The neural mechanisms and consequences of paternal caregiving

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Abstract | In recent decades, human sociocultural changes have increased the numbers of fathers that are involved in direct caregiving in Western societies. This trend has led to a resurgence of interest in understanding the mechanisms and effects of paternal care. Across the animal kingdom, paternal caregiving has been found to be a highly malleable phenomenon, presenting with great variability among and within species. The emergence of paternal behaviour in a male animal has been shown to be accompanied by substantial neural plasticity and to be shaped by previous and current caregiving experiences, maternal and infant stimuli and ecological conditions. Recent research has allowed us to gain a better understanding of the neural basis of mammalian paternal care, the genomic and circuit-level mechanisms underlying paternal behaviour and the ways in which the subcortical structures that support maternal caregiving have evolved into a global network of parental care. In addition, the behavioural, neural and molecular consequences of paternal caregiving for offspring are becoming increasingly apparent. Future cross-species research on the effects of absence of the father and the transmission of paternal influences across generations may allow research on the neuroscience of fatherhood to impact society at large in a number of important ways.

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Over the past decade, important strides have been made in understanding the neurobiology of mammalian paternal care. These include experiments that have established many of the molecular, cellular, endocrine and neural adaptations that accompany the emergence of paternal care as well as the unique benefits to offspring of paternal caregiving and the molecular and behavioural mechanisms by which a father's history impacts his offspring[1–3]. This field of research has matured to encompass a variety of methods that have been applied to both humans and animal models. These include methods examining biparental species, measuring the brain neurochemistry of offspring reared with or without the presence of fathers, genetic and optogenetic targeting of neural circuits to alter paternal behaviour in animals, quantitative genetics in comparative studies of paternal behaviour, neuroimaging studies of human fathers and the quantification of DNA methylation, histone modification and non-coding RNA (giving insights into the plasticity and stability of gene regulation) in the brain and reproductive systems of fathers and offspring[4–8]. In addition, research is beginning to focus on the importance of the psychobiological role of fathers and of paternal behaviour by investigating how the molecular information encoded in a father's sperm integrates with the effects of direct or indirect paternal caregiving to shape offspring brain and behaviour[9].

At the same time that these advances in scientific understanding have taken place, the involvement of human fathers in the care of their children has become a public issue: studies on fatherhood have been publicized in the media[10] and have reshaped custody laws in North America, Europe and Australia (reviewed elsewhere[11]). Although the mother–infant bond has been celebrated throughout human history in literature and the arts, the new so-called involved dad — defined as a father who partakes in the full range of childrearing activities and considers fatherhood an important part of his identity[12] — has presented a fresh image that has reformulated theories on the exclusivity of maternal care[13,14]. However, a comprehensive understanding of the father's unique contribution to child development is lacking.

Research has shown that mammalian paternal care is both phenotypically and biologically variable[1,15–18]; the neural adaptations that take place in new fathers are less canalized, uniform and hormone-dependent than those that take place in new mothers. Furthermore, these changes are shaped, to a great extent, by active caregiving, exposure to the pregnant or lactating female, the presence or absence of specific infant stimuli and, in humans, sociocultural practices and belief systems[5,15,19,20]. Some of the biological characteristics of mammals that have arisen during evolution, including internal fertilization, internal gestation and lactation, have meant

Biparental species
Species in which biological fathers participate in direct caregiving (such as carrying or grooming) and indirect caregiving (such as guarding or provisioning) of their offspring. Biparental care is observed in only 3–5% of mammalian species, and these species are typically socially monogamous.

Optogenetic targeting
The selective activation of neurons that have been genetically altered to express light-sensitive opsins.

that the young are exposed to the mother's biological signals via their intimate contact with the maternal body. The impact of this influence on the developing brain is known to be substantial[21,22]. By contrast, evolution has led to a wide variety of ways in which the young may be exposed to the father's biological inputs, ranging from exposure to the sperm only to the effects of primary caregiving by the father[18,23]. Such immense variability in a father's role renders the neurobiology of paternal behaviour both similar and distinct from that of maternal care, highlights the context-dependent plasticity involved in the transition to becoming a father and establishes the father–offspring relationship as a unique model to study parental effects on offspring development.

In this Review, we attempt to provide a cross-species perspective on paternal caregiving (BOX 1). We integrate human and animal research, advances in neuroscience and molecular biology, and developmental and social psychology studies to present the neurobiology of paternal care from diverse angles. To achieve this, we address four broad issues: the brain circuits and hormonal systems implicated in mammalian paternal caregiving (also addressing the extent of sexual dimorphism, that is, whether maternal and paternal behaviours utilize the same neural circuits and hormonal systems and have evolved along similar lines), the impact of the father's presence and caregiving on brain development in the offspring (and the associated implications of a father's absence for brain development), the mechanisms of the

Box 1 | **Paternal behaviour across mammalian species**

Rodents
Direct paternal care has primarily been studied in the laboratory in biparental rodent species, including the prairie vole (*Microtus ochrogaster*), mandarin vole (*Lasiopodomys mandarinus*), degu (*Octodon degus*), California mouse (*Peromyscus californicus*), Campbell's dwarf hamster (*Phodopus campbelli*) and Mongolian gerbil (*Meriones unguiculatus*).

Sensitization. Parental behaviour is induced in the laboratory through prolonged contact with infant stimuli. Increased sensitivity is indicated by shorter latencies to engage in parental behaviour when an infant is placed in close proximity.

Pup retrieval. This laboratory test examines the degree of motivation to approach and retrieve pups that have been placed outside of the nest. Short latencies to retrieve pups are indicative of increased parental behaviour.

Licking and/or grooming. A primary form of tactile stimulation of the infant by the parent that is necessary for physiological regulation and development.

Huddling. Observed throughout postnatal development and defined by close physical contact between parent and offspring. This behaviour facilitates thermoregulation of offspring and serves as a form of social affiliation.

Primates
Direct paternal care is rare in primates and has been studied mainly in biparental species, including several lemur species, New World marmosets, tamarins, titi monkeys and owl monkeys.

Carrying. The most studied paternal behaviour across biparental primate species. The time of onset after birth, the amount and the hormonal correlates of a father carrying its offspring differ within and among species. Carrying reduces maternal energy expenditure and decreases inter-birth intervals[75].

Feeding. In marmosets, tamarins, titi monkeys and owl monkeys, fathers carry food to the young, share food or engage in food transfer (in which the father allows the infant to take the food he holds), which provides important nutrient supplements at the transition out of weaning[236].

Grooming and licking. Marmoset, tamarin and titi monkey fathers groom their offspring by manipulating the coat with teeth or hands and exhibit anogenital licking[155,237,238].

Teaching. A father engages in a variety of physical, exploratory or social behaviour while its offspring observes and/or participates. Such behaviour facilitates the formation of the father–offspring bond and socializes offspring to life in social groups[239].

Playing. In titi monkeys, fathers are solely responsible for playing: this includes grappling, chasing, pushing or pursuing in a non-aggressive, non-food context.

Paternal responsiveness. Paternal behaviour that is responsive to an infant's distress calls, physical needs or social communication. Paternal responsiveness increases offspring survival and fitness[240].

Humans
Direct paternal care is observed in most human societies with great variability both within and across cultures[14]. Paternal involvement has long-term consequences for human children, enhancing their survival, mental health, cognitive competencies and social–emotional development[241]. Although fathers tend to engage in behaviours that are distinct from those of mothers, the long-term effects of paternal care are similar to those of maternal care and are related to warmth, reciprocity and nurturance[12,242]. Paternal care also enhances the mother–father partnership and emotional bond[243].

Stimulatory contact. A father's play with an infant is typically more stimulatory than that of the mother, involving physical manipulation of limbs, throwing the infant in the air or moving the infant in space[244]. Paternal stimulatory touch with the infant is associated with increased paternal plasma and salivary oxytocin and vasopressin levels[111].

'Rough-and-tumble' play. Fathers typically engage in physical exchange with their preschoolers, children and adolescents that often includes rough handling[245]. Such highly arousing physical play involves close physical contact and contributes to the regulation of aggression in the infant[246].

Exploration and/or attention to the environment. A father's interaction with infants, children and adolescents is often directed to elements in the environment and encourages physical and mental exploration[247]. Such exploration-enhancing behaviour is associated with increases in the father's plasma oxytocin, prolactin and vasopressin levels[248,249].

Skill learning. Fathers typically teach children and adolescents culture-specific (and subculture-specific) survival skills and social competencies[33].

Enhancing and/or regulating high positive arousal. Fathers often establish moments of high positive arousal (including laughter and motor excitement) with their infants and young children and teach them to tolerate and regulate such moments[226].

Socialization. A father's socialization style is often stricter than that of a mother, and fathers often express greater discipline than warmth[250].

Substantial cultural differences exist in the amount and range of direct caregiving and father–child contact, the age of onset of paternal care, the degree of accepted paternal control, the mode of paternal socialization and the extent to which special times for play versus guided participation in cultural activities and skill-learning play are set[251,252].

Phenotypic plasticity
The capacity to dynamically alter the phenotypic characteristics (including their patterns of behaviour) of an individual in response to environmental cues.

Allomothers
Adults (including juveniles and fathers), other than the biological mothers, that care for infants. Allomothering is widespread among primates, including humans, and is critical for infants to survive and thrive.

cross-generational transfer of paternal effects on offspring and the long-term implications of human paternal care for the child's mental health and social adaptation. Overall, we aim to investigate the parent–infant interface, the context in which Lorenz[24] and Darwin[25] initially suggested that structural and functional adaptations take place in the brain and behavioural repertoire, while keeping in mind the great diversity in the expression of paternal behaviour and the current social changes in family compositions and fathers' roles[26].

Paternal care across species

Although maternal care and its associated neurobiology are highly conserved across mammalian species[1,2,8], the nature of paternal care both within a species and among different species exhibits phenotypic plasticity: it is shaped by ecological provisions, environmental threats, neural constraints and niche-specific and species-specific social interactions[16,17,27–29]. Although paternal care is common among fish, birds and the insect species that engage in any form of parental caregiving[30–32], only 3–5% of mammalian species are biparental[33]. In these species, fathers engage in direct caregiving (such as carrying or grooming) and indirect caregiving[34] (such as provisioning, guarding and defence; BOX 1).

The rarity of paternal caregiving in mammals has been suggested to be driven by multiple factors. These include paternity uncertainty (due to internal fertilization), sexual selection (the balance of effort put into mating versus parenting), the operational sex ratio (the ratio between the numbers of sexually active males and females in a given territory at a given time) and male–male competition (which leads to a group structure characterized by social dominance that is common among primates; in this structure, dominant males sire more children and engage in less caregiving)[28,30,33,35,36]. The evolution of internal fertilization and internal gestation in mammals, together with lengthy inter-birth intervals, reduced paternity certainty, increased the operational sex ratio and decreased male motivation for paternal investment, particularly because the costs of mating efforts are high. With lactation becoming the central feeding mechanism of altricial young, the increase in maternal investment was sufficient to support infant growth in most species[37,38].

As parental investment is highly costly, the question is why paternal care evolved at all in those species where it is observed[28,30,33,36]. Comparative studies indicate that paternal care is associated with higher paternity certainty and tends to occur when it improves offspring survival and quality and when the investment cost (such as the loss of mating opportunities) is lower than the benefits to offspring[30,33,39–41]. Nevertheless, there are notable variations in paternal caregiving among species, within a species and even in the same individuals between breeding seasons, pointing to substantial social and ecological influences on the expression of paternal caregiving[29,38].

Direct paternal care is found mainly but not exclusively in socially monogamous species[42], in which paternal caregiving occurs in the context of maternal care[43]. Paternal caregiving is observed in 59% of socially monogamous species where it has been shown to be beneficial, being associated with increased offspring survival, a larger litter size and faster growth of offspring, as compared with non-socially monogamous species[37,44–49]. Because biparental caregiving is known to have evolved in several separate lineages, the ecological conditions leading to its emergence are debated, as are the pressures that led to human cooperative breeding (which is not found in most great apes[50]). One hypothesis is that once paternal care evolved in the context of monogamy, it stabilized monogamous mating systems and fostered the emergence of complex social behaviours[49,51]. Two studies provide alternative viewpoints on the evolutionary pressures leading to social monogamy and paternal caregiving. The first, combining data from 230 primate species, contends that monogamy evolved against the background of male infanticide. The lengthy period of dependency rendered primate infants vulnerable to male infanticide, and biparental caregiving both shortened lactation periods, as fathers participated in feeding the young, and reduced infanticide[51]. The second, pooling data from all non-human mammalian species for which information on social structure was available, suggests that social monogamy evolved from the ancestral condition of solitary individuals on the background of female–female intolerance and female dispersion, which increased males' motivation to defend their access to females and led to the construction of male–female monogamous units[42].

Among primates, the expression of paternal care shows great variability. In some species, fathers engage in little direct care but remain in close proximity to protect mother and young[51,52], thus participating in indirect caregiving, whereas in other biparental titi and callitrichine monkeys (such as marmosets and tamarins), the father is the primary caregiver[53].

Human paternal care similarly shows substantial variability across cultures; in some, fathers engage in daily caregiving, whereas in others, the exposure of the infant to the father is minimal[54,55]. Yet, despite the historical matricentric view of Western civilization[56], human infants across societies have typically been raised by the collaborative effort of mothers and non-maternal adults (also known as allomothers), including fathers and other surrogates[57], and although diversely expressed, paternal caregiving behaviour has always been universally evident[58,59]. In particular, throughout human history, fathers have been the main source of indirect care, controlling the material resources, physical conditions and social status with which infants develop[12,55]. Historical accounts point to close associations between paternal provisioning and child mortality in the pre-industrial United States and Europe[33,60], and anthropological studies in traditional societies indicate that men with more land or higher social status show greater reproductive success[61,62]. The involvement of fathers in caregiving in Western societies has markedly increased in recent decades. For instance, between 1965 and 2018, fathers in the United States tripled the amount of time that they spent on childcare and are currently as likely as mothers to consider fatherhood central to their identity[63]. Similarly, data from 30 countries describe increasing father involvement in childcare in recent decades and

point to its positive effects on child health and development[64]. These changes in family roles, attitudes and philosophies[63,65] may impact society at large in a number of important ways (BOX 2). On an individual level, the increased involvement of a father with his offspring may lead to a reorganization in the neural circuits underpinning paternal care that are sensitive to active caregiving[5,14,66].

Despite the rarity of biparental caregiving, in many uniparental species, prolonged exposure to infants elicits male parenting behaviour[7], providing a model to study the brain, hormonal and molecular mechanisms involved in the onset of paternal behaviour[6,67]. One important issue in the field is the so-called translational potential of the various animal models described above to the human situation. Only studies in animal models afford a window into the neural, cellular and molecular basis of paternal behaviour. However, one aim of experimental research is to unveil biological mechanisms underlying human paternal behaviour in order to guide interventions in cases of father absence. Unlike the animal models discussed in this article, humans are neither truly biparental nor singularly uniparental; hence, each type of animal model offers a different viewpoint. In addition, the large associative cortex and exclusive parent–infant bonds of humans and the centrality of the cultural context to human paternal caregiving patterns render laboratory rodents a limited (albeit important) lens on the neurobiology of fatherhood.

The paternal brain

The period following childbirth is accompanied by substantial changes in the brains of both mothers and fathers, with changes in the father's brain depending, to a much greater extent than those in the mother's brain, on exposure to infant stimuli and the amount of active caregiving. Studies in rodents, non-human primates and humans have reported changes in grey matter volume[68], altered receptor sensitivity[69], an increase in the number of adult-born neurons[70] and the emergence of new

Box 2 | **Fatherhood and society**

Although fatherhood is a core biological phenomenon, it is also a key sociocultural construct and a metaphor for social order and three millennia of monotheism[26]. It is thus important to ensure that the emerging neuroscientific findings are integrated with current sociocultural changes[14] to enable innovative research on the multiple ways by which a father's biological and cultural 'capital' transmits to offspring. The reorganization of family roles and rapid increase in father involvement in caregiving in Western societies[63,64] are changing societies in ways that touch upon the legal, occupational, political and philosophical domains. In several areas, neuroscientific studies of fatherhood may impact society at large.

Custody laws

Findings in animal models and humans indicating that there are long-lasting effects of father absence on the offspring's brain and socialization are being used in court by fathers to argue for shared custody[11].

Fathers and the work force

Balancing fathers' new childrearing responsibilities with their careers requires legal (parental leave) and attitudinal changes. Evidence for the increased brain plasticity in fathers that results from daily paternal caregiving and its association with the development of a collaborative social style in the father[5,138,253] suggests that involved fathering may be an asset to men in the workforce, particularly to those in creative and collaborative enterprises.

Multiple perspectives on how to parent

Research has shown that paternal caregiving presents a greater cultural variability than that presented in patterns of maternal care[54,58,224]. Such diversity highlights the multiple ways by which parenting can be practised and argues against a single (often Western) viewpoint on how to raise healthy children. The neuroscientific findings in both humans and animal models[26] show that a father's brain is sensitive to the amount and type of caregiving and that neural activations of the paternal brain are associated with long-term child socialization and mental health outcomes[138,253]. It is important to examine how culture-specific paternal care activities are associated with specific neural changes in the father and uniquely impact a child's brain and behaviour.

The reduction in aggression

It has been suggested that the reduction in aggression in European societies over the past seven decades[254] reflects positive social change involving more empathy and social consideration. One possibility is that as men become more involved in childrearing and take part in the give-and-receive intricacies of family life, their inclination to submit to absolute, divisive agendas may decline. Children reared by more involved dads exhibit greater impulse control, lower aggression and better social collaboration skills[251] and are able to manage conflict with peers with greater respect and empathy[227]. In non-human primates and rodents, social monogamy and paternal care are associated with more complex social behaviour in offspring and lower male–male aggression[49,51]. The neuroscientific and developmental studies described in this Review raise the possibility that greater father involvement may lead to less aggression and better social abilities in the next generation.

The nature of democracy

Research has shown that the neurobiological changes in the brains of fathers are shaped, to a great extent, by acts of caregiving[1,3,6,56,255]. This raises the possibility that neural changes in men (and women) could be driven by other alloparental roles, such as those taken by teachers, mentors, coaches, civil servants, physicians or judges. As described above, a father's brain provides a model for great neural plasticity driven by acts of committed daily caregiving that occur without the hormonal changes associated with pregnancy and childbirth and are associated with father–child reciprocity. These neuroscientific findings may give rise to the hope that, in a society in which adults are committed to allomothering, the young may thrive and produce a more empathic, accepting and equal society.

Reward value
The degree to which a stimulus, object or activity will result in approach responses.

Genome-wide association study
A study in which a genome-wide set of genetic variants in different individuals is associated with a trait.

Pair bonding
The formation of strong social affiliation between two individuals following mating, which typically results in a socially monogamous relationship.

Oxytocin
A peptide hormone and neuropeptide that is produced by the hypothalamus and has a role in social bonding and affiliation.

patterns of brain connectivity[5,8,71,72]. These alterations are likely to coalesce to support parenting behaviour[69,73,74], although establishing whether such changes have a causal role in the onset of parental care requires further research.

As will be outlined below, evidence suggests that mammalian paternal caregiving behaviours rely upon the same neural pathways as those supporting maternal caregiving, making use of the same neural substrates and hormonal systems. However, there is greater plasticity in these pathways in fathers than in mothers and greater variability among individuals and species[1,8,75]. Molecular and circuit-level studies indicate that although the same circuits support male and female parenting behaviours, sex-specific wiring means that there are inputs from different neuronal populations in males and females. These sex-specific inputs control parenting-related motor sequences, ensure that the parents' neural representations of their infants are imbued with reward value and integrate internal and contextual cues to govern parenting behaviour[76,77]. However, there are also important differences between the neural basis of maternal care and that of paternal care. For example, a genome-wide association study comparing two sister species of mice — *Peromyscus polionotus* and *Peromyscus maniculatus* — that display differences in parental behaviour identified 12 genomic regions that control parental care. Eight of these regions were sex-specific, suggesting that parenting behaviour evolved along independent lines in females and males[78]. Similarly, a longitudinal human study showed marked grey matter reductions in first-time mothers across pregnancy and the first two postpartum years but no grey matter change in fathers[79], indicating that neural adaptations in males and females are, at least partly, distinct.

Research on pair bonding in prairie voles shows comparability in the mechanisms underpinning parent–child bonding and pair bonding[80,81]. These mechanisms involve the combination of the effects of oxytocin with those of dopamine in the striatum via neurons that express both dopamine and oxytocin receptors[82] and enable the integration of general reward pathways with those mediating the social reward of affiliative bonds and driving approach orientation[80]. It therefore appears that different types of social bonds are flexibly assembled from the same neural circuits and neurotransmitter systems and adapted to context, purpose and species. Thus, the paternal-care-specific processes discussed below should be understood within the global context of mammalian social affiliation[80].

Animal models of the paternal brain. Research into the neural basis of parenting began with rodent mothers and highlighted the key role of the medial preoptic area (MPOA) in the hypothalamus in this behaviour[83]. Primed by the hormones of pregnancy, particularly oxytocin, prolactin and oestrogen, neurons in the MPOA — via their projections to the nucleus accumbens and ventral tegmental area (VTA) of the mesolimbic dopamine circuit — act to increase the mother's level of social engagement and reward by stimulating dopamine release in response to seeing, hearing or smelling the infant[84]. Neurons in the MPOA also project to the medial nucleus of the amygdala (MeA), where they act to inhibit competing social interactions and sustain maternal parenting behaviour[77]. Thus, activity in the MPOA and its projections sensitizes the limbic network underpinning mammalian maternal care[1,83,85,86]. The MPOA contains cells expressing various neurotransmitters and neuropeptides, and the diverse projections of these cells connect to multiple neural targets in the mammalian parenting network to support maternal behaviour. For instance, MPOA oestrogen-receptor-α-expressing cells send inhibitory projections to the VTA to inhibit non-dopaminergic cells and stimulate pup approach[87]. Similarly, MPOA excitatory galanin-containing neurons project to multiple targets in the maternal brain, including the VTA, the periaqueductal grey (PAG) and the MeA, to orchestrate maternal care[77]. Steroid-sensitive excitatory MPOA neurons that encode ethologically relevant social information project to VTA neurons, stimulating dopamine release to govern social approach behaviour[88]. In addition to priming these MPOA neurons, oxytocin acts directly on neurons in the VTA to facilitate dopamine release in the nucleus accumbens, and oxytocin-primed synaptic plasticity in the amygdala supports the formation of social memories of the attachment target[89]. Also included in the maternal caregiving circuit are parts of the mesolimbic dopamine network and several other regions rich in oxytocin receptors, including the bed nucleus of stria terminalis (BNST), the lateral septum and the ventral pallidum[90,91] (FIG. 1a).

The same subcortical circuit also supports paternal care in rodents. The MPOA is implicated in the process of sensitization[92,93] (the prolonged exposure of males to infant stimuli that elicit hormonal changes and paternal behaviour; see BOX 1). Lesions to the MPOA disrupt paternal behaviour in the biparental California mouse (*Peromyscus californicus*)[94], and increased neuronal activity in the MPOA has been observed following pup exposure[95]. The medial and basolateral amygdala[96], BNST[95], ventral pallidum[97] and lateral septum[72,98] have also been shown to be crucial to the emergence of paternal behaviour. For instance, in the California mouse, immunoreactivity for immediate early genes such as FOS (a marker of neuronal activation) increased in the BNST of new fathers, suggesting altered neural transmission in this area[95], and lesions to the basolateral amygdala impaired paternal behaviour[96]. In the biparental prairie vole (*Microtus ochrogaster*), exposure to pups increased FOS expression in the MPOA, medial amygdala, lateral septum and BNST[98]. Lesions to MeA in this species decreased paternal behaviour[98], and lesions to the ventral pallidum increased latency to retrieve and groom pups[97]. These regions integrate to form the rodent subcortical mammalian paternal network (FIG. 1a)

Although the circuit underlying parental care is similar in male and female rodents, its regulation is sex-specific and depends on both experience and, in male rodents, exposure to the pregnant and lactating dam. For example, studies in mice have shown that mating induces pheromone-mediated suppression of pup-directed aggression in males, creating a complex sex-specific, experience-specific balance between aggression and

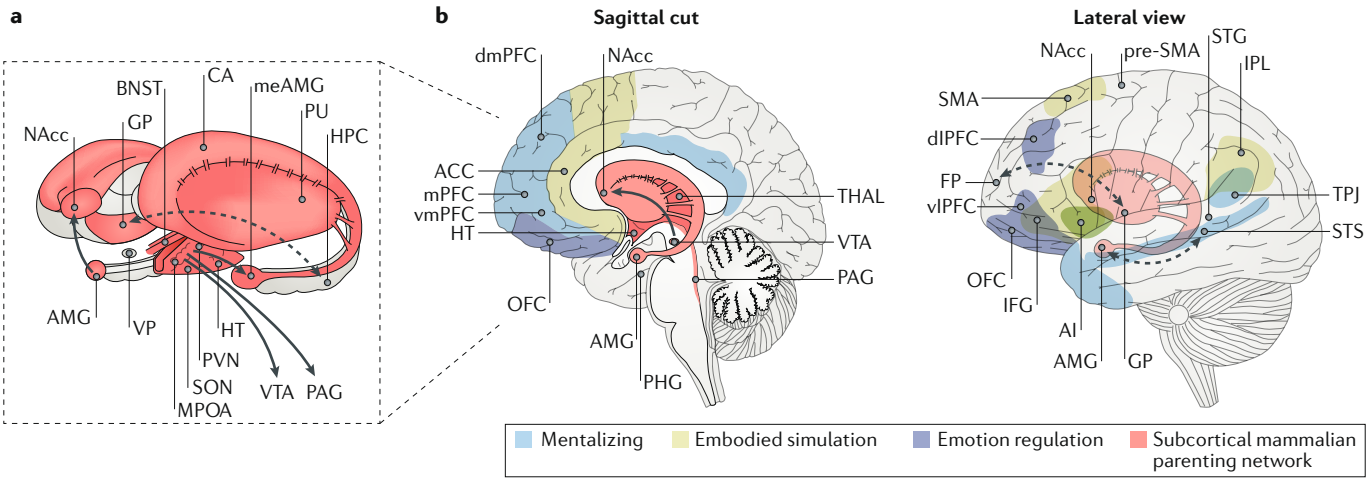

Fig. 1 | **The paternal brain.** The figure displays brain areas and associated connectivity patterns that have been implicated in paternal caregiving. **a** | Subcortical areas of the mammalian parenting network that have been highlighted by both rodent and human studies, shown here as they would appear in the human brain[5,72,94,95,97,98,114–116,123,256,257]. The arrows illustrate the patterns of connectivity between these regions that are thought to be important for parenting behaviour, as identified from studies in rodents (solid arrows)[76,77] and humans (dashed arrow)[143]. **b** | The global human paternal caregiving network, which includes both the subcortical mammalian parenting network and cortical networks involved in embodied simulation, mentalization and emotion regulation (solid arrow illustrates connectivity patterns identified on the basis of studies in animal models, and the dashed lines illustrate connectivity patterns based on human imaging studies)[5,123,139,141,144,185,258,259]. ACC, anterior cingulate cortex; AI, anterior insula; AMG, amygdala; BNST, bed nucleus of the stria terminalis; CA, caudate; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FP, frontopolar prefrontal cortex; GP, globus pallidus; HPC, hippocampus; HT, hypothalamus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; meAMG, medial amygdala; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PFC, prefrontal cortex; PHG, parahippocampal gyrus; PU, putamen; PVN, paraventricular nucleus; SMA, supplementary motor area; SON, supraoptic nucleus of the hypothalamus; STG, superior temporal gyrus; STS, superior temporal sulcus; THAL, thalamus; TPJ, temporoparietal junction; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VP, ventral pallidum; VTA, ventral tegmental area.

caregiving[76]. Similar to mothers, specific pools of MPOA galanin-expressing neurons in the paternal brain project to inhibitory PAG neurons to promote pup grooming, to VTA neurons to increase approach behaviour and to the MeA to suppress competing social stimuli to help fathers focus on pups[77].

Paternal behaviours are also influenced by communication with a female mate; lesions to the MPOA disrupt mate-dependent paternal behaviour in mice[97], and the expression of FOS is increased in the MPOA in male mice engaged in paternal care following ultrasonic vocalizations from the mother[20], suggesting that male–female communication may mediate some aspects of paternal caregiving and that the MPOA is involved in regulating this phenomenon.

Parenting emerges in the context of hormonal changes, and paternal behaviour, similar to maternal behaviour, has been associated with changes in the levels of oxytocin, prolactin, glucocorticoids and oestrogen[15,75,99,100]. In addition, studies in humans and in rodent and primate species that display paternal care indicate that levels of arginine vasopressin (AVP; a neuropeptide that is structurally similar to oxytocin) and the steroid hormone testosterone change around the time of birth of an infant[101,102]. Studies in biparental rodents and primates show that paternal behaviour is associated with these hormonal changes and with plasticity in the hippocampus and areas of the paternal brain (described below). Furthermore, the extent of these changes parallels the amount of active paternal behaviour[75,99,103,104]. Nevertheless, whereas pregnancy and childbirth are associated with marked increases in maternal oxytocin[105] and prolactin[106], such changes in fathers are more nuanced, and it is still not fully understood why fathers undergo hormonal changes, what triggers these changes and whether these changes are causal to the expression of paternal care[107].

The hormones mediating paternal behaviour have mainly been studied in biparental species. These include two primate species (cotton-top tamarins (*Saguinus oedipus*) and marmosets (*Callithrix jacchus*))[103] and five rodent species that have all arisen from a single major rodent lineage: prairie voles (*M. ochrogaster*), mandarin voles (*Lasiopodomys mandarinus*), California mice (*P. californicus*), Campbell's dwarf hamsters (*Phodopus campbelli*) and Mongolian gerbils (*Meriones unguiculatus*)[108]. Cotton-top tamarin and marmoset fathers show elevated levels of urinary prolactin, oestradiol and testosterone in the month before birth, which probably result from exposure to the pregnant female and are thought to prepare for the onset of paternal care[108,109]. Following the birth of an offspring, the degree to which the levels of these hormones change is influenced by the level of actual involvement by the father[75]. For example, testosterone levels in marmosets decrease in proportion to the amount of time the father spends carrying the infant[103], prolactin levels increase in tamarin fathers in

Global human caregiving network
A network of subcortical and cortical regions that underpins human parental behaviour.

a manner that is modulated by the father's experience (whether they are living with the infant[99]) and by the amount of carrying[104] and marmosets show a decrease in cortisol levels in relation to the amount of infant carrying[103]. Hormonal synchrony (correlated hormonal levels in male and female partners) is also observed in oxytocin and cortisol in humans[110,111] and in cotton-top tamarins[112], and in both species, the hormonal coordination is thought to be mediated by parental behaviour and to support the joint care of an infant by a mother and father[2,75].

In addition to these fluctuations in systemic hormone levels, paternal caregiving behaviour is associated with pronounced changes in oxytocin, prolactin, dopamine and AVP-mediated functions in the parenting circuit of the father's brain. For example, California mouse fathers participating in paternal caregiving showed lower levels of progesterone, oxytocin and AVP V1a receptor (AVPR1A) mRNA expression than shown in non-breeding males[113] and enhanced connectivity among brain areas implicated in learning, motivation and nurturing[72]. In mandarin voles, paternal caregiving increased the availability of oxytocin and dopamine receptors in the nucleus accumbens[114], and in prairie voles, paternal caregiving was associated with augmented hypothalamic *Avp* expression and increased availability of oxytocin receptors in the nucleus accumbens[115]. Hypothalamic and amygdala oxytocin-expressing neurons in prairie vole fathers show differential responses to the separation of the father from his pups according to infant age[116], suggesting that there may be some modulations in these systems across the course of offspring development. In primates, a study in marmosets indicated that paternal caregiving increases the density of dendritic spines and the abundance of AVPR1A on pyramidal neurons in the prefrontal cortex (PFC)[69].

In addition to hormonal changes, paternal caregiving behaviour is associated with structural changes (such as neurogenesis or altered synaptic spine density) in the hippocampus with consequences for learning and memory. These changes are triggered by offspring olfactory cues[117] and are modulated by the amount of parenting experience[118]. In California mice, paternal caregiving behaviour is also associated with increased dendritic spine density in dentate gyrus (DG) granule cells, an increase in the number of newborn cells in the DG and an increase in the number of basal dendrites present on pyramidal cells in CA1 (REFS[119,120]). Furthermore, in California mice, both spatial memory improvements and elevated FOS immunoreactivity in the CA1, CA3 and DG were observed during the acquisition phase of a spatial learning test in caregiving fathers, compared with pup-exposed virgin males[121]. Plasticity in other brain regions is also observed. For example, in transgenic mice, paternal recognition of offspring depends on the postnatal father–infant interaction and is associated with increased neurogenesis in the father's olfactory bulb[117].

Overall, studies in biparental rodents and primates show that paternal caregiving is associated with substantial hormonal changes and increased neural plasticity in key areas of the paternal brain and that these changes parallel the amount of active paternal behaviour. This indicates that the neurobiological changes that accompany paternal caregiving may be modulated, at least partly, by bottom-up caregiving experiences and by co-habitation with the pregnant and lactating female.

The human paternal brain. Research into the human paternal brain utilizes imaging techniques, particularly functional MRI (fMRI), to test fathers' brain responses to infant-related auditory, visual and multimodal stimuli (reviewed in REFS[1,19,80,122]). These studies have shown that neural activations and grey matter volume change in the same conserved subcortical circuit described in rodents and primates, including the hypothalamus, amygdala and structures of the subcortical dopamine reward circuit, are associated with the transition to fatherhood and with human paternal behaviour[1,2,68,71,123,124]. However, in humans, this conserved circuit is connected via multiple ascending and descending projections to several insular–cingulate and fronto-temporoparietal networks that coalesce to form a global human caregiving network that supports human maternal and paternal behaviour. This network acts to orient human parents to their infants, enabling them to understand the infant's moment-by-moment needs and social signals and to plan for long-term parenting goals[1,5].

The functioning of these cortical networks is hypothesized to enable human parenting behaviour in several ways. Parents are able to empathize with an infant's affective state, express sensitive caregiving and ground experience in the present moment through the insular–cingulate empathy network[125–128]. Perceptual–motor coupling and simulation of an infant's actions in the parent's brain occur via the embodied-simulation network, which helps the parent echo the child's motions and emotions and engage in coordinated social communications[129–133]. Parents can understand an infant's intentions on the basis of their non-verbal signals via the temporoparietal mentalizing network[134,135]. Finally, parents can engage in multitasking, emotion regulation and action selection (all components of parenting behaviour) to accommodate long-term goals by utilizing the emotion regulation and/or 'executive' network, believed to be the latest of these networks to evolve[136,137]. These cortical networks are partly overlapping, serve multiple functions and provide top-down regulatory control to the ancient limbic circuit identified in rodents (see above, FIG. 1b).

Human fathers that are involved in caregiving show increased activations in all regions of the human caregiving network in response to infant cues in comparison with non-fathers and show greater activations to stimuli relating to their own infant than shown relating to an unfamiliar infant[1,19,80,122,123,138–141]. The size of these activations is associated with a father's observed behaviour and with levels of paternal hormones, including oxytocin, vasopressin, cortisol and testosterone[5,123,139,141]. In addition, human paternal caregiving is associated with plasticity in these networks: an increase in grey matter volume has been found in fathers participating in

caregiving across the first postpartum months in several areas of the parental networks, including the striatum, amygdala, hypothalamus and PFC[68].

Despite similarities in activation of the human caregiving network in human mothers and fathers, two studies that directly compared mothers' and fathers' neural responses with cues related to their infant showed greater activation in the amygdala in mothers and higher cortical activity in fathers[5,71]. This result may suggest that the subcortical network plays a more primary role in parental behaviour in mothers and that the cortical networks are more important in male paternal behaviour; however, this hypothesis requires further research. To tease apart the effects of a parent's sex from their role in caregiving, brain activity, hormone levels and parenting behaviour were compared in three groups of first-time parents: mothers, fathers and homosexual fathers raising infants born via surrogacy (in which there is one biological father and one adoptive father and no maternal involvement after birth, providing a human model of father-only caregiving)[5]. Overall, similar activations across the human caregiving network emerged in all parents. However, mothers showed a fourfold increase in amygdala activation compared with that in fathers, whereas fathers exhibited greater activations in cortical regions designated as mentalizing nodes, particularly the superior temporal sulcus (STS). Interestingly, STS activation was similar in primary-caregiving fathers and non-primary-caregiving fathers, whereas activation in the amygdala of primary-caregiving fathers was similar to that of mothers, and the degree of functional connectivity between the amygdala and the STS was strongest in the group of primary-caregiving fathers. Among all fathers, the amount of daily involvement in childcare activities was associated with the degree of connectivity between the amygdala and the STS, suggesting that active paternal care may lead to greater coherence among subcortical and cortical circuits of the global human caregiving network.

Similar to non-human primates and rodents, the transition to become a caregiving father in humans is associated with hormonal changes, particularly an increase in plasma oxytocin levels[111], an increase in plasma prolactin levels[101] and a decrease in salivary testosterone levels[142]. An experimental increase in oxytocin levels via nasal administration of the hormone has been shown to impact the brain of a human father by decreasing the functional connectivity between the globus pallidus and the frontopolar cortex[143,144] and by altering the father's hormones (for instance, increasing endogenous oxytocin levels, decreasing cortisol levels and modulating testosterone levels)[145–147]. Nasally administered oxytocin also augments paternal behaviour, including touch and exploratory behaviour, in human fathers[148,149]; yet, it should be noted that it is still unclear whether intranasal oxytocin administration reaches the brain and impacts brain oxytocin activity[150]. Nevertheless, these findings suggest that bolstering the hormonal milieu that is associated with paternal caregiving augments the father-specific biological and behavioural markers of human parenting.

Effects of paternal care on offspring

Although research on the impact of early social experiences on offspring neurodevelopment has traditionally focused on mothers[151–153], studies in biparental species provide insight into the specific role of fathers in shaping the brain and the socio-emotional development of infants[108]. Research in animal models enables us to gain an understanding of the molecular impact of paternal care on neuronal and synaptic development and on changes in synaptic transmission and plasticity in the offspring's brain. Most experimental studies in this area apply paternal deprivation paradigms in which the father is removed from the social unit. These studies have demonstrated that the absence of paternal care alters behavioural traits in progeny, including anxiety, aggression, social behaviour and response to reward[154–159], with many effects being sex-specific[160,161]. However, to date, no systematic study has examined whether the effects of paternal deprivation on an offspring's brain and behaviour are specific to the absence of a male caregiver or result from exposure to a single-parent 'impoverished environment'. In addition, the use of different species and paternal deprivation paradigms and multiple methodological approaches, as well as the focus on only a few brain regions, has limited our ability to develop an overarching conceptual framework in order to better understand the specific functional brain circuits impacted by paternal deprivation and paternal care. In the course of reviewing the current literature, we attempt to put findings obtained in different biparental species into specific conceptual contexts, which — although still hypothetical — might kindle and refine future experimental approaches.

What environmental aspects provided by the father (or his absence) influence the development of his offspring's brain and behaviour, and what are the underlying developmental mechanisms? The considerable overlap between the brain regions that are activated in the paternal brain (FIG. 1) and those whose functions are altered in the paternally deprived offspring brain (FIG. 2; TABLE 1) raises the hypothesis that a father and his offspring activate the same brain areas when they interact with each other. This view is supported by functional imaging studies in offspring of the biparental degu (*Octodon degus*), which revealed that listening to their mother's contact calls activates the anterior cingulate and precentral medial PFC[162,163]. It is tempting to speculate that similar activations might occur in response to paternal vocalizations and other sensory stimulation provided by the father. Because brain development critically depends on environmental stimulation (underlying the concept of experience-dependent and experience-expectant brain development[164]), father-induced stimulation of the immature, still developing infant brain should be expected to promote the establishment and maturation of neural and synaptic functions, particularly in those brain areas that are activated during father–offspring interactions. As a lack of paternal stimulation may be considered to represent an impoverished socio-emotional and sensory environment, it appears likely that paternal deprivation should result in developmental delays or long-term impairment of brain maturational processes.

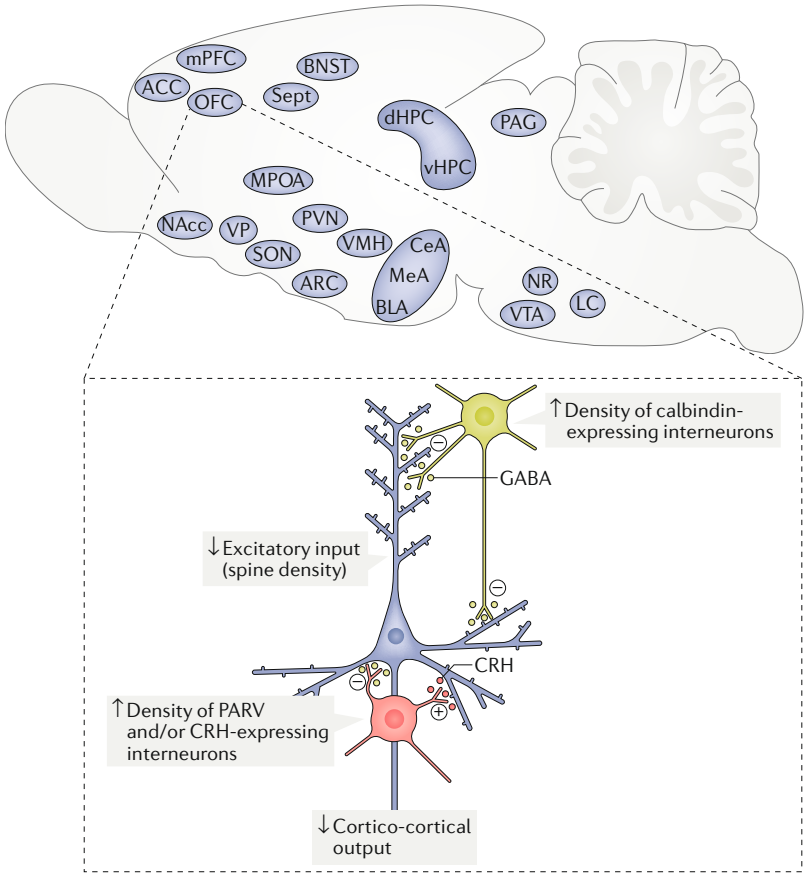

Fig. 2 | **The paternally deprived offspring brain.** An illustration of brain regions that have been shown to be histologically and molecularly altered in response to paternal deprivation (for references, see TABLE 1). These brain areas are part of functional circuits involved in reward and/or motivation, social and emotional functions, parenting, reproduction, stress, anxiety and aggression[77,260–262]. Please note that the brain regions are not depicted with the correct size and anatomical position. The inset provides a summary of neurohistological changes observed in the orbitofrontal cortex (OFC) of paternally deprived *Octodon degus* offspring. Paternal deprivation decreases excitatory input (through a reduction in spine synapses[166] and an increase in inhibitory interneurons expressing calbindin-D28k[167]) and dampens the output activity of pyramidal neurons (through an increase in the input from inhibitory interneurons expressing parvalbumin), which may result in an altered balance between excitation and inhibition and impaired communication between the OFC and other brain regions. ACC, anterior cingulate cortex; ARC, arcuate nucleus of the hypothalamus; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; CRH, corticotropin-releasing hormone; dHPC, dorsal hippocampus; LC, locus coeruleus; MeA, medial nucleus of the amygdala; mPFC, medial prefrontal cortex; MPOA, medial preoptic area of the hypothalamus; NAcc, nucleus accumbens; NR, nucleus raphe; PAG, periaqueductal grey; PARV, parvalbumin; PVN, paraventricular nucleus of the hypothalamus; Sept, septum; SON, supraoptic nucleus of the hypothalamus; vHPC, ventral hippocampus; VMH, ventromedial hypothalamus; VP, ventral pallidum; VTA, ventral tegmentum.

Changes in the excitation–inhibition balance can have major effects on ongoing neuronal activity and the homeostatic regulation of intrinsic excitability, which in turn may impair the communication between affected brain regions[165]. Findings from studies in animal models of paternal deprivation indicate that the absence of paternal care may result in changes in neuronal and/or synaptic homeostasis in the offspring brain (FIG. 2). This (currently hypothetical) interpretation is supported by neurohistological findings in the brains of paternally deprived degus (FIG. 2). These studies (summarized in TABLE 1) observed reduced densities of excitatory spine synapses[166] and increased numbers of inhibitory interneurons[167] in the orbitofrontal cortex of father-deprived male offspring, which may indicate a dampening of the input and the output activity of this brain area, thereby impairing its communication with other brain regions. Similar dampening of dendritic input and axonal output was observed in the hippocampal formation and nucleus accumbens[167], regions which are implicated in reward-related learning and memory functions[168]. Such changes in excitability might contribute to some of the cognitive and socio-emotional changes reported in father-deprived offspring.

Evidence for an altered excitatory–inhibitory synaptic balance following paternal deprivation has also been found at the level of synaptic molecules, suggesting that paternal care may be essential for the establishment of synaptic plasticity in the offspring's brain. For example, in California mice, paternal deprivation alters synaptic density, indicated by decreased expression of the postsynaptic density protein 95 (PSD95) and altered expression of the subunits of receptors for the excitatory transmitter glutamate, including increased *Grin2a* mRNA and reduced expression of *Grin2b* mRNA in the hippocampus of father-deprived offspring[169]. In the medial PFC of this species, paternal deprivation also leads to sex-specific changes in dopaminergic (modulatory) and glutamatergic (excitatory) neurotransmission in pyramidal neurons, and these are paralleled by behavioural changes[160]. Furthermore, pyramidal neurons in the prelimbic and anterior cingulate cortex of female offspring raised without a father show reduced responses to dopaminergic stimulation, whereas the physiological response to NMDA receptor stimulation was elevated in both male and female father-deprived offspring. In degus, a lack of paternal care reduces synaptic connectivity in the somatosensory cortex of male offspring[170], indicating that somatosensory stimulation, provided through body contacts with the father (such as licking, grooming and huddling) may promote synaptic development in this sensory cortical region.

In animal models, paternal deprivation also induces changes in so-called plasticity factors — that is, molecules that are critically involved in brain development and in adult synaptic plasticity. In mandarin voles, paternal deprivation decreases the density of neurons expressing glucocorticoid receptors and brain-derived neurotrophic factor (BDNF) in the hippocampal formation in male and female offspring, whereas reduced density of neurons expressing glucocorticoid receptors and BDNF occurred only in the DG in female offspring[171]. By contrast, in prairie voles, paternal deprivation induces lasting increases in the expression of BDNF as well as its receptor NTRK2, and there is some evidence that these changes might be epigenetically regulated[172]. BDNF regulates synaptic transmission and plasticity in several brain regions, contributes to various adaptive neuronal responses (including long-term potentiation and long-term depression) and modulates homeostatic regulation of intrinsic neuronal excitability[173].

The behavioural traits observed in father-deprived offspring may also relate to dysregulated catecholaminergic

Table 1 | **Neural and functional alterations in father-deprived offspring**

Brain region and species	Changes resulting from paternal deprivation	Proposed functions of the affected pathways	Refs
ACC			
O. degus	• Decreased number of symmetric shaft synapses • Change in E–I balance	Social behaviour, reward, attachment, parental behaviour and stress	263
OFC			
O. degus	• Increased number of CRH-expressing neurons in juveniles • Decreased number of spines in juveniles • Increased number of calbindin-expressing interneurons in juveniles • Increased number of parvalbumin-expressing interneurons in juveniles and adults • Change in E–I balance	Social behaviour, attachment, parental behaviour, aggression, addiction, cognition and stress	166,167,180
mPFC			
O. degus	Increased number of TH-immunopositive (dopaminergic and/or noradrenergic) fibres in juveniles and adults	Social behaviour, reward, parental behaviour, attachment, fear, stress, aggression and limbic system functions	174
NAcc			
O. degus	• Increased number of TH-immunopositive fibres in juveniles • Decrease in TH-immunopositive fibres in adults • Increased number of calbindin-expressing interneurons in juveniles and adults • Increase in PARV-expressing interneurons in juveniles • Change in E–I balance	Social behaviour, reward, parental behaviour, attachment, addiction and limbic system functions	159,161,167,174
Mandarin vole	• Decreased expression of *Drd1* and *Drd2* mRNA in females • Increased expression of *Drd1* and *Drd2* mRNA in males • Decreased expression of *Esr1* and *Oxtr* mRNA	Social behaviour, reward, parental behaviour, attachment, addiction and limbic system functions	159,161,167,174
HPC			
O. degus	• Increased number of TH-immunopositive fibres in CA1 and DG in juveniles and adults • Decreased number of CRH-expressing neurons in DG in juveniles and in CA1 in juveniles and adults • Increased number of calbindin-expressing interneurons in CA3, CA1 and DG in juveniles • Increase in parvalbumin-expressing interneurons in CA1 and DG in juveniles • Decrease in parvalbumin-expressing interneurons in CA1 and CA3 in adults • Change in E–I balance	Social behaviour, reward, fear, stress, aggression and limbic system functions	167,169,171,172,174,180,264
California mouse	• Increased expression of *Grin2a* mRNA • Decreased expression of *Grin2b* mRNA • Decreased expression of PSD95	Social behaviour, reward, fear, stress, aggression and limbic system functions	167,169,171,172,174,180,264
Mandarin vole	• Decreased expression of BDNF in CA1, CA2 and CA3 • Decreased expression of NR3C1 in CA1, CA2 and CA3 • Decreased expression of BDNF and NR3C1 in the DG of females • Decreased neurogenesis in the DG of females • Decreased numbers of spines in the DG	Social behaviour, reward, fear, stress, aggression and limbic system functions	167,169,171,172,174,180,264
Prairie vole	• Increased expression of *Bdnf* mRNA and BDNF • Increased expression of NTRK2 • Increased expression of NR3C1 (β-isoform) in females • Increased expression of CRHR2 in males • Decreased expression of *Crhr2* mRNA in males and females	Social behaviour, reward, fear, stress, aggression and limbic system functions	167,169,171,172,174,180,264
AMG			
O. degus	Increased number of CRH-expressing neurons in BLA of juveniles	Social behaviour, reward, fear, stress, reproduction, aggression and limbic system functions	161,180
Mandarin vole	Decreased expression of *Esr1* and *Oxtr* mRNA in MeA	Social behaviour, reward, fear, stress, reproduction, aggression and limbic system functions	161,180

Table 1 (cont.) | **Neural and functional alterations in father-deprived offspring**

Brain region and species	Changes resulting from paternal deprivation	Proposed functions of the affected pathways	Refs
BNST			
O. degus	• Decreased number of CRH-expressing neurons in the medial BNST of juveniles and adults • Increased number of calbindin-expressing interneurons in the medial BNST of juveniles • Decreased number of calbindin-expressing neurons in the lateral BNST of adults • Change in E–I balance	Social behaviour, reward, parental behaviour, attachment, fear, stress, reproduction, aggression and limbic system functions	157,181,183
California mouse	Decreased number of AVP-immunoreactive fibres in the dorsal BNST	Social behaviour, reward, parental behaviour, attachment, fear, stress, reproduction, aggression and limbic system functions	157,181,183
Mandarin vole	Decreased expression of ESR1	Social behaviour, reward, parental behaviour, attachment, fear, stress, reproduction, aggression and limbic system functions	157,181,183
PVN			
California mouse	Increased number of AVP-expressing neurons	Social behaviour, parental behaviour, attachment, stress and aggression	157,184
Mandarin vole	• Increased number of AVP-expressing neurons after stress challenge • Decreased number of OXT-expressing neurons after stress challenge	Social behaviour, parental behaviour, attachment, stress and aggression	157,184
MPOA			
Mandarin vole	Decreased expression of ESR1	Social behaviour, parental behaviour, attachment, reproduction and aggression	183
VMH			
Mandarin vole	Decreased expression of ESR1	Parental behaviour, attachment, reproduction and aggression	183
ARC			
Mandarin vole	Decreased expression of ESR1	Reproduction	183
SON			
Mandarin vole	Decreased number of OXT-expressing neurons after stress challenge	Social behaviour, parental behaviour, attachment and stress	184

ACC, anterior cingulate cortex; AMG, amygdala; ARC, arcuate nucleus of the hypothalamus; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CRH, corticotropin-releasing hormone (corticoliberin); CRHR2, corticotropin-releasing hormone receptor 2; DG, dentate gyrus; DRD1, D_{1A} dopamine receptor; DRD2, D_2 dopamine receptor; E–I balance, excitatory–inhibitory balance; ESR1, oestrogen receptor 1; GRIN2A, glutamate receptor ionotropic, NMDA2A; GRIN2B, glutamate receptor ionotropic, NMDA2B; HPC, hippocampus; MeA, medial nucleus of the amygdala; mPFC, medial prefrontal cortex; MPOA, medial preoptic area of the hypothalamus; NAcc, nucleus accumbens; NR3C1, glucocorticoid receptor; NTRK2, BDNF–NT-3 growth factors receptor; *O. degus*, *Octodon degus*; OFC, orbitofrontal cortex; OXT, oxytocin; OXTR, oxytocin receptor; PARV, parvalbumin; PSD95: postsynaptic density protein 95; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus of the hypothalamus; TH, tyrosine hydroxylase; VMH, ventromedial hypothalamus.

modulation and, in particular, to altered dopaminergic activity within the prefronto-limbic pathways involved in reward-related processes. In mandarin voles, for example, paternal deprivation induces sex-specific changes in dopamine receptor density in the nucleus accumbens. Whereas paternally deprived female voles show reduced expression of D_{1A} dopamine receptor (*Drd1*) and *Drd2* mRNA, the mRNA levels of these receptors are upregulated in male offspring[159]. In male degus, paternal deprivation increases dopaminergic innervation of medial prefrontal cortical regions, indicating dopaminergic 'hyper-innervation'[174] of these cortical areas, which are involved in the regulation of flexible behaviour, the development of habitual behaviours and emotional and working memory processes[175,176]. In the nucleus accumbens of father-deprived degus, an age-dependent biphasic impact of paternal care on the developing dopaminergic fibre innervation was observed: in 3-week-old juvenile offspring, fibre innervation was increased, whereas fibre density was strongly reduced in adulthood[174]. Because the nucleus accumbens is essentially involved in reward-related behaviours and has been proposed to play a key role in integrating cognitive and affective information processed by frontal and temporal lobe regions[177], these findings might be indicative of age-related changes in the neuromodulatory effects of dopamine contributing to these functions. The hippocampal formation of father-deprived juvenile degus also shows elevated density of dopaminergic fibres in CA1 and noradrenergic fibres in the DG[174], which may affect attention, arousal, stress reactions and learning and memory functions.

Paternal care also impacts the functional maturation of brain systems related to stress responses and the

Stress-hyporesponsive phase
A period during postnatal development during which the physiological and behavioural response to stress is blunted.

regulation of social, reproductive and emotional behaviours. In California mice, the offspring of fathers displaying low retrieval activity showed a lower density of AVP-expressing fibres in the dorsal BNST, and the opposite effect was observed in the ventral BNST[157]. The BNST is essentially involved in stress and anxiety[178,179] and was suggested to play a major role in stress-related mood disorders. The experimental reduction in paternal grooming in this species (induced by castrating the males) results in elevated numbers of AVP-immunoreactive neurons in the paraventricular nucleus (PVN) of the offspring. In prairie voles, father-deprived female offspring showed increased expression of the β-isoform of the glucocorticoid receptor (GRβ) in the hippocampus, whereas males showed increased corticotropin-releasing hormone receptor 2 (CRHR2) expression in this brain region[172]. In male degus, the density of corticotropin-releasing hormone (CRH)-expressing interneurons is altered in response to paternal deprivation in an age-specific and region-specific manner: a higher density of CRH-containing neurons was observed in the orbitofrontal cortex and basolateral amygdala of juvenile father-deprived degus (this effect was no longer observed in adulthood), whereas a reduced density of CRH-expressing neurons was found in some subregions of the hippocampal formation and in the medial BNST[180,181]. With the exception of the CA1 region and BNST, these deprivation-induced changes are no longer evident in adult males, indicating that socio-emotional experiences later in life may 'normalize' some of the deprivation-induced changes.

As pointed our earlier, the BNST is involved in stress-related and anxiety-related[178,179] behaviours, and CRH is a peptide hormone that is involved in the stress response through its stimulation of the synthesis of adrenocorticotropic hormone (ACTH) in the pituitary. It is also released from axon terminals in the brain during stress[182] and thereby may modulate synaptic function and plasticity. In mandarin voles, paternal deprivation upregulates levels of serum corticosterone and ACTH in female (but not male) offspring[171]. Furthermore, paternal deprivation reduces the expression of oestrogen receptor 1 (ESR1) in brain regions involved in parental care and stress responses, including the BNST, MPOA, ventromedial hypothalamus (VMH), medial amygdala, nucleus accumbens and arcuate hypothalamic nucleus[161,183]. In addition, reduced oxytocin receptor mRNA expression in the medial amygdala and nucleus accumbens (in both males and females) and reduced serum oxytocin concentrations (in females only) was observed in father-deprived offspring[161]. In this species, there is also evidence that paternal deprivation disrupts the stress-hyporesponsive phase in infants[184]. During this phase, paternally deprived pups showed increased ACTH and corticosterone levels following social isolation, as well as increased numbers of AVP-expressing neurons and decreased numbers of oxytocin-expressing neurons in the PVN and supraoptic nucleus compared with those shown by biparentally reared offspring.

These paternal-deprivation-induced neuroendocrine, neuropeptidergic and neuronal synaptic changes may represent the neuronal substrate underlying some of the behavioural changes observed in father-deprived offspring, including increased anxiety-like behaviour, changes in parental behaviour, impaired social repertoire and altered stress response[157–161,169,172,183]. However, further research is needed to tease apart the dimensions of paternal caregiving that have the strongest effects on offspring and the mechanisms by which paternal care affects offspring brain and behaviour. Research in biparental species is also needed to identify time windows along the neonatal, infant, peripuberty and puberty developmental axis during which paternal care is most critical. Evidence has recently emerged that human paternal behaviour and the brain responses to paternal behaviour in children differ according to the gender of the child[185]. Therefore, paternally evoked sex-specific cellular events in the offspring brain and their contribution to endocrine, neuronal and behavioural development have yet to be identified. It is also important to investigate whether care provided by another female (or a foster father) or other family members and peers can compensate for the absence of paternal care and protect offspring from the neuronal and behavioural consequences of paternal deprivation.

In humans, the neurobiological consequences of paternal deprivation and the quality of paternal care on children's brains have not been studied in detail. Future investigations should ask whether there are developmental and functional differences in the brain and behaviour of paternally deprived children and assess potential differences between children that are vulnerable or more resilient children to the effects of paternal deprivation. The functional brain pathways in which neuronal and synaptic maturation are delayed or permanently impaired by paternal deprivation need to be further characterized on the cellular and molecular levels in animal models, and studies in animals and humans should investigate the mechanisms by which the effects of paternal deprivation are transmitted to the next generation.

Cross-generational effects

The impact of paternal care on the neural systems regulating social behaviour and stress reactivity in offspring can lead to multigenerational continuity in paternal behaviour, similar to the mother–daughter transmission of maternal behaviour in mammals[186]. For example, cross-fostering studies in male California mice, in which offspring are reared by a foster father engaging in relatively higher or lower levels of paternal behaviour than engaged by the biological father, indicate that the quality of paternal care expressed depends on the males' own neonatal and adult experience of paternal care[156]. In mandarin voles, paternal deprivation reduces parental behaviour in both male and female offspring[184,187]. Male California mice raised by fathers in which paternal care was experimentally reduced engage in less huddling and grooming of their offspring[188]. Similarly, male Mongolian gerbils reared without a father display lower parental responsiveness, indicated by reduced nest attendance and grooming of their pups[189].

Similar to the cross-generational transmission of maternal behaviour[186], this paternal transmission is likely to involve altered gene regulation in neural systems associated with social and reproductive behavioural

phenotypes, resulting in a later recapitulation of the social context of early development. Likely targets include the dopaminergic, neuropeptide (oxytocin and AVP) and neuroendocrine (CRH) systems that are known to be impacted by paternal deprivation[156,161,174,181]. The roles of specific molecular mechanisms such as DNA methylation, histone modifications or the effects of non-coding RNA, as well as the roles of the enzymes that regulate these factors (such as DNA methyltransferase[190]), in this transmission require further investigation.

The observed presence of non-genomic paternal influences on offspring development in uniparental species, where the father is typically absent during the post-conception and rearing periods, has provided a novel perspective on parental influences via germ cells[9]. Manipulation of the preconception environment of male laboratory rodents has been demonstrated to impact the neurobiology of their offspring, resulting in a broad range of sex-specific behavioural effects (FIG. 3). In laboratory rats, for example, paternal pre-mating exposure to alcohol results in altered growth trajectories, increased impulsivity and reduced expression of enzymes that promote neurodevelopment and neuroprotection within offspring[191]. Similarly, studies in mice indicate that there is altered neurotrophic factor expression[192] and DNA methylation within imprinted genes[193]

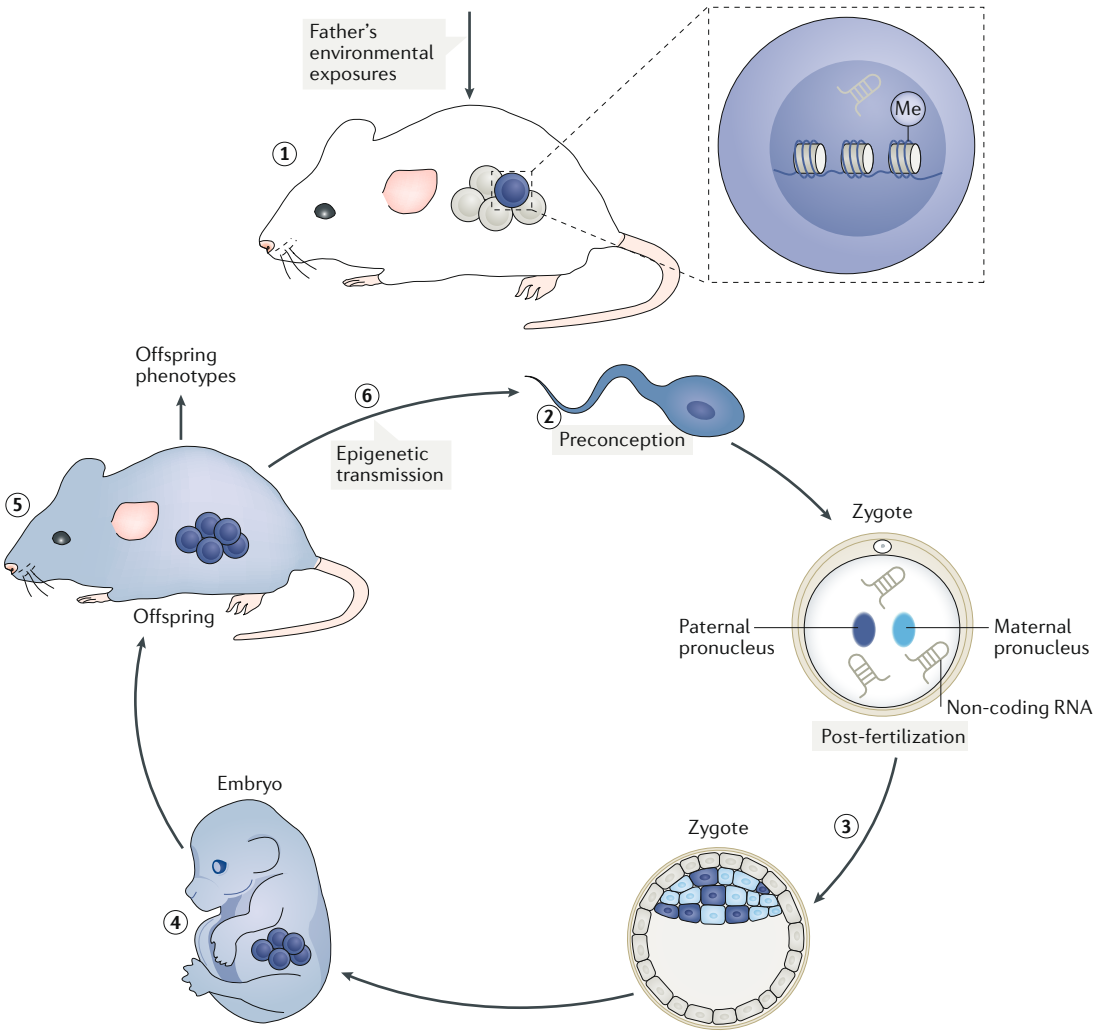

Fig. 3 | **Paternal transmission via germ cells.** Exposure to a variety of environmental signals (including famine, stress and toxins) across the lifespan can result in alterations to gene regulatory mechanisms in males, such as DNA methylation, histone modifications or expression of non-coding RNAs (1). This variation in gene regulation can be observed in the sperm cells produced by the male who was exposed to these signals (2). Despite the occurrence of widespread epigenetic reprogramming events after fertilization, the variations in DNA methylation and histone modifications associated with male environmental exposures can persist, perhaps being maintained by non-coding RNAs present in the zygote (3). The variation in paternal DNA methylation that persists following epigenetic reprogramming can be maintained in the blastocyst through DNA methyltransferase activity during cell divisions and will thus be present throughout embryonic tissue (4). The presence of the paternally transmitted effects on epigenetic variation in offspring then result in broad phenotypic variation through effects on gene regulation that regulate morphology, metabolism, neurobiology and reproduction (5). The maintenance of epigenetic variation in the germ line leads to a recapitulation of these events in the descendants of the male (6). Me, methyl.

Homeostatic synaptic plasticity
The feedback mechanism used by neurons to balance excessive excitation or inhibition by adjusting the strength and/or the number of synaptic connections. This capacity is essential for restraining network activity and maintaining a healthy level of synaptic plasticity needed for adaptations to the environment.

Epigenetic transmission
The transmission across generations of epigenetic variation that results in the transmission of associated traits.

in the brain of the offspring of alcohol-exposed fathers. Further studies have shown that in laboratory rodents, stress exposure at a broad range of developmental time points in the father's lifespan impacts the brain of his offspring. The effects include altered DNA methylation in genes regulating neural plasticity and stress reactivity[194], altered microRNA expression[195], global DNA methylation in the frontal cortex and hippocampus[196], altered hypothalamic transcriptional activity[197] and impairments in metabolic parameters within the lateral septum[198]. Preconception paternal stress also modifies brain architecture in developing offspring in a sex-specific and region-specific manner[199]. In rats, the male juvenile offspring of stressed fathers exhibit reduced dendritic complexity and reduced spine density in the orbitofrontal cortex, increased apical dendritic branching in the anterior cingulate cortex and shorter basal dendrites with reduced spine density in the parietal cortex[199]. By contrast, female offspring of stressed fathers exhibit reduced dendritic complexity in the orbitofrontal cortex, increased apical dendritic branching with reduced spine density in the anterior cingulate cortex, reduced apical and basal spine density in the parietal cortex and decreased dendritic length in the CA1 region and the nucleus accumbens. These effects suggest that the emergence of altered homeostatic synaptic plasticity in offspring can be influenced by fathers in the absence of direct father–offspring interactions.

A broad range of other environmental experiences to which fathers are exposed, from exercise[200] to toxicological exposures[201,202], have also been found to impact offspring development and to drive structural, cellular and molecular changes in the brain. In addition, increasing paternal age (which may represent an overall increase in cumulative environmental exposures) alters offspring developmental trajectories in both humans and animals[203,204], and it is considered unlikely that these paternal effects are exclusively attributable to induced or age-related genetic mutations[9]. Intriguingly, many of these paternal effects persist across generations via the patriline such that male descendants of exposed fathers similarly manifest molecular, neurobiological and behavioural alterations[205–207].

These transgenerational effects have led to increased speculation that environmentally induced changes in DNA methylation, histone modifications and expression of non-coding RNAs can lead to epigenetic transmission via the paternal germ line[9]. Evidence from animal models that stress[197], nutrition[208], drugs and/or toxins[205,209] induce changes in gene regulatory mechanisms in the sperm, including altered DNA methyltransferase expression, the presence of variable DNA methylation patterns, altered histone modifications and changes in microRNA expression, support this potential route of paternal influence. Moreover, it has been shown that the transgenerational impact of fathers can be recapitulated through the direct manipulation of gene regulatory mechanisms, particularly microRNAs, within the sperm[210,211]. This suggests that induced epigenetic variation in sperm cells is predictive of offspring developmental outcomes and challenges the historical view that germ cells are not susceptible to environmental influence to the extent that they can mediate the inheritance of acquired characteristics[212]. The possibility of epigenetic transmission through germ cells also suggests that the complete erasure of chemical modifications that are acquired in previous generations (such as DNA methylation) that has been assumed to occur pre-fertilization and post-fertilization may not occur. This germline transmission may create a unique pathway to convey a father's influence, which may have evolved in species in which a direct influence through care and resource transfer is absent[213]. It remains to be determined how this pathway operates within species in which biparental care has evolved.

Evidence suggestive of germline paternal transmission of environmental conditions has raised a number of questions regarding the role of these paternal influences in shaping offspring brain and behaviour. This evidence also suggests that it will be important to carefully consider the bidirectional and interactive influences that fathers, mothers and offspring have on each other in terms of behavioural and biological plasticity. Changes in an offspring's phenotype that emerge as a consequence of maternal influences have been hypothesized to better prepare them for the challenges of the environment in which they will live and reproduce[214]. For example, in rats, reductions in maternal care as a result of maternal stress exposure lead to enhanced sexual receptivity and stress reactivity in female offspring, traits that could potentially enhance reproduction under high threat conditions by shifting the timing of reproduction earlier in the rat's lifespan and increasing the frequency of reproductive output[214]. Similar effects have been observed as a consequence of paternal environmental exposures. For example, the exposure of male rats to hepatic damage results in an improved wound-healing phenotype in their male descendants that is associated with altered chromatin changes in the sperm[215]. Drug exposure in male rats is associated with reduced drug preference in offspring, which may improve the function of the offspring by avoiding harmful levels of drug exposure[216,217]. Although sperm-mediated mechanisms for the transmission of these phenotypes have been established, we do not yet know whether there is an interactive influence of fathers on the rearing environment that might serve to modulate paternal effects. In some biparental species, the mate quality of males (as it is perceived by females) is an important predictor of offspring development[218]. Mate quality can be impacted by genetic and environmental factors that shape physical and behavioural traits that are perceived at the time of mating[219]. It has been theorized that females select male mates and invest resources in the offspring of these mates dependent on these traits as a strategy to improve offspring fitness. In rodents, it has been shown that the environments experienced by males across their lifespan can alter the physical and behavioural characteristics (including weight and stress response) of the males before mating and impact the prenatal and postnatal maternal environment (for example, by influencing maternal weight gain during pregnancy or postnatal maternal behaviour) experienced by the offspring from these matings[220,221]. These paternally associated maternal effects are associated with neuroendocrine changes in the maternal brain[220,221] and

may modulate or propagate paternal effects on offspring. Using embryo transfer, it has also been demonstrated that eliminating maternal influences impacts the direction of paternal effects (that is, it increases the likelihood of behavioural impairments in offspring)[221,222], highlighting the interplay between mothers and fathers and its long-term effects on neurobiological and behavioural outcomes in offspring. There is evidence suggestive of a paternal transmission of environmental exposures in humans[222] and non-human primates[223]; however, it will be important to carefully consider the interplay between mothers and fathers when exploring the mechanisms of cross-generational transmission in these species.

Long-term effects of paternal care

Many human studies on fatherhood describe the long-term associations between the father's behavioural patterns, hormones and neural adaptations and children's social and emotional development. Owing to methodological limitations, these studies are typically correlational only. Thus, validations of the human findings in animal models are critical to understanding the impact of paternal care on human development, although the interpretations of findings from different animal models require caution. Further insight into the great diversity of human paternal care comes from cross-cultural field studies[13,14] in which observations of fathers in their natural habitat and their daily interactions with mothers, allomothers and children can be made. Overall, studies across cultures indicate that children reared by involved fathers fare better[58,224].

Studies have shown that human fathers and mothers create comparable levels of parent–infant interactive synchrony — the online match of non-verbal patterns between parent and child during social interactions, such as shared social gaze, joint laugh, co-vocalization and mutual affectionate touch[225]. However, fathers display a unique style of child engagement that involves more stimulatory contact, attention to the environment and highly arousing exchanges ('rough-and-tumble' play)[226]. In a longitudinal observational study of maternal and paternal behaviour as children progressed from infancy to adolescence[227], it was found that a reciprocal and synchronous relationship with fathers facilitated children's anger management and strengthened their conflict dialogue skills across childhood and adolescence. This outcome echoed the results of large-cohort studies showing that fatherless children are more prone to aggression, law-breaking and conduct problems[228,229]. In cases of maternal psychopathology (for example, when mothers suffer postpartum depression), direct paternal caregiving can mitigate some of the negative effects of maternal unavailability on children's mental health and social outcomes[230,231]; thus, paternal caregiving can function as a compensatory mechanism when maternal care is deficient. Higher levels of plasma oxytocin in the father and more father–infant interactive synchrony in the first 6 months of parenting was longitudinally associated with higher levels of salivary oxytocin in the child at 4 years and better social relationships with their best friends, indicating that father–child attachment sets the stage for the child's next attachment with close friends[232].

The reorganization of the father's brain in the postpartum period shows notable individual variations that carry long-term implications for children's social–emotional growth, neuroendocrine functioning and psychiatric well-being. One study measured the brain responses of mothers and fathers during their children's infancy and defined their network coherence — the degree to which nodes function as a neural network — in three key networks of the parental brain: the core limbic network, the embodied-simulation network and the mentalizing network[233]. Families were revisited when children were 3–4 years and 6 years old. When the father's brain showed greater coherence in the core limbic network, preschoolers expressed more positive emotions and used simpler proximity-seeking strategies to manage moments of heightened arousal. When the fathers' mentalizing networks showed greater coherence, the children expressed more socialized compliance, and coherence in the father's embodied-simulation network predicted the child's later ability to use more advanced tactics to manage moments of distress[138]. Furthermore, connectivity between the mentalizing network and the embodied-simulation network in the father's brain longitudinally predicted lower cortisol stress responses in the children and reduced behaviour problems at 6 years of age[140]. In another longitudinal study, higher levels of activity in the father's caudate when their infants were 3 months old were related to more positive fathering and less behaviour problems in the children at 18–24 months[234]. These findings are beginning to demonstrate how neural activations in the caregiving network in new fathers have long-term associations with children's hormones and behaviour, paralleling the findings described in rodents.

Conclusions and future directions

The neuroscience of fatherhood is an emerging field of research that has recently become more socially relevant in light of the growing involvement of fathers in childrearing[13,17]. However, several key topics require further inquiry. We therefore conclude by describing six timely directions for future research. In BOX 2, we also highlight several current social issues that may be impacted by a better understanding of the neuroscience of fatherhood.

An integrative view of the impact of fathers on the offspring. Animal studies have typically considered mothers and fathers as factors that can be dissociated from each other using a broad range of manipulations of reproductive and rearing environments. However, the complex biological and behavioural interplay between biological parents, caregivers and offspring is often overlooked. How this interplay functions under different ecological conditions and shapes the multigenerational continuity of neural and behavioural phenotypes in humans are topics that will be of interest in future investigations.

Transmission across generations. The phenomenon of cross-generational effects associated with paternal stress and nutrition has been observed in humans; however, the mechanism remains elusive. It is only in animal models that evidence suggestive of the germline

transmission of non-mutagenic environmental effects has been generated. It will be important to leverage this evidence to create hypothesis-driven approaches to the study of fathers and their impact in humans. In addition, we may be able to use our increasing understanding of fatherhood in humans to better design animal studies on cross-generational effects.

Matricentric view of human parenting. Most research on human parenting and its impact on child development has focused on mothers. There are very few longitudinal studies on the father–child relationship that span long developmental epochs, and there is similarly little research on the unique effects of fathering on social outcomes and nearly no empirical research on the long-term impact of fathering on children's brain maturation, hormones, immune functions or genes.

How to break the cycle of abusive fathering. Large epidemiological studies, typically relying on retrospective accounts, show that boys experiencing abusive fathering tend to become abusive fathers[235]. However, we know very little about the neurobiological, genetic and molecular mechanisms involved in such cross-generational transfer of abusive fathering and, particularly, about the important question of how to break this cycle.

Compensating for the effects of father absence on human children. We still have minimal understanding of how father absence impacts human children's brain maturation. Because a father's absence often co-occurs with other risk conditions (such as poverty, single parenting, maternal depression and food insecurity), it is difficult to tease apart the effects of these different factors. It will be important to learn whether other adults in the child's life can mitigate some of the negative effects of father absence and at which ages and with what frequency of contact and kinship level these father substitutes exert their greatest impact.

Paternal behaviour across cultures. The neurobiology of paternal behaviour and its effects on the infant's brain across a variety of cultural settings are still open topics of discussion. Are these effects moulded by nuclear versus extended-family dwelling, patriarchal versus egalitarian worldviews, primary versus secondary fatherhoods and cultural norms, habits, climate and meaning systems?

The clinical view. Can involved fathering mitigate the effects of maternal depression on a child's brain and behaviour? Can introducing opportunities for facilitated father–child relationships help improve the behaviour of incarcerated fathers and reduce recidivism? What are the mechanisms implicated in such benefits? These questions require research spanning from bench to bedside, integrating human and animal studies and combining the investigation of well-functioning families with high-risk and clinical populations. Much further research is needed to provide an integrative view of fatherhood that considers the dynamic biological and behavioural interactions between individuals within the social unit of caregiving, including parents, partners, extended kin and non-kin benevolent adults that combine to moderate the long-term multigenerational impact of fathers on offspring and on society at large.

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