper et al. (2011) tested fathers at the end of the lactational period. In the biparental prairie vole (*Microtus ochrogaster*), fathers tested on the day of birth of their second litter (i.e., around the age of weaning of their first litter) had significantly reduced cell survival (as indicated by BrdU staining) in the amygdala, dentate gyrus, and ventromedial hypothalamus compared to age-matched virgins (Lieberwirth et al., 2013). Together, these findings from prairie voles, California mice, and house mice suggest that neurogenesis and/or cell survival in the paternal brain increases during the early postpartum period but returns to, or even drops below, baseline levels by the late postpartum period.

In addition to fatherhood *per se*, effects of pup exposure on neurogenesis have been examined in adult virgin male prairie voles. In one study, virgin males (and females) that were exposed to unrelated pups once for 20 minutes had increased cell proliferation in the dentate gyrus, but not the medial or cortical amygdala, compared to pup-naïve virgins, and this effect was more pronounced in males that attempted to bite the pups than in those that behaved parentally (i.e., retrieved pups to the nest and crouched over them) (Ruscio et al., 2008). In another study of adult virgin male prairie voles, however, neither a single 20-minute pup exposure nor 10 daily 20-minute exposures affected neurogenesis or cell survival in the dentate gyrus, amygdala, or ventromedial hypothalamus (Lieberwirth et al., 2013). The differences in findings from these two studies might be due to differences in housing conditions or timing in experimental procedures: in Ruscio et al. (2008), adult males were housed in same-sex pairs, injected with BrdU hours after pup exposure, and sacrificed 48 hours after pup exposure. In Lieberwirth et al. (2013), adult males were housed with hormonally primed, ovariectomized females, injected with BrdU days before pup exposure, and sacrificed 24 hours after pup exposure.

Studies in uniparental rodents suggest that differences in neurogenesis between fathers and virgin males might be attributable, at least in part, to copulation. Male rats that experienced 30 minutes of sexual behavior, starting at first intromission, once or on 14 consecutive days, exhibited increased neurogenesis (as indicated by BrdU, NeuN, and TuJ1 expression) in the dentate gyrus compared to males that were paired with an ovariectomized, non-receptive female and males that were not exposed to a female (Leuner et al., 2010). Moreover, male rats that were allowed to pace the sexual interactions show an increased number of new neurons in the accessory olfactory bulb, but not the main olfactory bulb, compared to males that were not allowed to pace or that were separated from a female via a clear, porous, acrylic cage divider, suggesting that paced, but not non-paced, sexual interactions stimulate integration of new neurons into the accessory olfactory bulb (Portillo et al., 2012; Unda et al., 2016). In contrast, weekly mating of male Syrian hamsters (*Mesocricetus auratus*), a uniparental species, for 7 weeks did not increase cell survival or proliferation in the medial amygdala or medial preoptic area compared to non-mated controls, with the hippocampus not investigated (Antzoulatos et al., 2008).

In summary, males in several biparental and uniparental rodent species undergo changes in production and/or survival of new neurons, most notably in the hippocampus, during the transition to fatherhood. These changes may be activated by various components of reproduction, potentially including copulation, exposure to a pregnant or lactating female, and interactions with pups. Not surprisingly, therefore, plasticity in neuronal proliferation changes across reproductive stages and might be expected to subserve different functions at different time points.

2.2 Plasticity in neural activity

2.2.1 Acute neural responses to infant-related stimuli

Neuronal activation in response to brief exposure to infants or infant-related stimuli, and effects of fatherhood on these neural responses, have been studied in both rodents (Table 1, Fig. 1) and humans (Table 2). Rodent studies typically quantify expression of immediate early genes, such as *c-fos* and *erg1*, as markers of neuronal activity; however, colocalization of immediate early gene expression with other cellular markers,

such as cell type-specific markers or retrograde tracers, is necessary to determine patterns of activity in different cell types or pathway-specific patterns of activation. Studies of humans have used functional magnetic resonance imaging (fMRI) to quantify changes in metabolic activity in the brain in response to infants or infant-related stimuli. In both humans and rodents, patterns of brain activation in response to infants overlap, to a large extent, between mothers and fathers (Bales & Saltzman, 2016; Feldman, 2015). However, the functional role of these activated brain regions in parenting by fathers is poorly understood. Here, we present an overview of how neural responses of the male brain to infants are affected by fatherhood, focusing on sensory systems, cortex, and subcortical structures.

Acute responses to infant-related stimuli: sensory systems

Female rodents undergo changes in structure, function, and activity of neurons in the somatosensory, chemosensory, and auditory systems as they become mothers, allowing them to better detect and discriminate pup-related sensory stimuli (reviewed in Kinsley & Amory-Meyer, 2011; Valtcheva & Froemke, 2019). In rodent fathers, paternal care can be elicited by stimuli from pups (or, in some cases, from postpartum females) in several different sensory modalities, including chemosensory, auditory, visual, tactile, and thermal cues (Horrell et al., 2019a). Accordingly, as in females, parenthood can alter males' neural and behavioral responses to pup-related sensory stimuli (Table 1, Fig. 1).

Sensory plasticity in fathers has been studied mostly in the main and accessory olfactory systems. As described above, fatherhood in house mice results in the creation of olfactory neurons, generated from new cells arising in the subventricular zone, that preferentially respond to odors of adult offspring (Mak & Weiss, 2010). Fatherhood in house mice also affects responsiveness of the accessory olfactory system to pups: when exposed to pups, fathers exhibit lower expression of the immediate early gene product Fos in the sensory neurons of the vomeronasal organ (VNO) and accessory olfactory bulbs, compared to virgin males (Tachikawa et al., 2013). Conversely, fathers show increased Fos responses to pups, as compared to virgins, in several downstream projection sites (e.g., medial amygdala, bed nucleus of the stria terminalis (BNST), and

anterior hypothalamus), as described below (Tachikawa et al, 2013). Ablation of the VNO in virgin male house mice reduces pup-directed aggression and enhances paternal behavior (Tachikawa et al., 2013), suggesting that downregulation of the accessory olfactory system's response to pups plays a causal role in the suppression of infanticide and the onset of paternal care in fathers.

In the VNO of house mice, several candidate populations of neurons have been identified that appear to play a role in mediating paternal and infanticidal behavior. These include neurons expressing Gαi2, a G-protein alpha subunit (Trouillet et al., 2019), and Trpc2, which codes for the transient receptor potential channel 2, a cation channel that plays an essential role in signal transduction in the VNO (Leypold et al., 2002; Wu et al., 2014). To date, however, fatherhood-induced plasticity has been observed specifically in the olfactory neurons that express *Olfr692*, an odorant receptor gene; these neurons show markedly lower activation (as determined by mRNA expression of the immediate early gene Egr1) after pup exposure in house mouse fathers compared to virgins (Nakahara et al., 2016).

In addition to olfaction, mammalian mothers exhibit plasticity in somatosensation and audition, as mentioned above. Because these sensory systems have been implicated in paternal as well as maternal behavior (Horrell et al., 2019a), they, too, seem likely to undergo plasticity during the transition to parenthood in males. Thus, further investigation of parenthood-induced sensory plasticity is a promising topic for future studies.

Acute responses to infant-related stimuli: cortex

Studies using fMRI have found differences between human fathers and non-fathers in activation of brain regions associated with social cognition and emotion, in response to auditory or visual infant stimuli (Table 2). Seifritz and colleagues (2003) examined brain responses to recordings of infants crying and laughing in fathers of young children and in men without children. Fathers showed greater activation in cortical regions associated with socio-cognitive and emotional processes (mid-cingulate cortex, ventral prefrontal cortex, temporo-parietal junction, and insula) in response to an infant crying compared to an infant laughing. In the same brain regions, non-fathers showed the opposite

pattern of activation, with a greater response to infants laughing compared to crying (Seifritz et al., 2003). Another study found a difference between fathers and non-fathers in cortical activity in response to an image of an unknown child, where fathers had increased activity in the temporo-parietal junction, ventral prefrontal cortex, middle frontal gyrus, superior frontal gyrus, medial orbitofrontal cortex, and precuneus area, compared to non-fathers (Mascaro, Hackett, & Rilling, 2014).

Van 't Veer et al. (2019) used a longitudinal fMRI design to examine brain activity in men, both before and after the birth of their first child, in response to videos of their own imagined infant or an unrelated infant in threatening or neutral scenarios. Activation patterns in response to stimuli from threatening scenarios were mostly similar between the prepartum and postpartum periods, with increased activation in insular-cingulate and fronto-temporoparietal networks in response to infants in a threatening situation compared to infants in a neutral situation, regardless of the familiarity of the infant stimuli (imagined own vs unknown). However, an increase in the activation of the superior frontal gyrus, an area implicated in social knowledge, was observed in expectant fathers but faded after the birth of their offspring (van 't Veer et al., 2019). Collectively, the results suggest that functional alterations may occur in cortical regions associated with socio-cognitive and emotional processing during the transition into fatherhood in humans. Engagement of these circuits might facilitate the father's ability to infer the mental and emotional state of a distressed infant, but this possibility has not been tested

Acute responses to infant-related stimuli: hypothalamus, medial preoptic area, and extended amygdala

The medial preoptic area (MPOA) and BNST, brain regions implicated in the expression of parenting behavior in both sexes, are activated in a similar manner in paternally behaving male rodents, and this activation often differs between fathers and virgin males (Table 1). De Jong et al. (2009) found that exposure to stimuli (e.g., vocalizations and chemosignals) from an alien pup enhanced Fos-immunoreactivity (Fos-ir) in California mouse fathers in the MPOA and BNST, and that this effect was attenuated in virgins. Similarly, Lambert and collegues (2013) found that in both California mice and

uniparental deer mice, fathers had increased Fos expression in the MPOA in response to pups in distress, compared to virgins. Finally, house mouse fathers exposed to an unrelated conspecific pup show increased Fos expression in the MPOA and BNST, compared to virgin males (Tachikawa et al., 2013; Wu et al., 2014). In particular, Wu and colleagues (2014) found that a population of MPOA neurons that express the neuropeptide galanin are activated in response to interactions with pups in fathers but not in virgin males. Moroever, genetic ablation of these galanin-positive MPOA neurons causes deficits in parental behavior in fathers, while optogenetic activation of these neurons promotes paternal behavior and reduces aggression toward pups (Wu et al., 2014). Thus, these authors demonstrated that rodent fathers show increased responsiveness to pups not only in brain structures associated with the control of paternal behavior but within specific neurochemically defined cell populations critical for fathering.

Acute responses to infant-related stimuli: other subcortical structures

The lateral septum, a subcortical region implicated in social cognition, social behavior, and aggression (Ophir, 2020), can be activated in male rodents in response to pups (Kirkpatrick et al., 1994b), and this response may be suppressed by prior experience with pups: Lambert et al. (2011) found that in California mice, pup-naïve virgin males had higher Fos expression in the lateral septum, following interactions with a pup, than either fathers or virgin males previously exposed to pups. In contrast, other studies of California mice have found no changes in Fos expression in the ventral lateral septum in virgin males, new fathers, or expectant fathers in response to distal cues from a pup (de Jong et al., 2009, 2010). The differences between these results and those of Lambert et al. (2011) likely reflect differences in methodology: whereas Lambert et al. (2011) allowed adult males to interact physically with pups and quantified Fos-ir in the entire lateral septum, de Jong et al. exposed males to pups that were confined in a wire-mesh ball, preventing direct contact (de Jong et al., 2009), and Fos-ir was assessed only in the ventral lateral septum (de Jong et al., 2009, 2010).

California mice also show plasticity in activation of the serotonergic caudal dorsal raphe in response to pups: after exposure to a pup in a wire-mesh ball, fathers exhibit

increased Fos-ir in this brainstem structure, compared to virgin males (de Jong et al., 2009). The serotonergic system plays a key role in modulating stress-responsiveness, emotion, mood, and cognition (Charnay & Léger, 2010), and the dorsal raphe nucleus directly innervates many of the subcortical regions implicated in rodent paternal care (Muzerelle et al., 2016; Vertes, 1991; Waselus et al., 2011); however, to our knowledge, a role for the serotonergic system in the onset or maintenance of paternal care has not been investigated.

In summary, fatherhood alters patterns of acute neural activation in response to infants or infant-related stimuli in numerous brain regions, including areas associated with chemosensation, parental care, cognition, social behavior, emotion, and stress. The mechanisms underlying this plasticity are largely unknown; however, they may involve changes throughout the nervous system, not necessarily limited to changes within those brain regions that exhibit altered Fos expression.

2.2.2 Plasticity in electrophysiological properties of neurons

Motherhood can modulate electrophysiological characteristics of neurons in female rodents. For example, ultrasonic vocalizations from pups elicit greater inhibitory responses in the auditory cortex of mouse mothers than of virgin females, particularly in regions tuned to frequencies lower than those of pup calls (Galindo-Leon et al., 2009). This effect is thought to enhance mothers' ability to detect and discriminate vocalizations from pups when background noise is present (Galindo-Leon et al., 2009). Similarly, in a recent study of female mice, calcium imaging of mitral cells in the olfactory bulb found that mothers show significantly stronger inhibitory responses to pure (monomolecular) odors, compared to pup-naïve females, but stronger excitatory responses to natural, biologically relevant odors, including odors from conspecifics and food (Vinograd et al., 2017).

To our knowledge, only two studies have evaluated effects of fatherhood on electrophysiological properties of neurons. Horrell and colleagues (2019b) investigated electrophysiology of MPOA neurons in California mice using *in vitro* blind, whole-cell patch-clamp experiments and found a variety of spiking patterns, with fathers exhibiting lower maximal inhibitory current elicited by local stimulation, compared to virgin males.

No other measures of intrinsic or synaptic properties of neurons differed between virgins and fathers (Horrell et al., 2019b). In house mice, neurons in the amygdalohippocampal area that project to the MPOA have recently been implicated in paternal care (Sato et al., 2020). Whole-cell patch-clamp experiments revealed no differences in passive membrane properties of these cells between virgins and fathers; however, administration of oxytocin into the bathing solution of the slices increased spontaneous inhibitory postsynaptic current frequency in both virgins and fathers, with a larger increase seen in fathers, suggesting greater sensitivity to oxytocin (Sato et al., 2020). Studies of other regions, especially those involved in peripheral and central detection and processing of pup-related stimuli, might yield additional evidence of fatherhood-induced plasticity in electrophysiological properties of neurons.

2.3 Plasticity in neuronal morphology

In rats and mice, the onset of motherhood is associated with changes in neuronal morphology in several brain regions (reviewed in González-Mariscal & Melo, 2017; Leuner et al., 2010). Most notably, density of dendritic spines is higher in mothers than in virgin females in the dentate gyrus, CA1, and CA3 of the hippocampus, as well as in the prefrontal cortex and medial amygdala. Length and branching of dendrites in CA1 and CA3 are also higher in mothers than in virgins.

Fatherhood, too, can affect neuronal morphology in biparental rodents and monkeys (Table 1, Fig. 1). Two studies have quantified dendritic length, branch points, and spine density of granule cells in the dentate gyrus and pyramidal cells in the hippocampus of California mice (Glasper et al., 2016; Hyer & Glasper, 2017). Both studies found differences in morphology of pyramidal cells in CA1 between fathers and virgin males housed with tubally ligated females: spine density of basal dendrites was higher in fathers, whereas length and number of branch points of apical dendritic trees were lower, suggesting less connectivity in the apical dendritic trees of fathers than of virgins. Additionally, Hyer and Glasper (2017) found that fathers had decreased spine density on apical dendrites of pyramidal cells in CA3 compared to virgins, while Glasper et al. (2016) found increased spine density on secondary and tertiary dendrites on granule cells in the dentate gyrus of fathers.

Plasticity in the morphology of pyramidal cells in layer II/III of the prefrontal cortex has been investigated in three biparental species. In common marmoset monkeys (*Callithrix jacchus*), fatherhood increased spine density on apical and basal dendritic trees of these neurons but did not affect dendritic length (Kozorovitskiy et al., 2006); no effects of fatherhood on dendritic spine density and length were seen in pyramidal neurons in area V1/V2 of the occipital cortex. Branch points were not quantified in this study (Kozorovitskiy et al., 2006). A similar analysis in mandarin voles (*Microtus mandarinus*) revealed that fatherhood increased spine density, dendritic length, and branch points in layer II/III pyramidal neurons in the prefrontal cortex (Wang et al., 2018a).

Finally, two studies of the MPOA in California mice found no differences in neuronal morphology between virgins and fathers. Fatherhood had no effect on soma size (Gubernick et al., 1993; Horrell et al., 2019b) or branch points, total neurite length, length of longest neurite, or number of neurons leaving the soma (Horrell et al., 2019b). However, these studies did not differentiate among types of neurons in the MPOA; morphological analysis of a particular neuronal phenotype, categorized by gene expression or connectivity, might reveal effects of fatherhood (Tsuneoka et al., 2015; Tsuneoka, 2019). Seelke et al. (2018) used RNA sequencing to identify genes differentially expressed in the MPOA of prairie vole fathers compared to virgin and pair-bonded males. Of the many differences in gene expression that were found between fathers and one or both of the control groups, several involved genes associated with synaptic plasticity and remodeling of dendritic spines. Neurons that express these genes may be good candidates for analysis of plasticity.

In sum, findings to date indicate that fatherhood, like motherhood, might commonly affect dendritic branching patterns and spine density in the hippocampus and prefrontal cortex. However, little is known about possible effects of fatherhood on neuronal morphology in other brain regions, including those most closely associated with the control of parental behavior.

2.4 Plasticity in morphology of brain regions

MRI studies of human women have revealed changes in size of the entire brain as well as of several specific regions during pregnancy and the postpartum period (reviewed in Kim, 2016). Two published MRI studies have similarly investigated effects of fatherhood on morphology of the human brain (Table 2). Using a longitudinal design in which fathers were scanned twice, roughly one month postpartum and again four months postpartum, Kim et al. (2014) found changes in gray matter in several cortical and subcortical regions (Table 2). In a study comparing elderly fathers with one child to age-matched men without children (Orchard et al., 2020), fathers had increased gray matter in the right temporal pole and decreased gray matter in the left caudal anterior cingulate cortex, regions implicated in socio-emotional processing, similar to findings in Kim et al. (2014).

To our knowledge, only a single study has investigated fatherhood-induced plasticity in morphology of brain regions in nonhuman mammals: Gubernick et al. (1993) found no differences between California mouse fathers and male virgins in volume of the MPOA or in number and density of neurons in the MPOA. Given the current availability of sophisticated methods to characterize changes in specific neuronal populations, studies of volumetric changes in brain regions may be of limited value.

2.6 Plasticity in neuroendocrine and neuropeptide signaling pathways

Fatherhood modulates signaling by numerous hormones and neuropeptides, including actions on both hormone/neuropeptide secretion and expression of receptors. This topic has been reviewed thoroughly in several recent papers (e.g., Bales & Saltzman, 2016; Glasper et al., 2019; Gromov, 2020; Horrell et al., 2019b). Therefore, we present only a brief overview, focusing on central signaling pathways and how they may change in association with fatherhood (Table 1, Fig. 1).

2.6.1 Plasticity in neuropeptide signaling pathways

The closely related neuropeptides oxytocin and vasopressin have been studied extensively in relation to parental behavior. Traditionally, studies of females have tended to focus more heavily on oxytocin, whereas studies of males have emphasized vasopressin. However, evidence suggests that intracerebral signaling by both

neuropeptides can modulate male parental care and, in turn, can be altered by fatherhood.

Oxytocin

In female mammals, oxytocin (OT) is essential for both physiological and behavioral components of new motherhood: peripherally, oxytocin acts on smooth muscle in the uterus and mammary glands to stimulate parturition and milk letdown, respectively, while centrally it enhances social and affiliative behaviors, including maternal care. Not surprisingly, the onset of motherhood is associated with extensive plasticity in central oxytocinergic signaling pathways (Kim & Strathearn, 2016).

The transition to fatherhood, too, is associated with plasticity of the central oxytocinergic systems, although these effects may differ among species. Effects of fatherhood on OT signaling have been studied extensively in the socially monogamous and biparental mandarin vole. First-time fathers show increased oxytocin immunoreactivity (OT-ir) in the PVN and supraoptic nucleus (SON), two hypothalamic nuclei that synthesize OT, compared to virgin males without paternal experience (Song et al., 2010; Wang et al., 2015). New fathers also have more OT-ir neurons in the MPOA and fewer OT-ir cells in the lateral habenula, compared to virgins (Wang et al., 2015). Several studies have also found differences in expression of oxytocin receptors (OTR) between mandarin vole virgins and fathers. Fathers have higher expression of both OTR mRNA and OTR protein in the MPOA (Yuan et al., 2019), and higher expression of the OTR gene in the medial amygdala and nucleus accumbens, compared to virgins (Wang et al., 2015). On the other hand, OTR gene expression does not differ between fathers and virgins in the PVN, SON, BNST, lateral septum, ventromedial hypothalamus, and entire amygdala (Wang et al., 2000). In one interesting study, new mandarin vole fathers had higher protein levels of OTR in the nucleus accumbens than experienced fathers (Wang et al., 2018b).

Similar to mandarin voles, fathers show increased OTR binding in numerous brain regions in the polygamous, facultatively biparental meadow voles (*Microtus pennsylvanicus*). Fathers in this species have higher OTR binding in the accessory olfactory nucleus, lateral amygdala, BNST, and lateral septum compared to virgin males

493 that are unresponsive to pups (Parker et al., 2001), while in the biparental California
494 mouse, fathers show reduced OTR gene expression in the BNST compared to virgins
495 (Perea-Rodriguez et al., 2015). No differences in OT-ir or OTR mRNA gene expression
496 between fathers and virgins have been reported in any other regions analyzed in the
497 California mouse, including the PVN and hippocampus (de Jong et al., 2009; Hyer et al.,
498 2017). Finally, prairie vole fathers have more OT-ir in the PVN, but lower OT-ir in the
499 BNST, than virgins (Kenkel et al., 2014). Collectively the majority of studies support the
500 conclusion that fatherhood increases oxytocin signaling in several brain regions
501 implicated in male pup-affiliative behavior, but the functional significance of the changes
502 in central OT signaling during the transition to fatherhood is not well understood.
503
504 **Vasopressin**
505 Vasopressin (AVP) is another neuropeptide that has been implicated in the regulation of
506 a variety of social behaviors, including territorial defense, aggression, social dominance,
507 and paternal care (Carter, 2017; Ophir, 2017). Numerous studies have reported
508 alterations in central AVP signaling that may mediate the transition from pup-aggressive
509 to pup-affiliative behaviors in rodent fathers (Saltzman et al., 2017). In the biparental
510 prairie vole, fathers show a reduction in AVP-ir fiber density in the lateral septum and
511 lateral hypothalamus compared to virgin males (Bamshad et al., 1993,1994). Although
512 Bamshad and colleagues (1994) did not find a difference between groups in AVP-ir in
513 the PVN, others have reported an increase in AVP gene expression in the PVN and
514 SON of prairie vole fathers compared to virgins (Wang et al., 2000). In mandarin voles,
515 MPOA expression of neither the vasopressin V1a receptor (V1aR) gene nor its protein
516 product differs between fathers and virgin males (Yuan et al., 2019).
517 In facultatively biparental meadow voles, fathers show higher AVP receptor
518 binding than non-fathers in the anterior olfactory nucleus, while showing less AVP
519 binding in the lateral septum (Parker et al., 2001). Conversely, the California mouse
520 exhibits more paternal behavior, as well as more AVP-ir fibers in the lateral septum and
521 BNST, compared to fathers in a uniparental congener, the white-footed mouse
522 (*Peromyscus leucopus)* (Bester-Meredith et al, 1999). In California mice, fathers have
523 lower V1aR gene expression than virgin males in the BNST and hippocampus (Hyer et

al., 2017; Perea-Rodriguez et al., 2015). Finally, fatherhood can affect AVP signaling in a biparental nonhuman primate, the common marmoset, in which fathers have increased expression of V1aR in the prefrontal cortex compared to non-fathers (Kozorovitskiy et al., 2006). Collectively, these findings indicate that central expression of both AVP and the V1a receptor is frequently altered by fatherhood in biparental mammals, but that these effects are somewhat region- and species-specific.

2.6.2 Plasticity in steroid hormone signaling pathways

Gonadal steroid hormones, including androgens, estrogens, and progestogens, readily enter neurons and bind to either intracellular or membrane receptors to exert both slow, genomically mediated effects and rapid, non-genomic effects, respectively, on physiology and behavior (Hammes & Levin, 2007; Tsai & O'Malley, 1994). These hormones can dramatically influence parental behavior in both male and female mammals; thus, it is not surprising that signaling by them is modulated by parenthood (Table 1).

Testosterone

Testosterone has traditionally been thought to inhibit parental care in males (e.g., Clark & Galef, 1999; Nunes, Fite, & French, 2000); however, experimental studies of several biparental rodent species have found that testosterone can suppress, promote, or have no effect on paternal behavior, with differences found both between and within species (reviewed in Horrell et al. 2019a). On the other hand, fatherhood consistently reduces peripheral testosterone levels in numerous species (e.g., Brown et al., 1995; Reburn & Wynne-Edwards, 1999; Trainor et al., 2003; Ziegler & Snowdon et al., 2001). Surprisingly little is known about effects of fatherhood on androgen signaling in the brain. A recent study in the biparental Mongolian gerbil (*Meriones unguiculatus*) reported increased androgen receptor immunoreactivity (AR-ir) in the olfactory bulb, MPOA, and medial amygdala in sexually experienced males exhibiting paternal behavior compared to non-parental virgin males (Martínez et al., 2019). Furthermore, fathers on postnatal day 6 had a higher number of AR-ir cells in the medial amygdala compared to fathers on the day their pups were born (Martínez et al., 2019). Thus,

androgen signaling in the brain might increase with fatherhood, in spite of the drop in peripheral testosterone levels.

Estrogen

Relatively little is known about effects of fatherhood on peripheral estrogen concentrations. In California mice and in one study of Campbell's dwarf hamsters (*Phodopus campbelli*), fathers exhibited higher levels of plasma estradiol compared to virgins or males cohabitating with ovariectomized females (Hyer et al., 2017; Romero-Morales et al., 2020). However, another study found no such alterations in plasma estradiol levels in dwarf hamsters once they became fathers (Schum & Wynne-Edward, 2005).

The onset of fatherhood is associated with plasticity in central estrogen signaling, particularly through estrogen receptor α (ERα), in biparental rodents. A recent study of Campbell's dwarf hamsters found that fathers paired with intact females had higher ERα-ir in the MPOA than males paired with either tubally ligated or ovariectomized females, and males paired with tubally ligated females had higher ERα-ir in the same region compared to males housed with ovariectomized females; the groups did not differ in ERα expression in the medial amygdala (Romero-Morales et al., 2020). On the other hand, an earlier study of the same species found no differences in ERα-ir between fathers and non-fathers in any brain regions analyzed (MPOA, medial amygdala, BNST; Timonin et al., 2008). The disparity between the results of these two studies might reflect differences in the timing of brain collection: fathers' brains were collected 24 h after the birth of pups in Romero-Morales et al. (2020) and 3 days after parturition in Timonin et al. (2008). The studies also differed in housing conditions of the control groups: Romero-Morales et al. (2020) compared fathers to pup-exposed males cohabitating with either tubally ligated or ovariectomized females, while Timonin et al. (2008) compared fathers to pup-naïve virgin males housed with same-sex siblings and males recently mated with intact females.

In mandarin voles, first-time fathers exhibit reduced ERα-ir in the MPOA and BNST, as well as more ERα-ir in the ventromedial hypothalamus, medial amygdala, and central nucleus of the amygdala, compared to virgin males without prior pup exposure

(Song et al., 2010). California mouse fathers, in contrast, do not show any differences in ERα mRNA expression in the MPOA, BNST, or medial amygdala compared to virgin males (Perea-Rodriguez et al., 2015). However, fathers in this species have higher activity of aromatase, the enzyme that converts androgens to estrogen, in the MPOA, compared to mated males that have not yet produced offspring, as well as a trend toward higher aromatase activity in the MPOA than virgin males (Trainor et al., 2003). Because California mouse fathers also have lower peripheral testosterone levels than mated males without offspring (Trainor et al., 2003), it is unclear whether fatherhood alters central estrogen levels in this species.

Studies of ERα and ERβ knockout mice suggest ERα and ERβ play distinct roles in the regulation of behavior: ERα seems to be essential for reproduction, while ERβ signaling has been implicated more strongly in cognition (Hill & Boon, 2009). However, both ERs may be important for social learning as they are both involved in the regulation of social recognition in mice (Choleris et al., 2006). Although the majority of research has focused on ERα signaling in fathers, Hyer and colleagues (2017) reported that California mouse fathers exhibited changes in ERβ gene expression in the hippocampus throughout the postpartum period: ERβ expression temporarily increased on PND16 in fathers compared to virgins, while no differences in gene expression were observed between groups on PND2 or PND30.

Collectively, the mixed findings in regard to the relationship between central estrogen activity and fatherhood suggest that phylogenetic variation exists in the effects of fatherhood on estrogen signaling in the brain, whereas within-species differences in findings may be due to disparities in timing of experimental procedures or housing conditions across studies.

Progesterone

Progesterone receptor- (PR-) mediated signaling has pronounced effects on infant-directed behavior in male house mice: decreased expression or blockade of PR inhibits infanticide and increases affiliative behavior toward pups in adult males, whereas progesterone treatment has the opposite effects (Schneider et al., 2003). In California mice, circulating progesterone concentrations are lower in fathers 2-3 weeks

postpartum than in sexually inexperienced males (Trainor et al., 2003), and in Campbell's dwarf hamster, fathers' serum progesterone levels rise around the time of the pups' birth before declining again (Schum & Wynne-Edwards, 2005). However, effects of fatherhood on progesterone signaling in the brain have received little attention. California mouse fathers show reduced PR mRNA expression in the BNST, as well as a trend toward lower PR mRNA expression in the MPOA, compared to virgin males (Perea-Rodriguez et al., 2015). Overall, these findings in California mice and house mice suggest that fatherhood inhibits progesterone signaling within the brain and, conversely, that progesterone inhibits paternal care and increases aggression toward pups in adult males.

2.6.3 Plasticity in prolactin signaling pathways

Perhaps the most consistent finding in the endocrinology of paternal care is that peripheral prolactin concentrations are elevated in fathers, compared to non-fathers. This pattern has been observed in many biparental species, including rodents and primates (reviewed in Bales & Saltzman, 2016; Horrell et al., 2019a). Very few studies, however, have investigated effects of fatherhood on prolactin signaling in the brain. In common marmosets, central prolactin activity increases with paternal experience; hypothalamic explants from experienced fathers have higher prolactin and lower dopamine levels compared to explants from non-fathers (Woller et al., 2012). A study of the biparental Campbell's dwarf hamster examined prolactin receptor (PRL-R) mRNA transcript levels in the choroid plexus of the hypothalamus in fathers across their mate's gestational and postpartum periods (Ma et al., 2005). Fathers' PRL-R mRNA expression in the choroid plexus was lowest on the day before birth of their offspring and increased during the early postnatal period, specifically on the first and fifth days postpartum (Ma et al., 2005). The results suggest that prolactin activity is elevated in the brain of biparental males when fathers are engaged in pup-interactive behaviors. Finally, in male California mice, fathers exhibited a downregulation in gene expression of PRL-R in the hippocampus compared to virgins (Hyer et al., 2017).

3. DISCUSSION AND FUTURE DIRECTIONS

As summarized above, fathers in biparental species and in some facultatively biparental species undergo changes in birth and survival of new neurons; activity and morphology of existing neurons; and morphology of brain regions. The onset of fatherhood is also associated with plasticity in central and/or peripheral concentrations of numerous hormones and neuropeptides, as well as in the expression and distribution of their cognate receptors. However, research to date has, most likely, barely scratched the surface of this plasticity. For example, fatherhood likely induces additional structural, functional, and neuroendocrine changes in brain regions both that do and do not have direct influences on paternal care, and virtually nothing is known about the mechanisms or functions of neural plasticity in fathers.

3.1. Potential mediators of neuroplasticity in fathers

3.1.1. Neuroendocrine mediators of neuroplasticity

Neural plasticity in mammalian mothers has been ascribed largely to hormonal changes occurring during pregnancy, parturition, and lactation. In pregnant rats, for instance, changes in estrogen and progesterone levels induce remodeling of neurons in the MPOA (Keyser-Marcus et al., 2001), and in pregnant mice, prolactin mediates increased neurogenesis in the subventricular zone (Shingo et al. 2003). As described above, fathers in biparental species undergo systematic changes in some of the same central signaling pathways as mothers; thus, these neuroendocrine shifts might underlie at least some of the neural plasticity associated with the onset of fatherhood. On the other hand, neuroendocrine alterations are typically less pronounced and more variable in males than in females, and some of the neuroendocrine changes in mothers are not paralleled in fathers. In at least one species, the uniparental rat, for example, lactation increases mothers' basal corticosterone production, which in turn inhibits neurogenesis in the hippocampus (Leuner et al., 2007), whereas studies of glucocorticoids in males of biparental species have typically found either lower levels in fathers than non-fathers or no differences between groups (reviewed in Horrell et al., 2019a). Thus, mediators of neural plasticity are likely to differ, to some extent, between mothers and fathers. Furthermore, sex differences in numbers and distribution of receptors for mediators of neuroplasticity may lead to corresponding differences in the effects of these mediators.

For example, estrogen receptor distributions in the brain differ between the sexes in both rats (Zhang et al., 2002) and humans (Kruijver et al., 2002); hence, specific effects of estrogen on neural plasticity might differ to some extent as well.

In house mouse fathers, as in mothers, prolactin has been implicated in promoting neurogenesis in the subventricular zone (Mak & Weiss, 2010). Given the ubiquity of increased prolactin levels in fathers, especially in biparental species (Glasper et al., 2019; Horrell et al., 2019a), it is possible that prolactin, in addition to neuropeptides and steroid hormones, might similarly modulate neurogenesis in fathers in other species. Estrogen, too, has been implicated in neurogenesis in fathers: Hyer et al. (2017) found that treatment with the estrogen receptor modulator tamoxifen reduced neurogenesis and survival of new neurons in the dentate gyrus of California mouse fathers but not virgin males. Finally, fMRI studies of human fathers have found that intranasal treatment with oxytocin can alter fathers' responses in several brain regions to photographs of children, including the globus pallidus, anterior cingulate cortex, and caudate nucleus (Li et al., 2017; Wittfoth-Schardt et al., 2012). Additional studies that block, simulate, or enhance the endocrine and neuropeptide effects of fatherhood will be important for elucidating the neurochemical mediators of fatherhood-induced neuroplasticity. Moreover, conducting comparable studies in multiple biparental species might provide insight not only into the proximate drivers of interspecific differences in plasticity but also, potentially, into the evolutionary pathways leading to both similarities and differences in plasticity among species.

3.1.2. Experiential mediators of neuroplasticity

Plasticity in the male brain can be influenced not only by fatherhood *per se* but also by experiences associated with the onset of fatherhood, such as mating, cohabitation with a (pregnant or lactating) female, and interactions with pups. In some strains of house mice, for example, ejaculation elicits neural changes that suppress infanticide several weeks later, at the time that the male's pups would be born; however, the mechanism underlying this plasticity is not known (Perrigo et al., 1992). In virgin male prairie voles, cohabitation with an unrelated female for as little as three days upregulates expression of vasopressin mRNA in the BNST and downregulates expression of vasopressin

peptide in the lateral septum and lateral habenular nucleus (Bamshad et al., 1994; Wang et al., 1994). Moreover, as described above, exposure to pups for 20 minutes increases neurogenesis in the dentate gyrus of virgin male prairie voles, similar to effects of fatherhood (Ruscio et al., 2008). Neurogenesis in male prairie voles can also be affected by brief (6h) exposure to an ovariectomized, estrogen-treated (i.e., sexually receptive but infertile) female, even when physical contact and mating are prevented, as well as by longer (48h) cohabitation with such a female (Castro et al., 2020). These findings suggest that different components of reproductive experience can affect different aspects of neural plasticity and, in some cases, may have redundant effects on the brain.

In humans, too, interactions with females preceding the onset of fatherhood might influence neuroplasticity. Although effects of marital status or pair-bonding on the brain are not yet known, numerous studies, including several longitudinal studies, have demonstrated that marriage or cohabitation with a female mate is associated with declines in men's circulating or salivary testosterone levels, whereas divorce shows the opposite pattern (Gettler et al., 2011; Holmboe et al., 2017; Mazur & Michalek, 1998). While a causal relationship between marital/relationship status and testosterone concentrations has not been firmly established, some evidence suggests that testosterone levels are influenced by marriage/pair-bonding and divorce, rather than or in addition to vice versa (Gettler et al., 2011; Holmboe et al., 2017). Moreover, Holmboe et al. (2017) suggested that marital status affects central regulation of the hypothalamic-pituitary-testicular axis, indicative of neuroplasticity. Additionally, interactions with infants might affect neural responses even in men who are not biological fathers: in an fMRI study of homosexual couples, Abraham et al. (2014) found that patterns of neural activation in response to interactions with an infant differed between primary and secondary male caregivers.

The proximate cues mediating effects of different types of reproductive experience, such as ejaculation, odors from female mates, or auditory, olfactory, or tactile cues from infants, are not well understood. An important topic for future research will be to tease apart the mechanisms by which different aspects of reproductive

experience interact to elicit neuroplasticity in fathers, as well as the sensory and neurochemical mechanisms by which they do so.

An intriguing possibility is that both hormonal and experiential modulators of plasticity in the paternal brain are mediated by perineuronal nets (PNNs), specialized aggregates of extracellular matrix that surround neurons and proximal dendrites in the central nervous system (Celio et al., 1998). PNNs serve a variety of functions, including regulating synaptic plasticity, protecting neurons from damage, and modifying signal processing (reviewed in Sorg et al., 2016). Few studies have examined PNNs in the context of an ecologically relevant behavior; however, recent studies of female rodents found changes in PNN expression in association with reproductive events. Lau et al., (2020) found that PNN expression in primary somatosensory cortex (SS1) of virgin female mice was altered following interactions with pups (pup-retrieval) in a subregion- and hemisphere-specific manner. Moreover, manipulations of PNNs in the auditory cortex blocked experience-dependent pup-retrieval in virgin female mice (Krishnan et al., 2017). In female rats, PNNs in the MPOA undergo dynamic reorganization during the reproductive cycle, particularly during gestation, and this effect can be mimicked by treatment of ovariectomized females with estrogen, progesterone, and prolactin (Uriarte et al., 2020). Together, these findings suggest that hormonal changes experienced by new mothers – and fathers – as well as interactions with pups might alter some components of neural plasticity through modulation of PNNs. A promising avenue for future research would be to determine the role of PNNs in plasticity of the paternal brain during the transition to fatherhood.

3.1.3. Energetic mediators of neuroplasticity

An intriguing possibility is that plasticity of the paternal brain is mediated, in part, by the energetic costs of parenting. Fatherhood is associated with energetic or metabolic changes in at least several biparental mammals. Prairie vole (Campbell et al., 2009; Kenkel et al., 2014), California mouse (Harris et al., 2011; Saltzman et al., 2015), common marmoset (Ziegler et al., 2006) and cotton-top tamarin [*Saguinus oedipus*], Ziegler et al., 2006) fathers undergo systematic changes in body mass across their mates' gestational and lactational periods; prairie vole fathers additionally undergo

771 reductions in subcutaneous fat and circulating leptin levels, as well as changes in time
772 spent feeding, across reproductive bouts (Campbell et al., 2009; Kenkel et al., 2014).
773 California mouse fathers show few energetic or metabolic differences from non-fathers
774 when housed under standard laboratory conditions; however, differences in basal
775 metabolic rate, maximal oxygen consumption, body mass, and fat mass emerge when
776 mice are housed under energetically challenging conditions (Andrew et al., 2017, 2018,
777 2019; Zhao et al., 2017, 2018).
778 Studies of humans and rodents indicate that changes in energy intake or
779 expenditure can influence structure and function of the brain. For example, both chronic
780 aerobic exercise and intermittent energy restriction can enhance neurogenesis and
781 synaptic plasticity in the hippocampus (El-Sayes et al., 2019; van Praag et al., 2014).
782 Given that fathers in biparental species, especially under natural conditions, may
783 experience changes in both physical activity and food availability in association with the
784 demands of parenthood (e.g., reduced time available for foraging, increased
785 thermoregulatory demands, costs of transporting offspring; Kleiman & Malcolm, 1981;
786 Saltzman & Ziegler, 2014), the resulting shifts in energy balance could have significant
787 impacts on the paternal brain.
788 In summary, fatherhood-induced changes in brain structure and function are
789 likely mediated by a number of intrinsic (e.g., energy balance, metabolism, hormones,
790 neuropeptides) and extrinsic influences (e.g., sensory stimuli from and interactions with
791 reproductive females and pups). Elucidation of the factors that modulate specific
792 components of neuroplasticity at different stages of reproduction, as well as how these
793 factors interact with one another, is a key challenge for our understanding of the
794 paternal brain.
795
796 **3.2. Potential functions of neuroplasticity in fathers**
797 In males, as in females, the functional significance of parenthood-induced neural
798 plasticity is largely unknown. In mothers, plasticity within brain regions closely linked to
799 parental care, such as changes in steroid and neuropeptide signaling pathways within
800 the MPOA and BNST, are likely to contribute directly to the expression of maternal
801 behavior. In contrast, the functional significance of plasticity in other brain regions, such

802 as the hippocampus and prefrontal cortex, is less clear but is thought to mediate
803 affective and cognitive changes in mothers (Galea et al., 2013; Lambert, 2012; Leuner
804 et al., 2010).

805 Only a single study has experimentally evaluated the function of neural plasticity
806 in fathers. In new *Mus* fathers, newly generated neurons in the olfactory bulbs respond
807 preferentially to odors of the male's adult offspring and appear to mediate reduced
808 aggression toward them (Mak & Weiss, 2010). Thus, neurogenesis in house mouse
809 fathers may be important for long-term recognition and preferential treatment of
810 offspring.

811 Paternal behavior, too, might be affected by plasticity in neuroendocrine and
812 neuropeptide signaling pathways, especially within brain regions implicated in the
813 control of paternal care. Most notably, in biparental rodents the MPOA is highly
814 responsive to stimuli from pups, as evidenced by studies of immediate early gene
815 expression (see Table 1), and is essential for paternal behavior, as determined by
816 studies using lesioning and optogenetics (Kirkpatrick et al., 1994a; Wu et al., 2014). As
817 described above, fatherhood alters several neuroendocrine signaling systems within the
818 MPOA in biparental rodents, including, in some but not all studies, changes in
819 expression of oxytocin, oxytocin receptors, androgen receptors, ERα, and aromatase
820 (see Table 1, Fig. 1); thus, a reasonable hypothesis is that fatherhood-induced changes
821 in signaling pathways within the MPOA mediate, at least in part, changes in males'
822 behavioral responses to infants, possibly by affecting the valence of pup-related stimuli
823 (Numan, 2020). A similar argument can be made for several other brain regions,
824 especially the medial amygdala: in male biparental rodents, this region, like the MPOA,
825 shows altered Fos expression in response to pups (Table 1); lesioning or genetic
826 manipulation of the medial amygdala alters paternal behavior (Cushing et al., 2008;
827 Kirkpatrick et al., 1994a); and fathers show differential expression of oxytocin receptor
828 mRNA, androgen receptor immunoreactivity, and ERα immunoreactivity, compared to
829 non-fathers (Table 1).

830 In several uniparental species (e.g., rat, house mouse, sheep), pregnant and/or
831 lactating females show striking reductions in anxiety-like behavior and in behavioral,
832 neural, and hormonal responses to acute stressors (reviewed in Macbeth & Luine,

2010). Studies of males in biparental species, in contrast, have provided only limited evidence that fatherhood modulates affective behavior and stress reactivity. In California mice, new fathers and non-fathers do not differ in basal corticosterone concentrations or in neuropeptide (corticotropin-releasing hormone, vasopressin) or endocrine (corticosterone, testosterone) responses to acute or chronic stress (Chauke et al., 2011, 2012; de Jong et al., 2013; Harris & Saltzman, 2013). Moreover, in a variety of test paradigms, fathers and non-fathers show few differences in anxiety-like behavior and behavioral responses to stress (Bardi et al., 2011; Chauke et al., 2011, 2012; Glasper et al., 2011; Perea-Rodriguez et al., 2018; Zhao et al., 2017, 2018). Prairie vole fathers exhibit enhanced anxiety-like and depression-like behavior, compared to virgins, at 6 days postpartum (Lieberwirth et al., 2013), but reduced anxiety-like behavior 6 weeks postpartum (Kenkel et al., 2014). Clearly, effects of parenthood on affective behavior and stress reactivity are less consistent and less robust in fathers than in mothers, and whether these effects of fatherhood are mediated by plasticity in the paternal brain is not known.

Cognitive function in females, like affective behavior and stress reactivity, is commonly altered by motherhood (reviewed in Lambert, 2012; Leuner et al., 2010; Macbeth & Luine, 2009). For example, mothers often perform better in tests of cognitive flexibility, short-term memory, and spatial memory than virgins, differences that are thought to be mediated by plasticity in the hippocampus and prefrontal cortex. Very few studies have evaluated effects of fatherhood on cognition in males. California mouse fathers perform better than virgins in a dry-land maze (Franssen et al., 2011), but no differently in an object-recognition test (Glasper et al., 2011). Whether fatherhood-induced plasticity in the hippocampus or other brain regions contributes to these cognitive differences is unknown.

3.3. Interspecific differences in neuroplasticity in fathers

Numerous measures of neural plasticity appear to differ among species, as described above (Table 1, Fig. 1). In some cases, these disparities might reflect methodological differences among studies, such as in housing or reproductive conditions of male subjects (e.g., new vs. experienced fathers, virgin males housed with other males vs.

males housed with ovariectomized females), timing of data collection relative to the birth of offspring (e.g., early vs. late postpartum period), or techniques (e.g., immunohistochemistry vs. autoradiography vs. in situ hybridization). Nonetheless, given that paternal care has evolved convergently in multiple taxa (Kleiman & Malcolm, 1981; Stockley & Hobson, 2016), plasticity occurring during the transition into fatherhood likely differs among species in meaningful ways. Thus, another interesting future direction is to more systematically characterize interspecific differences in fatherhood-induced neuroplasticity and to elucidate the sources and significance of these differences.

At the mechanistic level, studies could address the extent to which interspecific differences in neural plasticity are associated with differences in neuroendocrine and neuropeptide changes in fathers. At the functional level, it is possible that interspecific differences in type, sites, and degree of neural plasticity correspond to differences in the extent and nature of paternal care provided, or in the degree to which the onset of fatherhood necessitates changes in males' behavior. For example, virgin male prairie voles commonly provide alloparental care for their younger siblings and tend to exhibit nurturant responses when tested with unrelated pups, showing few, if any, differences from fathers in their pup-directed behavior (Kenkel et al., 2014; Lonstein & De Vries, 2000). In mandarin voles, California mice, and Mongolian gerbils, on the other hand, virgin adult males are more reluctant to interact with pups than are fathers and often avoid or attack pups, although some individuals behave paternally (De Jong et al., 2009; Gubernick & Nelson, 1989; Martínez et al., 2019; Wang et al., 2015; Yuan et al., 2019). Virgin adult male house mice, in contrast, are usually aggressive toward pups and exhibit little or no nurturant behavior, whereas fathers in some laboratory strains of *Mus* engage in high levels of paternal care, especially when housed with their mate or exposed to cues from the mate (Gandelman et al., 1970; Mayer et al., 2019; McCarthy & vom Saal, 1986; Nakahara et al., 2016). Consequently, the onset of paternal care might require more pronounced behavioral adjustments in house mice than in prairie voles, with intermediate levels of adjustments in mandarin voles, California mice, and Mongolian gerbils, and therefore might be associated with different patterns of neural plasticity.

As another example, increased neurogenesis in the hippocampus and subventricular zone of house mouse fathers mediates recognition of adult offspring (Mak & Weiss, 2010), whereas California mouse fathers do not consistently demonstrate increased neurogenesis (Glasper et al., 2011). Glasper et al. (2011) speculated that this difference between species might reflect differences in mating and social systems: inbreeding might pose more of a threat in promiscuous species, such as house mice, than in monogamous species, such as California mice and prairie voles. Consequently, the ability to discriminate between kin and non-kin, as well as the underlying neural mechanisms, might undergo more intensive natural selection in promiscuous species.

Additionally or alternatively, interspecific differences in fatherhood-induced neural plasticity might result from species differences in neural plasticity in mothers. Our current understanding of the parental brain indicates that the neural substrates of parental care overlap substantially between males and females (Numan, 2020). Because maternal care in mammals evolved before paternal care, this overlap suggests that the neural substrates of paternal behavior and its corresponding plasticity evolved from those underlying maternal behavior. Thus, the neural mechanisms of paternal care in each species evolved from, and may have been constrained by, the species-specific template present in conspecific females. To date, no biparental species are available in which parenthood-induced neuroplasticity has been elucidated in both sexes; however, by further identifying interspecific differences in neural plasticity in fathers and then examining potential corresponding differences in mothers, we may gain new insights into both proximate and ultimate influences on neuroplasticity of the paternal brain.

Another possible explanation for some interspecific differences is that females in some species routinely undergo postpartum estrus and conception, leading to concurrent pregnancy and lactation. Among socially monogamous species, this overlap in female reproductive state, as well as the close correspondence between birth of offspring and the mate's postpartum estrus, could potentially affect the degree or timing of behavioral and neural plasticity occurring in fathers. To our knowledge, systematic analyses characterizing phylogenetic effects on neural plasticity and possible associations with species' natural histories have not been conducted in mammals.

However, comparative studies of poison frogs (family Dendrobatidae*)* have elucidated links between ecological measures, plasticity in parental behavior, and neural activation during parental care (O'Connell, 2020).

3.4 Conclusions

Mammalian mothers must undergo profound shifts in physiology, morphology, and behavior in order to produce and successfully rear their offspring. Perhaps it is not surprising, then, that the onset of motherhood is also associated with changes in the brain, activated by both neuroendocrine alterations and experience with infants. Although the functions of these neural changes are not well understood, they seem likely to enhance mothers' ability to care for offspring by modifying cognitive, affective, sensory, and motivational processes.

Fathers, in contrast, need not undergo pronounced physiological and morphological changes in order to become parents, even in species in which paternal care is necessary for survival and normal development of offspring. Nonetheless, fathers undergo numerous neuroendocrine changes similar to those in mothers, as well as changes in neural structure and function. The physiological, environmental, and neuroendocrine mediators of neuroplasticity in fathers have received little attention thus far but likely differ from those in mothers in meaningful ways: because endocrine changes in fathers are much less pronounced than those in mothers, experiential and environmental influences, such as copulation, cues from the pregnant or parturient mate, and stimuli from offspring, may play larger roles in males than in females. Moreover, the functions of neuroplasticity in fathers are mostly unknown; however, given the similarity of maternal and paternal behavior in many biparental species, at least some of the neural changes in fathers likely have functions similar to those in mothers. Further investigations into the extent, mechanisms, and functions of neuroplasticity in fathers, across a range of species, will provide new insights into the demands of mammalian fatherhood, the effects of parenthood on fathers, and, ultimately, the evolution of paternal care.

CONFLICT OF INTEREST

The authors have no conflicts of interests to disclose.

DATA AVAILABILITY STATEMENT

Not applicable.

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Figure Legend

Fig. 1. Summary of effects of fatherhood on the brain in four well-studied rodent species: facultatively biparental house mice (A), and obligately biparental California mice (B), prairie voles (C), and mandarin voles (D). See Table 1 for fuller descriptions and references. AH – anterior hypothalamus, AOB – accessory olfactory bulbs, AMY – amygdala, BNST – bed nucleus of stria terminalis, D1R – dopamine 1-type receptor, D2R – dopamine 2-type receptor, DG – dentate gyrus, ER – estrogen receptor, ir – immunoreactivity, LHb – lateral habenular nucleus, MOB – main olfactory bulbs, DRN – dorsal raphe nucleus, MPOA – medial preoptic area, NTS – nucleus of solitary tract, OT – oxytocin, PRL-R – prolactin receptor, PVN – paraventricular nucleus of hypothalamus, SNc – substantia nigra pars compacta, SON – supraoptic nucleus, SVZ – subventricular zone, TMX – tamoxifen, TuJ1 – neuron-specific class III beta-tubulin, V1aR – vasopressin 1a receptor, VMH – ventromedial nucleus of hypothalamus.

Table 1. Summary of reported effects of fatherhood on the brain in nonhuman mammals. Effects indicate findings in fathers as compared to non-fathers of various types (virgins, males paired with an ovariectomized or tubally ligated female, etc.). Negative findings are not included. All species listed are biparental except Siberian hamsters, which are uniparental, and house mice, deer mice, and meadow voles, which are facultatively biparental. D1R - dopamine 1-type receptor, D2R - dopamine 2-type receptor, ER - estrogen receptor, V1aR - vasopressin 1a receptor, BrdU - bromodeoxyuridine, ir - immunoreactivity, BNST – bed nucleus of the stria terminalis.

Brain Region	Method	Effect of Fatherhood	Species	References
Forebrain				
Hippocampus	Immunohistochemistry	Decreased neurogenesis	California mouse	Glasper et al., 2011
Hippocampus	Immunohistochemistry & Western blot	Decreased neurodegeneration and astrogliosis in response to kainic acid injection; downregulation of monomeric prolactin receptor; upregulation of dimeric isoform of prolactin receptor	House mouse	Anagnostou & Morales, 2019
Hippocampus	Immunohistochemistry	Increased Fos in response to dry-land maze	California mouse	Franssen et al., 2011
Hippocampus	Immunohistochemistry	Increased survival of newborn cells in the dentate gyrus; increased number of TuJ1-positive cells	California mouse	Hyer et al., 2016
Hippocampus	Quantitative PCR	Increased ER β; reduced V1aR & PRL-R	California mouse	Hyer et al., 2017
Hippocampus	TMX treatment & immunohistochemistry	Increased inhibition of survival of adult born neurons by TMX	California mouse	Hyer et al., 2017

Hippocampus	Immunohistochemistry	Decreased cell survival in dentate gyrus	Prairie vole	Lieberwirth et al., 2013
Hippocampus	Immunohistochemistry	Increased neurogenesis	House mouse	Mak & Weiss, 2010
Hippocampus	Golgi staining	Increased spine density of CA1 basal dendrites; decreased length and number of branch points in apical dendritic trees	California mouse	Glasper et al., 2016; Hyer & Glasper, 2017
Hippocampus	Golgi staining	Decreased spine density on apical dendrites in CA3	California mouse	Hyer & Glasper, 2017
Hippocampus	Golgi staining	Increased spine density in dentate gyrus	California mouse	Glasper et al., 2016
Prefrontal Cortex	Golgi staining	Increased spine density on layer II/II pyramidal neurons	Common marmoset	Kozorovitsky, 2006
Prefrontal Cortex	Golgi staining	Increased spine density, dendritic length, and branch points on layer II/II pyramidal neurons	Mandarin vole	Wang et al., 2018a
Lateral habenular nucleus	Immunohistochemistry	Decreased vasopressin-ir	Prairie vole	Bamshad et al., 1993
Lateral habenular nucleus	Immunohistochemistry	Increased vasopressin-ir	Meadow vole	Bamshad et al., 1993
Lateral septum	Immunohistochemistry	Decreased vasopressin-ir	Prairie vole	Bamshad et al., 1993
Lateral septum	Autoradiography	Decreased vasopressin binding	Meadow vole	Parker et al., 2001
Lateral septum	Autoradiography	Increased oxytocin binding	Meadow vole	Parker et al., 2001
Amygdala (lateral and central)	Autoradiography	Increased oxytocin binding	Meadow vole	Parker et al., 2001
Amygdala	Immunohistochemistry	Decreased cell survival	Prairie vole	Lieberwirth et al., 2013
Vomeronasal organ	Immunohistochemistry	Decreased pup-induced Fos	Mouse	Tachikawa at al., 2013

Vomeronasal organ	In situ hybridization	Decreased pup-induced activity of Olfr692-expressing neurons	House mouse	Nakahara et al., 2016
Choroid plexus	Reverse transcriptase-PCR	Increased prolactin receptor mRNA	Campbell's dwarf hamster	Ma et al., 2005
Central amygdala	Immunohistochemistry	Increased ERα-ir	Mandarin vole	Song et al., 2010
Subventricular zone	Immunohistochemistry	Increased neurogenesis	House mouse	Mak & Weiss, 2010
Olfactory bulb	Immunohistochemistry	Increased number of new neurons that respond to offspring odor	House mouse	Mak & Weiss, 2010
Olfactory bulb	Immunohistochemistry	Increased androgen receptor-ir	Mongolian gerbil	Martínez et al., 2019
Accessory olfactory bulb	Immunohistochemistry	Decreased pup-induced Fos	House mouse	Tachikawa at al., 2013
Anterior olfactory nucleus	Autoradiography	Increased vasopressin binding	Meadow vole	Parker et al., 2001
Anterior olfactory nucleus	Autoradiography	Increased oxytocin binding	Meadow vole	Parker et al., 2001
Posterior medial amygdala	Immunohistochemistry	Decreased pup-induced Fos	House mouse	Tachikawa at al., 2013
Medio-posterior division of the BNST	Immunohistochemistry	Decreased pup-induced Fos	House mouse	Tachikawa at al., 2013
Dorsal subnucleus of the posterior medial amygdala	Immunohistochemistry	Increased pup-induced Fos	House mouse	Tachikawa at al., 2013
Medial/intermediate subnuclei of the medio-posterior division of the BNST	Immunohistochemistry	Increased pup-induced Fos	House mouse	Tachikawa at al., 2013
Prefrontal cortex	Immunohistochemistry	Increased V1aR	Common	Kozorovitskiy et al.,

			marmoset	2006
Nucleus accumbens	Real-time quantitative PCR	Increased oxytocin receptor mRNA; increased D1R & D2R receptor mRNA	Mandarin vole	Wang et al., 2015
Medial amygdala	Real-time quantitative PCR	Increased oxytocin receptor mRNA; decreased D1R & D2R receptor mRNA	Mandarin vole	Wang et al., 2015
Medial amygdala	Immunohistochemistry	Increased androgen receptor-ir	Mongolian gerbil	Martínez et al., 2019
BNST	Immunohistochemistry	Increased pup-induced Fos	California mouse	De Jong et al., 2009
BNST	Immunohistochemistry	Decreased oxytocin-ir	Prairie vole	Kenkel et al., 2014
BNST	Immunohistochemistry	Decreased ERα-ir	Mandarin vole	Song et al., 2010
BNST	Autoradiography	Increased oxytocin binding	Meadow vole	Parker et al., 2001
BNST	Real-time quantitative PCR	Decreased oxytocin receptor mRNA	California mouse	Perea-Rodriguez et al., 2015
BNST	Real-time quantitative PCR	Decreased V1aR mRNA	California mouse	Perea-Rodriguez et al., 2015
BNST	Real-time quantitative PCR	Decreased progesterone receptor mRNA	California mouse	Perea-Rodriguez et al., 2015
Zona incerta	Immunohistochemistry	Increased tyrosine hydroxylase-ir	Mandarin vole	Wang et al., 2015
Medial preoptic area	RNA sequencing and NanoString	Changes in mRNA	Prairie vole	Seelke, 2018
Medial preoptic area	Immunohistochemistry	Increased pup-induced Fos	House mouse	Wu et al., 2014
Medial preoptic area	Immunohistochemistry	Increased Fos in response to pup in wire-mesh ball	California mouse	De Jong et al., 2009
Medial preoptic area	Immunohistochemistry	Increased Fos in response to pup in wire-mesh ball	California mouse	Lambert at al., 2013
Medial preoptic area	Immunohistochemistry	Increased Fos in response to pup in wire-mesh ball	Deer mouse	Lambert at al., 2013
Medial preoptic area	Immunohistochemistry	Increased pup-induced Fos	House mouse	Tachikawa at al.,

				2013
Medial preoptic area	Immunohistochemistry	Decreased ERα-ir	Mandarin vole	Song et al., 2010
Medial preoptic area	Immunohistochemistry	Increased ERα-ir	Campbell's dwarf hamster	Romero-Morales et al., 2020
Medial preoptic area	Titrated water essay	Increased aromatase activity	California mouse	Trainor et al., 2003
Medial preoptic area	Immunohistochemistry	Increased tyrosine hydroxylase-ir	Mandarin vole	Wang et al., 2015
Medial preoptic area	Immunohistochemistry	Increased oxytocin-ir	Mandarin vole	Wang et al., 2015
Medial preoptic area	Real-time quantitative PCR & western blot	Increased oxytocin receptor mRNA and protein	Mandarin vole	Yuan et al., 2019
Medial preoptic area	Immunohistochemistry	Increased androgen receptor-ir	Mongolian gerbil	Martínez et al., 2019
Ventral medial hypothalamic nucleus	Immunohistochemistry	Decreased cell survival	Prairie vole	Lieberwirth et al., 2013
Ventral medial hypothalamic nucleus	Immunohistochemistry	Increased ERα-ir	Mandarin vole	Song et al., 2010
Ventral medial hypothalamic nucleus	Immunohistochemistry	Increased tyrosine hydroxylase-ir	Mandarin vole	Wang et al., 2015
Paraventricular nucleus	Immunohistochemistry	Increased oxytocin-ir	Mandarin vole	Song et al., 2010
Paraventricular nucleus	Immunohistochemistry	Increased oxytocin-ir	Mandarin vole	Wang et al., 2015
Paraventricular nucleus	In situ hybridization	Increased vasopressin mRNA	Prairie vole	Wang et al., 2000
Supraoptic nucleus	Immunohistochemistry	Increased oxytocin-ir	Mandarin vole	Song et al., 2010
Supraoptic nucleus	Immunohistochemistry	Increased oxytocin-ir	Mandarin vole	Wang et al., 2015
Supraoptic nucleus	In situ hybridization	Increased vasopressin mRNA	Prairie vole	Wang et al., 2000
Hypothalamus	HPLC & enzyme-linked immunosorbent assay	Decreased dopamine; increased oxytocin & prolactin	Common marmoset	Woller et al., 2012

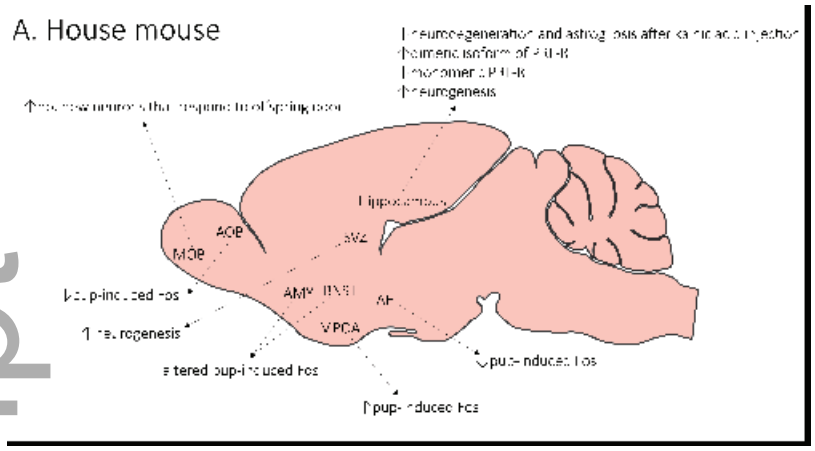
	assay of hypothalamic explants			
Lateral Hypothalamus	Immunohistochemistry	Decreased oxytocin-ir	Mandarin vole	Wang et al., 2015
Paraventricular nucleus	Immunohistochemistry	Increased oxytocin-ir	Prairie vole	Kenkel et al., 2014
Anterior hypothalamic area	Immunohistochemistry	Decreased pup-induced Fos	House mouse	Tachikawa at al., 2013
Midbrain				
Ventral tegmental area	Immunohistochemistry	Increased tyrosine hydroxylase-ir	Mandarin vole	Wang et al., 2015
Substantia nigra pars compacta	Immunohistochemistry	Increased tyrosine hydroxylase-ir	Mandarin vole	Wang et al., 2015
Hindbrain				
Caudal dorsal raphe nucleus	Immunohistochemistry	Increased pup-induced Fos	California mouse	De Jong et al., 2009
Nucleus ambiguus	Immunohistochemistry	Increased oxytocin-ir	Prairie vole	Kenkel et al., 2014
Nucleus tractus solitarius	Immunohistochemistry	Increased oxytocin-ir	Prairie vole	Kenkel et al., 2014

Table 2. Summary of effects of fatherhood on the brain in humans. MRI = magnetic resonance imaging, fMRI - functional magnetic resonance imaging.

Brain Region	Method	Effect of Fatherhood	References
Left caudal anterior cingulate cortex	MRI	Decreased gray matter	Orchard et al., 2020
Right temporal pole	MRI	Increased gray matter	Orchard et al., 2020
Hypothalamus	MRI	Increased gray matter	Kim et al., 2014
Amygdala	MRI	Increased gray matter	Kim et al., 2014
Striatum	MRI	Increased gray matter	Kim et al., 2014
Subgenual cortex	MRI	Increased gray matter	Kim et al., 2014
Superior temporal gyrus	MRI	Increased gray matter	Kim et al., 2014
Lateral prefrontal cortex	MRI	Increased gray matter	Kim et al., 2014
Orbitofrontal cortex	MRI	Decreased gray matter	Kim et al., 2014
Posterior cingulate cortex	MRI	Decreased gray matter	Kim et al., 2014
Insula	MRI	Decreased gray matter	Kim et al., 2014

Fusiform gyrus	MRI	Decreased gray matter	Kim et al., 2014
Caudal middle frontal gyrus	fMRI	Increased neural activity in response to child picture stimuli	Mascaro et al., 2014
Temporo-parietal junction	fMRI	Increased neural activity in response to child picture stimuli	Mascaro et al., 2014
Medial orbitofrontal cortex/ventromedial prefrontal cortex	fMRI	Increased neural activity in response to child picture stimuli	Mascaro et al., 2014
Precuneus	fMRI	Increased neural activity in response to child picture stimuli	Mascaro et al., 2014
Mid-cingulate cortex	fMRI	Increased neural activity in response to auditory child crying stimuli	Seifritz et al., 2003
Ventral prefrontal cortex	fMRI	Increased neural activity in response to auditory child crying stimuli	Seifritz et al., 2003
Temporo-parietal junction	fMRI	Increased neural activity in response to auditory child crying stimuli	Seifritz et al., 2003
Insula	fMRI	Increased neural activity in response to auditory child crying stimuli	Seifritz et al., 2003
Middle frontal gyrus	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Insula	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Pre-central gyrus	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Anterior/posterior cingulate cortex	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019

Parietal operculum	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Lingual gyrus	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Occipital pole	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Lateral occipital cortex	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Juxtapositional lobule cortex	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Superior parietal lobule	fMRI	Increased neural activity in response to video of child in threatening scenario stimuli	van ‘t Veer et al., 2019
Superior frontal gyrus	fMRI	Decreased difference in neural activity in response to video of a related or unrelated child in threatening scenario	van ‘t Veer et al., 2019



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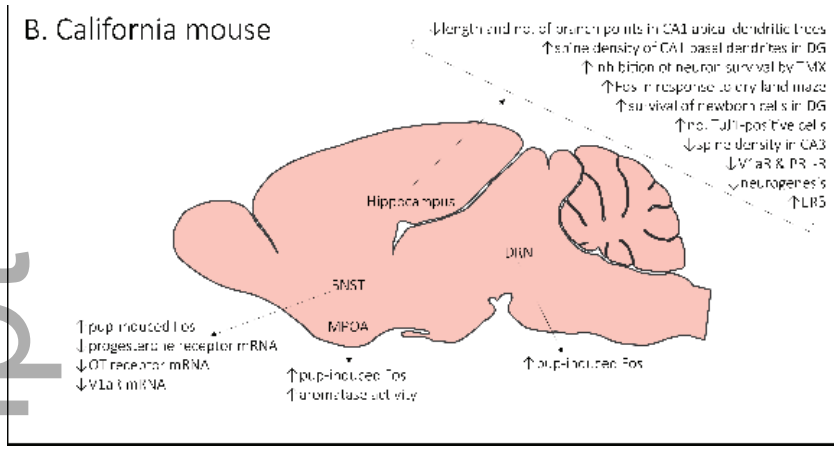

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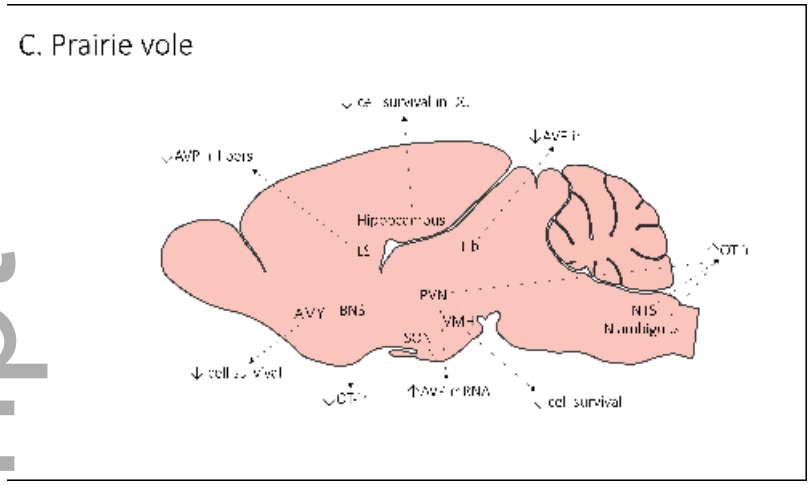

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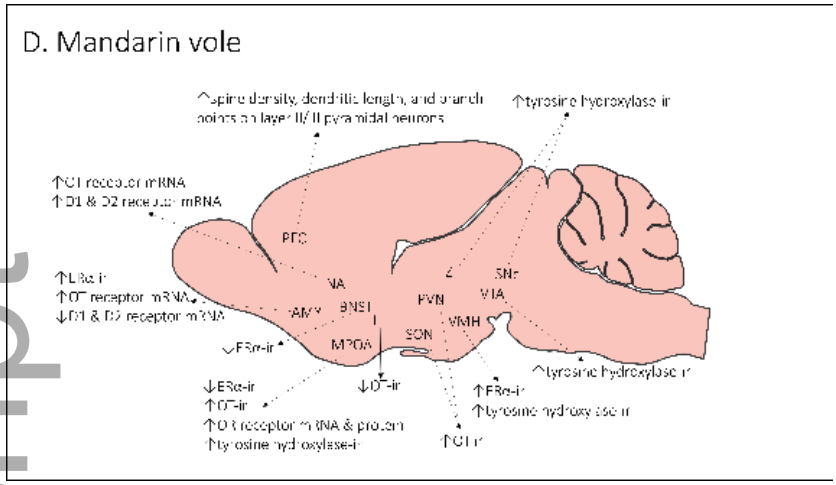

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