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Early life stress, the development of aggression and neuroendocrine and neurobiological correlates: What can we learn from animal models?

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ABSTRACT

Early life stress (child and adolescent abuse, neglect and trauma) induces robust alterations in emotional and social functioning resulting in enhanced risk for the development of psychopathologies such as mood and aggressive disorders. Here, an overview is given on recent findings in primate and rodent models of early life stress, demonstrating that chronic deprivation of early maternal care as well as chronic deprivation of early physical interactions with peers are profound risk factors for the development of inappropriate aggressive behaviors. Alterations in the hypothalamic–pituitary–adrenocortical (HPA), vasopressin and serotonin systems and their relevance for the regulation of aggression are discussed. Data suggest that social deprivation-induced inappropriate forms of aggression are associated with high or low HPA axis (re)activity and a generally lower functioning of the serotonin system in adulthood. Moreover, genetic and epigenetic modifications in HPA and serotonin systems influence the outcome of early life stress and may even moderate adverse effects of early social deprivation on aggression. A more comprehensive study of aggression, neuroendocrine, neurobiological and (epi)genetic correlates of early life stress using animal models is necessary to provide a better understanding of the invasive aggressive deficits observed in humans exposed to child maltreatment.

1. Introduction

Positive relationships between parent and child and among peers are important for appropriate social, emotional, and cognitive development. By contrast, exposure to early social deprivation or trauma, including child and adolescent abuse and neglect, can have detrimental effects on the normal development of various neuroendocrine and neurobiological systems and can cause structural and functional brain alterations [56,116]. These brain alterations may play a significant role in the emergence of social problems or even psychiatric disorders. Indeed, humans exposed to child maltreatment are at increased risk for the development of conduct disorders, personality disorders, major depression, post-traumatic stress disorder, schizophrenia, and anxiety disorders [2,36,57,77,114,144]. This broad variety of psychopathologies as well as the high rate of comorbid disorders in maltreated children suggests that child maltreatment is a non-specific risk factor for multiple forms of psychopathology [4,18], making it more difficult to find common neuroendocrine and neurobiological correlates of early life stress. This is also due to the fact that early life stress is a general term that encompasses a wide variety of different types of early life stress that may vary in length, severity and age of onset. In this review, the term early life stress is used to refer to a period of severe and/or chronic social deprivation or trauma occurring early in postnatal life. Details on type, length, severity and onset of each of the different early life stressors that appear in this review will be specified and discussed in the respective paragraphs.

Importantly, aggression is one of the core symptoms that occur in most, if not all, of the above-mentioned disorders [89,95,99,138,145,165,311,332]. Moreover, compelling evidence from multiple studies demonstrates that early life stress significantly contributes to the development of excessive and impulsive aggression [11,69,74,85,125,179,183,338]. Nonetheless, the onset, course, and psychopharmacology of aggression in humans showing maladaptive aggression are less well known. Methodological limitations might be one of the main reasons for this. The utilization of relevant animal models of early life stress is an essential alternative in gaining insights in the impact of different types of early postnatal stressors on the development of aggression and its neuroendocrine and neurobiological correlates.

Aggression is expressed by virtually all mammalian species and is of vital importance for the survival of the individual. There are qualitatively distinct subtypes of aggression. In humans, a distinction is made between controlled-proactive–instrumental–predatory aggression and impulsive–reactive–hostile–affective aggression

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[323]. The former subtype of human aggression may show parallels with *offensive aggression* in animals, a behavior mostly expressed by adult males when competing for or protecting resources and utilities like food, territory, and mating [22]. The latter subtype of human aggression may show parallels with *defensive aggression* as displayed by animals that are attacked by a conspecific or by a predator [22,100]. Additional subtypes of aggression in animal research include: *play-fighting*, expressed mostly at juvenile age and is essential for the appropriate development and use of adult aggression [235,239]; *maternal aggression*, expressed by females to protect their young against potentially threatening intruders [184]; and *predatory aggression*, expressed by animals to hunt prey for food [231]. As these types of aggression are functionally and phenotypically different, it is likely that underlying neuroendocrine and neurobiological circuitries are different as well. In this review, the main focus will be on *male offensive and defensive aggression*. Aggression between two conspecifics involves risks (e.g. serious wounding) for both the recipient and perpetrator. As a result, the constraint of aggressive behaviors is equally important as the expression of aggressive behaviors. Aggression is a ritualized behavior in social species and is signaled in advance to offer the weakest one to withdraw. Each society, troop or colony has its species-specific rules for the expression of aggressive behaviors. It is important to note that aggression in itself is an adaptive behavior. However, when species-specific rules are disregarded or when aggression occurs out of context, aggressive behaviors can become inappropriate or pathological and may eventually turn into violence.

The high prevalence of high and inappropriate aggression in humans exposed to child maltreatment warrants investigation into its biological foundation. This review will discuss recent findings in preclinical research, in which the link between chronic early social deprivation (deprivation of maternal care and/or deprivation of early physical interactions with peers) and disturbances in aggression (mostly male offensive/defensive aggression) and their underlying neuroendocrine and neurobiological pathways were investigated in non-human primates and in rodents.

2. Link between early social deprivation and aggression in animal models

Diverse models of early social deprivation have been developed in non-human primates and in rodents. These models are briefly introduced and main findings on social and emotional alterations, especially in relation to changes in aggressive behaviors, are discussed.

2.1. Non-human primate models of early social deprivation

Most non-human primate species are highly social animals living in large groups with moderately stable social organization and clear matriarchal dominance hierarchies. The mother–infant relationship is very intense and maternal care-giving spans a considerable period of infant and juvenile development. The high amount of physical contact with the mother is, apart from warmth and nutrition, important for the infant's overall maturation, as it provides a sense of security and constraints physiological and behavioral responses to stressful stimuli. Interactions with the mother, but also with peers and other members of the group, is essential for the development of social skills. Disruption of this early contact with the mother and/or other members of the group can have severe consequences for the development of these social skills.

2.1.1. Infant abuse and neglect

The closest model of human child maltreatment is the spontaneous occurrence of infant physical abuse and neglect among non-human primates [193]. In large captive groups of rhesus monkeys and pigtail macaques, 5–10% of the infants born are subjected to physical abuse or neglect by their mothers [195]. Abusive mothers were more aggressive and less affiliative toward other adult group members and were less often approached by other individuals than non-abusive mothers [191]. This pattern of anti-social behaviors suggests that motherhood is more stressful for abusive than for non-abusive mothers, or that abusive mothers are more vulnerable to stress, which subsequently affects their parenting style. In pigtail macaques, infant abuse was most frequent shortly after stressful social situations such as intra-group aggression or infant kidnapping [189,192]. Moreover, Japanese macaque abusive mothers have high anxiety (indicated by their behavioral response to interruption of contact with their infants) and their abusive behavior could be reduced by treatment with anxiolytic drugs [300]. These findings suggest alterations in emotional regulation in abusive mothers. This may also explain why periods of violent abuse towards infants are alternated with protective and attentive maternal care [191]. Interestingly, violent and abusive behaviors towards infants are more likely to occur within certain families of non-human primates [190], which is a result of early experience rather than genetic inheritance [197]. This suggests that, at least in females, early abuse and neglect induces long-lasting alterations in aggressive and emotional behaviors, which may comprise a risk factor for the development of maladaptive behaviors, especially during stressful and challenging periods, like motherhood.

Despite its relevance as a model for child maltreatment in humans, data on the developmental impact of infant physical abuse and neglect in non-human primates are limited. Infant maltreatment alters the early behavioral development, as reflected by the higher expression of anxiety and irritability (distress calls, scratching, tantrums, screams), and delayed and altered social development (longer dependence of mother, less exploration and play-fighting, more solitary play) [194,196,200,208]. Although perhaps the most interesting model of child maltreatment, the effects of infant abuse and neglect on aggressive behaviors in *adult male* non-human primates have not been characterized yet.

2.1.2. Variable foraging-demand

In the early 1980s, Rosenblum and Paully developed the variable foraging-demand model in bonnet macaques [251]. In this model, nursing mothers were exposed to unpredictable foraging-demand conditions, which irregularly reduced the time the mother could respond to and spend with her infant. This resulted in insecure and unstable mother–infant attachment patterns compared with infants raised by mothers that lived in stable low- or high-demand environments. Macaques raised under variable foraging-demand conditions showed sustained clinging to mother and lower levels of play-fighting at infant age and were less socially competent as adults as reflected by low affiliative social engagement, social subordination when placed in new groups, and avoidance of antagonistic encounters compared with predictably low- or high-demand reared macaques [5,6,252]. The finding that the variable foraging-demand condition has a higher impact than the high-demand condition is somewhat surprising. It suggests that it is the unpredictable parenting time rather than the reduced parenting time that plays a major role, which in itself might be worthwhile investigating in more detail. The variable foraging-demand model demonstrates that disturbances of early mother–infant attachment relationships result in a socially withdrawn behavioral profile associated with low aggression and low social competence.

2.1.3. Early social deprivation

Early chronic separation from the mother and/or from conspecifics has been the most widely used model of early adverse experiences in non-human primates [289]. The severity and age of

separation largely determined the outcome on social and emotional development of the offspring.

The most severe early separation model consists of tactile social isolation during at least the first 6 months of life. These studies started in the 1960s by Harlow and co-workers and were the first to demonstrate the devastating consequences of social isolation on normal development [109]. Isolated infants showed a total lack of exploration and social interaction, extreme high levels of fear, freezing in response to aggression of other animals, and self-directed and stereotypic motor activity [109,110,203,212,280]. As adolescents and adults these monkeys exhibited excessive and inappropriate aggression towards other monkeys. Reversal of most of these early social isolation-induced behavioral deficits was observed when infants were exposed to a normal social environment within the first 6 months of life [50,111]. This social isolation model may mimic parental loss and severe early social deprivation as experienced by children reared in orphanages [88]. The lack of a one-to-one relationship with a primary caregiver is the major cause of disturbed social and emotional development in children in institutional care [137]. Similar to non-human infants, the extent of recovery in these orphans is largely determined by the age at the time of move from the orphanage to a beneficial family environment [226,275].

Additional studies in non-human primates have examined the effects of less severe variations in early social isolation. These models include intermittent tactile isolation of infants from their mother, peers and social group at birth for up to 12 months, mother-only rearing for up to 12 months, and peer-only rearing from birth for up to 6 months. Monkeys reared under these socially-deprived conditions show significant alterations in social functioning. For example, monkeys that were isolated and nursery-reared for the first 2 months showed increased aggressive behaviors and decreased affiliative behaviors compared with socially-reared monkeys when pair-housed with another monkey [341]. Mother-only reared monkeys showed higher rates of submission and stereotypic behaviors than socially-reared individuals and reacted with agonistic behavior to non-threatening social situations [149]. This latter model suggests that deprivation of physical contact with peers induces incompetent social behaviors.

The most commonly used early social deprivation paradigm in non-human primates is peer-rearing from birth. In this paradigm, infants are separated from their mothers at birth, hand-reared in a multi-animal nursery for the first month, and then reared with same age peers until 6 months of age. After this period, peer-reared monkeys are moved into larger groups that also contain mother-reared age-mates. Although the peer-reared monkeys readily develop strong attachment bonds to each other, they lack the secure and comfort base normally provided by their mother. As a consequence, peer-reared infant monkeys are more fearful and behaviorally inhibited when exposed to unfamiliar objects or peers and display extreme behavioral reactions to brief social separation (higher levels of self-directed behaviors, more distress vocalizations, and more passive behaviors) compared with mother-reared monkeys [289,290]. Importantly, early peer-rearing induced also changes in aggressive behaviors as shown at juvenile age in the context of play-fighting (also known as rough-and-tumble play) and at adolescent and adult age as impulsive, excessive and inappropriate aggression towards other members of the group [124,289,290]. These social behavior deficits may result in a lower social rank as observed in peer-reared monkeys compared with mother-reared monkeys [15]. Four-year old peer-reared subjects that showed excessive aggression also had higher rates of alcohol consumption than mother-reared subjects [118,124]. This latter observation is of interest, as in men, impaired impulse control and violent and anti-social behaviors are often associated with excessive alcohol consumption [117]. Together, early deprivation of maternal care is an important risk for the pathogenesis of aggressive behaviors in rhesus monkeys.

2.2. Rodent models of early social deprivation

Pups of most rodent species are poorly developed at birth and require intensive care by the dam to ensure homeostatic control and normal sensory and motor development. Later on, additional interactions with conspecifics is required for the development of appropriate social behaviors. Manipulations of dam–pup interactions as well as of early interactions with conspecifics can serve as useful tools to investigate the importance of the early social environment for the development of social, emotional, and cognitive systems. Here, only those rodent models in which effects of postnatal stress on aggressive behaviors were studied are discussed.

2.2.1. Maternal separation

Different forms of maternal separation have been studied in rats and mice, including early handling (15 min separation of the litter from the dam per day across several postnatal days) [173,176], single maternal separation (single 24 h separation period of the litter from the dam) [170,174,310], repeated maternal separation (the litter is separated from the dam for several hours per day across several postnatal days) [101,241,339], and early deprivation (pup is separated from dam and litter for several hours per day across several postnatal days) [244,256]. These postnatal manipulations have been compared with either non-handling or animal facility rearing as control condition. Non-handling consists of a complete absence of any external stimulation of dam and litter until weaning [172,214]. In animal facility rearing, the dam and the litter experience the disturbance of routine husbandry, including cage cleaning [244]. Despite the use of different control conditions, each having its pros and cons [for discussion, see [169,245]], these different postnatal manipulations have yielded important insights in the effects of early life stressors on changes in behavioral and brain development.

Among the above-mentioned models, repeated maternal separation is the most widely used and well-established model and will therefore be discussed in more detail. Maternal separation consists of the separation of the litter from the dam for 3 h per day during the first 2 weeks of life [114,241,339]. Accumulating evidence shows that maternal separation is associated with long-lasting alterations in behavioral, emotional and cognitive functions [101,160,230,269]. For example, rats and mice exposed to maternal separation and tested in adulthood showed decreased exploration of a novel environment, decreased time on the open arms of the elevated plus-maze, increased freezing in an open-field and increased acoustic startle responses, which are all indicative of increased non-social fear- and anxiety-related behaviors [29,131,141,339]. Moreover, maternally separated rats showed increased floating behavior in the forced swim test, which may reflect behavioral despair or depressive-like behavior [3,187,315]. Thus, maternal separation induces behavioral changes that resemble symptoms associated with anxiety and depression. Chronic antidepressant treatment with either paroxetine or desipramine was found to reduce anxiety and depression-like behaviors in maternally separated rats [131,187], supporting the ethological relevance of maternal separation as model of mood disorders.

Only recently, the possible link between early life stress and the development of aggression was studied in this animal model, demonstrating species-dependent consequences of maternal separation on aggression. In male Wistar rats, exposure to maternal separation (3 h/day, day 1–14) induced an increase in aggressive behaviors at juvenile (play-fighting) and adult (intermale aggression) age [315,321]. Play-fighting is an essential behavior for the

development of adequate adult social behaviors [213,236,313] and consists of behavioral patterns related to adult aggressive behaviors [236,239]. At juvenile age, maternal separation increased the number of attacks towards the nape of the neck (more than 70 attacks, an almost two-fold increase), decreased the number of supine behaviors (a submissive play behavior), and induced the emergence of offensive pulling and biting (a behavior hardly expressed by controls) towards an unknown age-matched play partner during the 10-min resident-intruder test [321]. In adulthood, maternally separated rats showed significant increases in key elements of aggression, including lateral threat, offensive upright and keep down, when being exposed as a resident to an unknown male intruder rat [315]. These data indicate that maternal separation promotes the expression of aggressive behaviors in male rats across development. In contrast to male rats, maternal separation of C57Bl/6 mice induced a decrease in intermale aggression, as shown by longer attack latencies in maternally separated adult males compared with control males [316]. However, maternal separation of C57Bl/6 mice induced an increase in maternal aggression towards a male CD1 intruder mouse during the first week of lactation [316]. Taken together, maternal separation manifests long-lasting changes in aggressive behaviors, in which the direction of change may vary according to the species or sex. The effects seen in the maternal separation model might mimic some emotional and behavioral aspects of child neglect in humans. Future use of different species and different social settings may give more detailed knowledge of the effects of maternal separation on aggressive behaviors.

2.2.2. Post-weaning social isolation

In most laboratories, post-weaning social isolation is performed by housing rat or mouse pups in individual cages from the first day of weaning from the dam (between postnatal day 21 and 28) for a period of 4–8 weeks. Isolated rats or mice are normally reared in a room with other isolated-reared or group-housed rats or mice. Thus, isolation-reared rats or mice have visual, auditory and olfactory contact with other conspecifics, but they are restricted from any form of physical interaction with their conspecifics. Interestingly, post-weaning social deprivation has more devastating effects than social isolation at adult age. Clearly, normal social, emotional and cognitive development requires physical interactions during the developmental period until early adulthood. Post-weaning social isolation was shown to induce changes in a wide variety of non-social behaviors, including hyper-reactivity to a novel environment, impaired prepulse inhibition of acoustic startle, increased ethanol intake and increased anxiety [for reviews, see [87,166]]. Moreover, post-weaning social isolation altered several social behaviors. For example, post-weaning socially-isolated males showed reduced levels of play-fighting and social grooming [324], reduced submissive behaviors towards residents [304], and increased aggressive behaviors towards conspecific in dyadic interactions or when being placed in a colony [19,55,185,301,346]. A recent study showed that the high level of adult aggression displayed by socially-deprived male rats is associated with abnormal attack patterns towards intruders in the resident–intruder test. Here, socially-deprived rats showed an increase in attacks aimed at vulnerable body parts of the intruder (head, throat, and belly) and an increase in the attack/threat ratio [297]. This pattern of violent and abnormal aggressive behaviors suggests that post-weaning social deprivation of male rats induces robust disturbances in adult social functioning. More detailed knowledge about the development of aggressive and other social behaviors is important to understand the mechanisms through which early physical interactions with peers as well as its deprivation shapes later social behaviors. In particular the lack of early social experience in the form of juvenile play-fighting is likely to play a crucial role in the development of inappropriate social behaviors [304]. Although it can be debated whether post-weaning social isolation over a period of several weeks is a suitable model of child neglect, it clearly induces an important and interesting phenotype, which may correspond to certain forms of violent aggression as seen in humans exposed to child maltreatment.

2.2.3. Post-weaning social deprivation

Effects of post-weaning social deprivation have been studied in male guinea pigs [261,262]. Guinea pigs live in heterosexual colonies in which they build up complex and long-lasting stable social relationships. Post-weaning social deprivation consists of taking males out of the colonies at 30 days of age, which is beyond weaning but before sexual maturity, and house them individually or with a female until adulthood. Under these conditions, male guinea pigs are deprived of exposure to agonistic interactions with older dominant males. These early interactions seem to be crucial for the development of appropriate social skills. Indeed, when two males reared either single or with one female were confronted with one another at adult age, they were, unlike colony-reared males, unable to form a stable dominance relationship due to the display of high and escalating levels of aggressive behaviors [258,259]. Moreover, socially-deprived males were frequently involved in threat displays and fighting when introduced into a colony [260]. In contrast, colony-reared males easily adjust to new social situations (e.g. when being introduced into an unfamiliar colony) as they gradually integrate into new social networks [261,262]. Thus data demonstrate that, in guinea pigs, early social interactions are crucial for the acquisition of social skills needed to fit into stable social structures and to adapt to unfamiliar conspecifics in a non-aggressive way. Early social deprivation and hence, a lack of early male–male agonistic interactions, prevents the acquisition of these social skills resulting in high and inappropriate aggressive behaviors.

2.2.4. Post-weaning social subjugation

Social subjugation (or social defeat) is a natural stressor in most social animals. Similar to the wild, adult rats and hamsters in laboratory settings will defeat intruders placed into their home cage. This natural feature is used in the social subjugation paradigm. Post-weaning social subjugation consists of placing a juvenile male in the home cage of an aggressive adult male for a 30 min period between postnatal days 26–40 (which corresponds with prepuberty in rats) or days 28–42 (which corresponds with puberty in hamsters). During these sessions, experimental animals are exposed to aggressive behaviors of the adult conspecific. Adult male Long–Evans rats exposed to post-weaning social subjugation showed an increase in aggression towards a larger intruder [51]. Adult Syrian golden hamsters exposed to post-weaning social subjugation showed enhanced and atypical aggression (shorter attack latency, higher number of attacks, lower number of retreats) towards intruders [64,81,82,344]. Moreover, social subjugation was found to accelerate the development of aggressive behavior, as subjugated hamsters initiate adult-like responses an earlier age [344]. This accelerated development was particularly apparent in those hamsters showing less submissive behaviors when confronted with the aggressive adult during the daily social subjugations [343]. Thus, social subjugation of rats or hamsters during (pre)adolescence enhances aggressive behaviors. Interestingly, social subjugation during adulthood is rather associated with a consistent absence of aggressive behaviors and a marked increase in submissive behaviors when exposed to conspecifics [65,128,242,246,303]. These data clearly demonstrate that social subjugation during the developmental period, in comparison with adulthood, can have distinctly different effects on aggressive behaviors. Post-weaning social subjugation of rats or hamsters

might be a useful animal model of adolescent abuse in humans. The adolescent period is characterized by pronounced remodeling of the brain, which is required to achieve social and sexual maturity [286]. Exposure to social stressors, including physical abuse may have a severe impact on the development of social skills and may result in the expression of inappropriate aggression. Adolescent physical abuse occurs at a high incidence rate in humans and is a serious risk factor for the development of psychopathologies associated with violence and anti-social behaviors [93,142,237,265,276].

2.3. Summary of early social deprivation models and aggression

The above-mentioned studies in non-human primates and rodents convincingly demonstrate that disruptions of the early mother–infant relationship as well as disruptions of early interactions with conspecifics are profound risk factors for the development of inappropriate aggressive behaviors later in life (see Table 1).

These findings underscore the importance of appropriate child care. In non-human primates, secure early mother–infant attachment is necessary for optimal psychosocial development and involves a high amount of physical contact between mother and infant [155]. In rodents, tactile stimulation of pups by the mother is required for normal physiological and behavioral development [157]. In fact, the finding of naturally occurring variations in tactile stimulation of pups by Long Evans hooded rat mothers has been the basis for a set of studies by Meaney and colleagues demonstrating that different levels of tactile stimulation during the first week of life program adult stress coping abilities [216] (see Section 4.2). These findings may imply that deprivation of early tactile stimulation may be one of the key factors that underlies early life stress-induced changes in aggressive behaviors (see Fig. 1A). The importance of early physical contact was also demonstrated in humans. For example, isolated premature human babies receiving supplemental tactile stimulation in the form of massage showed marked gains in weight and in behavioral development [157]. Moreover, massage therapy was found to lower aggression in

Table 1
Effects of early life stress in humans, non-human primates and rodents on aggression, HPA, vasopressin and 5-HT parameters. See text for detailed explanations.

	Aggression	HPA axis	Vasopressin (VP) system	5-HT system
Humans	↑ **Male/female aggression**	↑Cort in infancy	↓ VP in urine	↑ 5-HT activity in infancy
		↑/↓ Cort in adulthood		↓ **5-HT activity in adulthood**
Non-human primates				
Infant abuse and neglect	↑ **Maternal aggression**	↑ Basal Cort (1 month of age)	n.d.	↓ **CSF 5-HIAA (infant females)**
	Male aggression n.d.	↓ Basal Cort (3 month of age) ↓ ACTH, ↑ Cort to CRH challenge (up to 3 years)		↑ **CSF 5-HIAA (adult females)**
Variable foraging-demand	↓ Male aggression	↑ CSF CRH	n.d.	↓ Response to 5-HT1/2 agonist
		↓ CSF Cort		↑ CSF 5-HIAA in adulthood
Social deprivation	↑ Male aggression	↓ Cort response to soc. isolation	Changes in central V1aR	n.d.
Mother-only reared	↑ Female aggression	n.d.	n.d.	n.d.
Peer-reared	↑ **Male aggression**	↓ Basal ACTH ↓ HPA response to soc. stimuli/isolation ↑ HPA response to soc. separation	n.d.	↓ **CSF 5-HIAA** ↓ 5-HT transporter binding
Rodents				
Maternal separation				
Rats	↑ **Male aggression** ↓ Maternal aggression	↑ HPA response to non-soc.stimuli	↑ **Hypothalamic VP (males)**	↓ **5-HT IR in AH (males)** ↓ 5-HT responsiveness (males) ↑ 5-HT turnover brain stem (males) ↓/ = [5-HT] in PFC, Hippo (males)
Mice	↓ **Male aggression** ↑ Maternal aggression	↑ HPA response to non-soc.stimuli	↑ **Hypothalamic VP (males)** No change in hypothalamic VP (females)	
Post-weaning social isolation (Rats)	↑ Male aggression	↑ HPA basal, response to non-soc.stimuli ↓ HPA basal, response to non-soc.stimuli ↑ Cort to CRH challenge ↓ Suppression of Cort to Dex/CRH test	No change in hypothalamic VP	↓ 5-HT responsiveness in Hippo ↑ 5-HT responsiveness in NAcc ↑/↓ 5-HT responsiveness in PFC ↑ 5-HT1A autorec. function in DR
Post-weaning social deprivation (Guinea pigs)	↑ **Male aggression**	↑ **HPA stress response**	n.d.	n.d.
Post-weaning social subjugation				
Rats	↑ Male aggression	↑ HPA basal		
Hamsters	↑ **Male aggression**	↓ Cort response to soc.stimuli	↓ **Hypothalamic VP (*)**	↑ **5-HT IR in AH (*)**
Overall hypothesis:	↑ Male aggression	↑ HPA activity in infancy ↑/↓ HPA activity in adulthood	↑ Central VP	↑/↓ 5-HT activity in infancy ↓ 5-HT activity in adulthood

An increase in aggression can be high, excessive, or inappropriate compared with control groups. AH, anterior hypothalamus; CRH, corticotropin releasing hormone; Cort, cortisol/corticosterone; CSF, cerebrospinal fluid; DR, dorsal raphe, Hippo, hippocampus; NAcc, nucleus accumbens; PFC, prefrontal cortex; n.d., not determined; * measured immediately in response to aggressive encounter, no basal groups included. Text marked bold: direct link between that parameter and aggression.

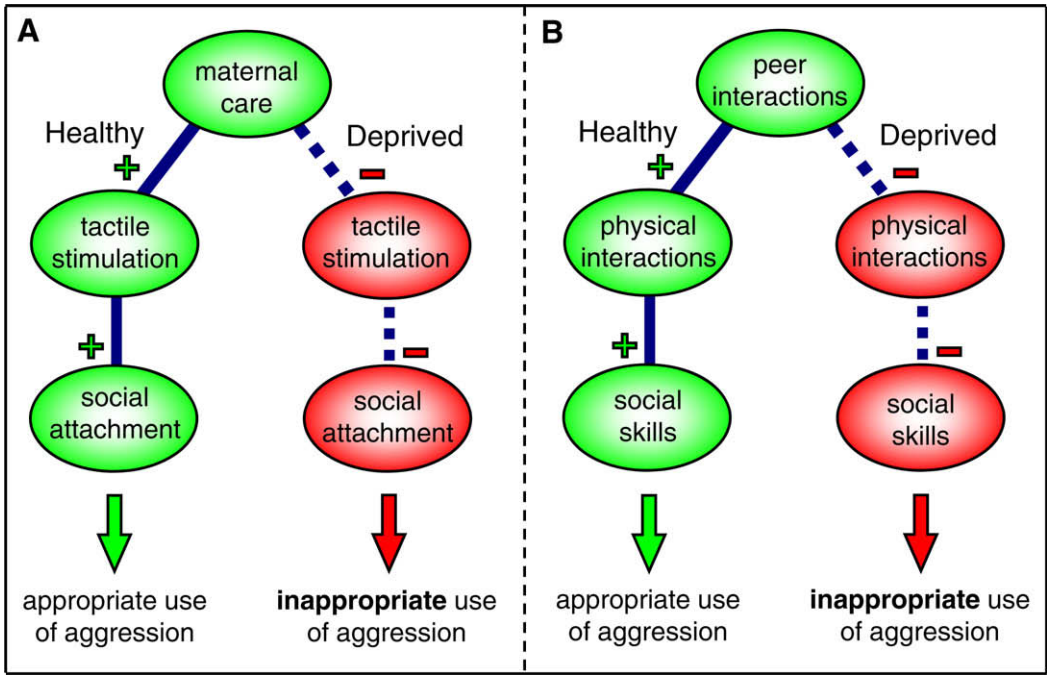

Fig. 1. (A) The mother–infant relationship is very intense and consists of a high amount of tactile stimulation. This tactile stimulation provides a form of secure social attachment and is required for normal development of brain and behavior, including the appropriate use of aggression. Deprivation of early tactile stimulation in animal models of early life stress (primates: infant abuse and neglect, variable foraging-demand, social isolation, peer-rearing; rodents: maternal separation) might be one of the key factors underlying the observed inappropriate use of aggression. (B) Physical interactions with peers, particularly in the form of juvenile play-fighting, are essential for the development of social skills and social competence. Disruption of this early physical contact with peers in animal models of early life stress (primates: social isolation; rodents: post-weaning social isolation, post-weaning social deprivation) is likely to play a crucial role in the development of inappropriate aggressive behaviors.

children and in violent adolescents [67,84,94,325]. It is tempting to speculate that in humans exposed to child maltreatment, deprivation of physical contact and physical affection may have played an important role in the development of high and inappropriate aggression. Although further research is required, intervention with massage could be a promising therapy to reduce aggression in humans.

It was further demonstrated that early physical interactions with conspecifics are essential for the appropriate development of aggressive and other social behaviors. Early interactions with peers allow juveniles to practice the proper settings, the intensity and the skilled use of aggression [286,304], thereby enhancing their social skills and competence (see Fig. 1B). Likewise, peer interactions among humans positively contribute to the development of social interaction skills and social competence and is associated with suppressed aggressiveness [21,163]. More research is needed to understand the mechanisms through which early social interactions as well as deprivation of early social interactions shape aggressive behaviors.

Interestingly, early life stress-induced alterations in aggression were particularly observed during acute stressful situations, like exposure to an unknown intruder or new cage-mate, or placement in a new colony. Similarly, non-social behavioral changes related to anxiety and depression-like behaviors were especially apparent upon exposure to an acute stressful challenge, such as acute social isolation or placement in a novel environment. Accordingly, early negative rearing conditions may have primarily altered the regulation of emotional and stress responsiveness (see 3.1 "Hypothalamic–pituitary–adrenocortical axis"), which is accompanied by an altered expression of aggressive behaviors in a challenging social context.

2.3.1. Adaptation versus pathology

In general, the constraint of aggressive behaviors is of vital importance. Yet, a society, troop or colony without any aggression is likely impossible. In fact, as long as aggression has advantages for the individual, it will be present. To determine whether early life stress-induced changes in the level and/or form of aggression are functional adaptations or are likely to result in the development of a pathology, the following issues need to be addressed.

The severity and the probability of the early life stressor and thus the likelihood that behaviors differ from the norm should be taken into account in defining adaptation or pathology. For example, chronic social isolation/deprivation (primates, rodents) or peer-rearing (primates) are severe disruptions of normal rearing conditions that likely challenge species-normative patterns of social development. These severe forms of early life stress induced an inappropriate and high expression of aggressive behaviors, which might have important consequences for the health and survival of the individual. Indeed, rhesus monkeys in the wild who demonstrate excessive impulsive and aggressive behaviors were more likely to face premature death when being a male [122,124,217] or hold a low social dominance and show abusive maternal behaviors when being a female [121,291]. Dyadic encounters of post-weaning socially-deprived guinea pigs resulted in escalated fighting, a situation that did not occur in socially-experienced guinea pigs [262]. Actually, these fights were terminated in advance by the investigator to prevent irreversible injuries and possibly death [262]. In humans, there are indications that high aggression as a result of early childhood trauma correlates with increased suicide attempts [274]. These findings suggest that severe forms of early life stress associated with inappropriate and high aggression may enhance the risk for the development of pathological behaviors and reduce the survival of the individual.

On the other hand, animal models using mild, natural, or less prolonged forms of early life stress are less likely to cause dramatic changes in behavior leading to pathology. In fact, mild forms of developmental stress may be adaptive by enhancing stress coping abilities in later life. For example, mild forms of early maternal

rejection in macaques promote the offspring independence and the development of low social anxiety [277]. Exposure to brief stressful experiences at juvenile age was associated with better cognitive performance in the Morris water maze [9]. Offspring receiving a low amount of maternal licking and grooming showed a better contextual fear memory than offspring receiving a high amount of maternal licking and grooming [35]. These early life stress-induced emotional and cognitive alterations may prepare the individual for a potential stressful environment later on. Similarly, alterations in aggressive behaviors as observed in less severe forms of early life stress, such as maternal separation and post-weaning social subjugation, might be interpreted as adaptations to a more harsh environment in which more social competition is likely to occur. Despite several indications that mild forms of early stress can be adaptive, direct evidence of beneficial effects of altered levels of aggression in animal models of early life stress is lacking so far and should be tested in future studies.

Finally, early life stress-induced changes in aggression should be placed in a broader ecological context. As suggested above, when being reared in a deprived or harsh social environment, it might be adaptive to show alterations in aggression. This is likely true when the adult social environment corresponds with the early social environment. However, when being introduced in a social environment which differs considerably from the early developmental environment, behaviors that were adaptive at first might become maladaptive with the risk of turning into a pathology. In most studies, animals are placed in a 'normal' social environment after exposure to the early life stress paradigm. Accordingly, the behavioral consequences of early life stress are measured in a social environment that may largely differ from the early developmental environment. Future studies may consider these aspects.

2.3.2. Impact of differences in social structure between species, strain or breed

An understanding of the function and characteristics of species-specific social structures is important for the understanding of the implications of early life stress on aggression. Factors to be considered include: (i) *The aggression level of a species, strain or breed*. The direction of behavioral changes upon early life stress may depend on the aggression level of the given species, strain or breed. This might explain the opposing effects of maternal separation on inter-male aggression in rats [315] versus mice [316]. Species differences in the expression and regulation of aggression as well as species differences in domestication and inbreeding effects on the level of aggression [23,58,158] may influence the outcome of early life stress on aggression. The importance of differences in social organization for the expression of aggression upon stress exposure is further demonstrated by the opposite effects of adult social isolation on aggression in mice and guinea pigs. While isolated adult mice show an increase in aggression, isolated adult guinea pigs show a decrease [25,257]. Moreover, even among closely related primate species, early social isolation induced more severe aggression and other behavioral abnormalities in rhesus compared with pigtail and crab-eating monkeys [263,264]. These results indicate the need to study the link between early life stress and aggression in several species, even if they are closely related; (ii) *Social structure and housing conditions*. The social structure of a species or strain as well as the housing conditions of both treatment and control groups should be taken into account when interpreting behavioral changes upon early life stress. There are differences in social structure between rats (live in colony and are territorial), guinea pigs (live in heterosexual colonies and bond with individual guinea pigs) and hamsters (live solitary and are territorial), which may result in a different organization of brain and behavior. Moreover, despite efforts to keep animals in semi-natural conditions (at least in the case of primates), the complexity of the social environment as found in naturalistic settings is less likely to be mimicked in laboratory settings. This may in particular apply for the housing conditions of rats and mice. With reference to the latter, field studies demonstrated that female mice rear their offspring in communal nests. Communal nesting provides the developing pup with high levels of social stimulation, which enhances its social competence. For example, male mice reared in a communal nest quickly established a dominant-subordinate relationship during a dyadic encounter, while male mice reared in a single nest needed five encounters to establish such a relationship [26]. These results illustrate that standard laboratory conditions may already represent a socially impoverished environment, which should be considered when interpreting behavioral effects of early life stress; (iii) *Reversal of aggressive behavior deficits*. Data from adoption studies in humans demonstrate that behavioral deficits observed in socially-deprived children can partly be reversed upon placement in a beneficial family environment [226,275]. Similar effects were found in studies using the social isolation model in non-human primates [50,111]. It would be of interest to investigate whether alterations in aggression as a consequence of early life stress can be reversed in other species and models, and which social conditions are required to stimulate this reversal.

3. Neurobiological correlates of early social deprivation and aggression

Primate and rodent models have indicated the importance of early social separation stress in the pathogenesis of aggressiveness. Investigating neurobiological mechanisms underlying these early life stress-induced changes in behaviors in both primates and rodents may be helpful in the search for preventative and pharmacological treatment strategies. Numerous studies have investigated neuroendocrine and neurobiological correlates of early life stress with the development of emotional and behavioral changes [for reviews, see [114,269]]. Alterations in three key systems that play an important role in the regulation of aggression are addressed below.

3.1. Hypothalamic–pituitary–adrenocortical axis

The hypothalamic–pituitary–adrenocortical (HPA) axis is one of the principle pathways to respond to a stressor. HPA axis activation consists of the release of corticotropin releasing hormone (CRH) and vasopressin from the paraventricular nucleus of the hypothalamus (PVN) into the anterior pituitary gland, where CRH and vasopressin stimulate the secretion of adrenocorticotropic hormone (ACTH) into blood. ACTH, in turn, stimulates the adrenal glands to produce and release glucocorticoids (cortisol in humans, primates, guinea pigs and hamsters; corticosterone in rats and mice). The activity of the HPA axis shows diurnal as well as hourly variations, which is important for the regulation of physiological and behavioral processes during day-night cycles and during stress exposure, respectively [350]. Glucocorticoids facilitate adaptation to the stressor through binding of the widespread glucocorticoid receptor (GR; periphery and brain) and the mineralocorticoid receptor (MR; brain) [61,210,248]. The GR and MR act as ligand inducible transcription factors activating or repressing the transcription of a wide variety of genes [136,218]. Rapid, non-genomic effects may also occur via interactions of glucocorticoids with cellular membranes or via membrane-bound GRs and MRs [108,233,288,294]. MRs promote whereas GRs inhibit neuronal excitability via the release of glutamate, at least in the hippocampus [63,143]. Ligand-bound GRs and MRs exert a negative feedback on the production of HPA axis hormones to control its activation. Actions of HPA hormones are supportive, but can become harmful when hormonal release is excessive, sustained or inadequate [62]. Indeed, disturbances

in the HPA axis responses have frequently been reported in several stress-related disorders [49,70,126,326,348].

The HPA axis also plays a key role in the regulation of aggression [153]. High HPA axis responses, often related to a state of hyperarousal, have been associated with high aggression in several psychiatric disorders, including mood disorders [207,302]. Chronically low HPA axis activity, often linked to a state of hypoarousal, has been associated with high aggression in conduct and personality disorders [206,292,309]. Thus, a hyper- as well as a hypo-active HPA axis is associated with increased aggression in psychopathological conditions. The expression of high aggression via opposing HPA axis actions is confirmed in rodent studies. Acute HPA axis activation promotes aggression in rodents, likely via fast non-genomic effects of glucocorticoids [103,104,156,221]. On the contrary, adrenalectomized rats given low glucocorticoid treatments demonstrated high and violent forms of aggression [102,105]. Thus, dysregulation of HPA hormones may contribute to the escalation of violent behavior, in particular under stressful conditions.

The HPA axis is immature at birth and its early activity can be strongly regulated by early social experiences. For example, children receiving insensitive and unresponsive care-giving showed elevated cortisol responses to mild stressful situations, while children receiving sensitive and high responsive care-giving did not [reviewed in: [293]]. Moreover, children in deprived rearing environments (such as growing up in orphanages) show marked disturbances in diurnal cortisol rhythms, characterized by a blunted peak in early morning cortisol levels followed by the absence of a decrease in cortisol levels over the course of the day [32]. Effects of child abuse/neglect are more diffuse, and have been associated with a high as well as a low HPA axis activity. Nevertheless, taken into account their current diagnosis, it seems that maltreated children with anxiety and depressive disorders generally have elevated basal cortisol levels, whereas maltreated children with conduct and aggressive disorders have low basal cortisol [reviewed in: [293]]. Thus, lack of appropriate care-giving alters the early development of the HPA axis.

Poor or absent parental care has also long-lasting effects on HPA axis function. Adults that were maltreated as children show alterations in basal cortisol levels and in HPA axis responsiveness, which can strongly vary depending on psychiatric diagnosis, current life stress and treatment [114,293,312]. For example, blunted as well elevated ACTH and/or cortisol responses to psychological/social stressors or CRH challenges have been reported in men and women with a history of child maltreatment [27,113,115,250,284]. Moreover, transitions from hypercortisolism in maltreated children to hypocortisolism in adulthood have been observed [see [293]], suggesting an altered maturation of the HPA axis under the influence of early adversity. These early life stress-induced alterations in HPA axis function, although initially adaptive, might have detrimental effects on aggressive and emotional behaviors on the long term.

3.1.1. Non-human primate models of social deprivation

Non-human primates exposed to social deprivation during infancy also exhibit alterations in HPA axis function [reviewed in [175,270]]. For example, infant rhesus monkeys exposed to *maternal abuse and neglect* had higher basal morning cortisol levels compared with non-abused control infants during their first month of life, which was positively correlated with aggression, anxiety, and distress vocalizations [209]. However, at 3 months of age, maltreated infants had lower basal cortisol levels and an overall lower HPA response to maternal separation than controls. Abused infants further exhibited a greater cortisol response, but a blunted ACTH response, to a CRH challenge than non-abused control infants across the first 3 years of life [272], suggesting alterations in sensitivity at pituitary and adrenal level. These findings indicate that the HPA axis development is affected by early adversity in rhesus monkeys and parallels findings from studies of child maltreatment in humans. Longitudinal studies are required to investigate whether these changes in HPA axis are carried into adulthood and if so, whether they are linked to alterations in aggressive behaviors.

Non-human primates reared under *variable foraging-demand* conditions exhibited elevated cerebrospinal fluid (CSF) CRH concentrations compared with primates reared under constantly low or high foraging-demand conditions [44,46]. The heightened CRH levels were, however, accompanied by relatively lower CSF cortisol levels [44]. This dissociation between increased CRH and decreased cortisol levels may resemble the neuroendocrine profile observed in patients with posttraumatic stress disorder [349], a disorder often associated with a history of childhood maltreatment [279,284,322].

Non-human primates that have been completely deprived from maternal care during infancy exhibit changes in HPA axis function under baseline conditions as well as in response to acute stressors. *Early social deprivation* of infant rhesus monkeys (nursery-reared with intermittent peer experience) was found to reduce the cortisol response to a 30-min social isolation compared with mother-reared monkeys [31,282]. Six-month old *peer-reared* monkeys had lower baseline levels of ACTH, but similar baseline levels of cortisol compared with mother-reared monkeys [37]. Exposure to a stressor (movement to new cage, social separation, observing the capture and removal of another monkey in an adjacent cage, housing with unfamiliar age-mates) resulted in a blunted ACTH and/or cortisol response in peer-reared compared with mother-reared monkeys [37,39,219]. The HPA hyporesponsiveness may reflect lower attachment bonds in socially-deprived monkeys. On the contrary, others found increased CRH and cortisol responses to social separation in 6-month old peer-reared rhesus monkeys compared with mother-reared rhesus monkeys [76,118,120]. This increased HPA response to social separation was associated with the display of more extreme behavioral reactions (higher levels of self-directed behaviors, more distress vocalizations, and more passive behaviors) in peer-reared monkeys [289,290]. These ambiguous findings in HPA axis reactivity may be due to a combination of factors including differences in procedures, type and severity of the stressors, and genetic risk factors (see Section 4.1). To clarify the discrepancy in effects of peer-rearing on HPA axis function, it would be important to investigate the link between HPA axis reactivity and the occurrence of excessive aggression in peer-reared monkeys. So far, only indirect evidence exists for such a link. Here, high cortisol responses to social separation [76,118] as well as high levels of aggression [118,124] were associated with high rates of alcohol consumption in peer-reared monkeys. These preliminary findings suggest that changes in aggression and alcohol consumption due to a lack of maternal care may be mediated, at least in part, by developmental changes in the activity of the HPA axis.

3.1.2. Rodent models of social deprivation

In rodents, the impact of *maternal separation* on HPA axis parameters has extensively been studied [131,141,222,241,315,339]. Maternal separation (more than 2 h) disrupts the so-called stress hyporesponsive period, which last from postnatal day 1–12, resulting in elevated plasma corticosterone concentrations [60,278]. Exposure to 3-h daily maternal separation increased early dark phase corticosterone levels in 35-day old juvenile male rats, which was associated with an increase in aggressive behaviors during play-fighting [321] (Fig. 2). The higher levels of corticosterone may reflect an accelerated maturation of the HPA axis. Indeed, early dark phase corticosterone levels were found to rise with age, with highest levels during adolescence (Fig. 2). This corresponds with findings in humans, where serum cortisol levels increase dur-

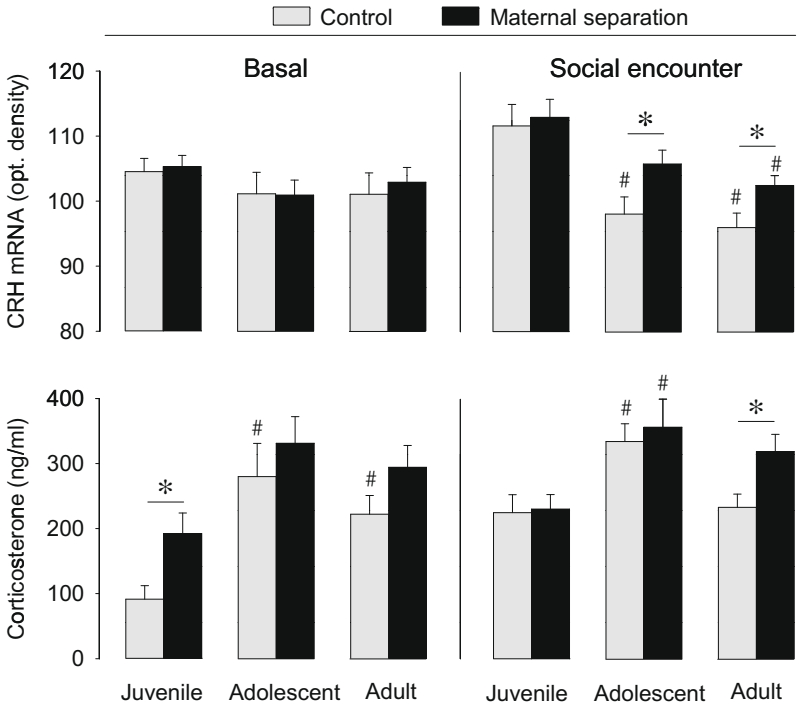

Fig. 2. Effects of maternal separation of male Wistar rats across development on CRH mRNA expression in the PVN and plasma corticosterone concentrations (obtained during the early dark phase) under basal conditions or 1 h after a 10-min exposure to an age-matched male rat (social encounter). CRH mRNA expression in response to a social encounter decreased with age ($F_{(2,41)} = 15.3$, $p < 0.001$) whereas corticosterone levels increased with age (basal: $F_{(2,56)} = 5.84$, $p < 0.05$; social encounter $F_{(2,56)} = 8.40$, $p < 0.005$) with highest levels during adolescence. Maternal separation induced an increase in CRH mRNA expression in response to a social encounter ($F_{(1,41)} = 6.94$, $p < 0.05$) at adolescent and adult age, and in corticosterone (basal: $F_{(1,56)} = 5.84$, $p < 0.05$) at juvenile (basal) and adult (social encounter) age. Juvenile, 5-weeks of age; adolescent, 8-weeks of age; adult, 16-weeks of age. Data are means + S.E.M. $^{*}p < 0.05$ versus control, $^{\#}p < 0.05$ versus respective juvenile group, ANOVA followed by Bonferroni *post hoc* test.

ing development and peak at puberty [72,140,151]. In other words, levels of glucocorticoids are lowest at early age. This may functionally be important by protecting the developing brain from the potentially negative effects of chronic high circulating levels of glucocorticoids on brain structure and plasticity [273,314]. This protecting mechanism is clearly disrupted by exposure to maternal separation, which may have enduring effects on HPA axis function. Indeed, maternal separation has been associated with long-term alterations in HPA axis parameters, especially in response to an acute stressor. In detail, maternally separated adult rats showed increased CRH mRNA expression in the PVN, increased CRH concentrations in the median eminence, and increased ACTH and/or corticosterone responses to acute stress [132,141,159–161,182,215,241,315,339] (Fig. 2). The decrease in GR and increase in MR mRNA expression levels in the hippocampus suggest additional alterations in feedback regulation [161]. These alterations in HPA axis are associated with increases in anxiety and depression-like behaviors. Interestingly, exposure to a chronic stressor in adulthood resulted in lower baseline corticosterone concentrations in maternally separated mice [320] and a diminished ACTH and corticosterone response in maternally separated rats [162] compared with control groups. These findings suggest a shift from a hyperactive HPA axis in response to an acute stressor to a rather hypo-active HPA axis as adaptive response to chronic stress in maternally separated rodents. Additional research is required to investigate the link between HPA axis function and altered juvenile and adult aggressive behaviors in maternally separated rodents.

Post-weaning social isolation induced clear alterations in HPA axis parameters, but the direction differed across studies. One study reported an increase in baseline ACTH levels and an increase in ACTH and corticosterone response accompanied by enhanced anxiety-related behaviors in post-weaning socially-isolated adult male rats [333]. Others found that social isolation decreased baseline ACTH and corticosterone levels [266,267,281], likely due to a decrease in the spontaneous electrical activity of neurons within the PVN [266]. Moreover, post-weaning socially-isolated rats showed a smaller decrease in CRH immunoreactivity in the median eminence, a lower number of ACTH-immunoreactive cells in the anterior pituitary and lower plasma corticosterone levels in response to restraint stress compared with group-housed rats [267]. Lower corticosterone concentrations were also found in socially-isolated compared with group-housed rats exposed to the open field [98]. Intracerebroventricular administration of CRH induced a greater increase in plasma corticosterone level in isolated rats, whereas dexamethasone induced a less severe suppression of corticosterone release in isolated compared with group-housed rats [281], indicating an impaired negative feedback regulation. Thus far, it is unknown how increased aggression in socially-isolated rats correlates with alterations in HPA axis function. Interestingly, the abnormal attack pattern observed in socially-deprived male rats [297] shows parallels with the attack pattern in another rat model of abnormal aggression. Here, experimentally-induced glucocorticoid-deficient rats show a dramatic increase in attacks aimed at vulnerable body parts of intruder conspecifics [102,105,106]. Although further research is required, these studies may suggest a link between HPA axis hypofunction and abnormal forms of aggression in socially-isolated rats.

Post-weaning social deprivation of male guinea pigs resulted in an extreme increase in plasma cortisol concentrations, when being exposed to another adult male in the presence of a female or when being introduced into a new colony [258,260]. This was further accompanied by increased aggression and a substantial decrease in body weight compared with colony-reared guinea pigs [258,260]. Thus, early social deprivation of male guinea pigs induced a high HPA axis responsiveness which was associated with high and inappropriate aggressive behaviors.

Early social subjugation of adult Long–Evans rats induced an increase in basal light phase plasma corticosterone concentrations and an increase in intermale aggression [51]. Early social subjugation of male Syrian golden hamsters did not alter basal plasma cortisol concentrations [343,345]. However, social subjugation had long-lasting effects on HPA axis responsiveness. Here, socially subjugated hamsters showed a diminished cortisol response compared with control hamsters when exposed to an aggressive hamster [81,129,345]. In contrast, when male hamsters were exposed to social subjugation in adulthood, an increase in cortisol concentrations under baseline conditions and in response to an aggressive adult hamster was observed [129]. It is tempting to speculate that the differential effects of early and late social subjugation on HPA axis responsiveness may underlie, to a certain extent, the opposing long-lasting behavioral effects, i.e. early social subjugation is associated with HPA axis hypofunction and enhanced and atypical aggression, whereas late social subjugation is associated with HPA axis hyperfunction and decreased aggression.

Together, exposure to early life stress has robust acute and long-lasting effects on HPA axis functioning in primates and rodents, but the observed effects are not uniform across models (see Table 1). Nevertheless, early life stress induced in general an increase in HPA axis activity during early infancy. This is in accordance with the idea that the primary caregiver functions as a 'social buffer' by preventing the infant HPA axis from overshooting and promoting a healthy development of HPA axis function. Evidently, the role of the primary caregiver exceeds beyond the mere presence and involves active care-giving aspects (the extent may differ depending on the species) that determine the quality of care, like tactile stimulation, responsiveness, protectiveness, and support. Thus, poor infant care-giving results in a premature activation of the HPA axis.

During ongoing maturation, effects of early life stress on HPA axis function become more diverse, which may be explained by a variety of factors, including the type of early life stressor, age of onset of early life stress, characteristics of control groups, type of species, genetic factors (see 4.1), and experimental procedures. Nonetheless, even by using the same type of early life stressor and the same species differential effects on HPA axis parameters were reported. These inconsistencies question the generality of early life stress effects on adult HPA axis function and may limit its interpretation. However, these findings underscore the complex effects of early life stressors and highlight an important role for individual variation in coping with early life stress. As mentioned above, HPA hyper- as well as hypo-activity may be associated with increased and inappropriate forms of aggression [107]. An excessive acute HPA response is an important characteristic for hyperarousal-driven aggressiveness, which is observed in mood disorders and intermittent explosive disorder while a chronic hypo-active HPA axis is a key feature of hypoarousal-driven aggressiveness and seen in personality disorders. Thus, although the outcome might be similar, i.e. high and inappropriate aggression, underlying neuroendocrine mechanisms might be different. A careful and more detailed analysis of early life stress-induced HPA axis alterations linked to specific changes in aggressive behaviors, would be an important step forward in identifying the role of the HPA axis in aggressive deficits. Additional manipulation of HPA axis activity is required to investigate the causal involvement of HPA hormones in abnormal aggression.

3.2. Vasopressin

Vasopressin is a highly conserved neuropeptide synthesized in the hypothalamic PVN, supraoptic nucleus (SON), and suprachiasmatic nucleus, and in extrahypothalamic nuclei, the bed nucleus of the stria terminalis (BNST) and the medial amygdala. Vasopressin regulates body fluid and electrolyte homeostasis and stimulates, in the presence of CRH, the release of ACTH from the anterior pituitary. Vasopressin is also released in the brain where it plays a key role in the regulation of emotional (anxiety, stress coping) and social (social attachment, parental care, social recognition, aggression) behaviors [30,73,164,319].

During the early postnatal period the mother–infant relationship consists of important pro-social behaviors, like social attachment and bonding, which are strongly regulated by vasopressin and by its closely related neuropeptide oxytocin [24,78,178, see also I.D. Neumann, same issue]. Disruption of these early social interactions alters the development and expression of social behaviors, which, among others, may be mediated via changes in the vasopressin system. First indications in humans indeed show that early social experience can alter vasopressin concentrations. Here, orphanage-reared children had lower levels of vasopressin in urine than family-reared children [90]. A limitation of this study is that vasopressin concentrations in urine less likely reflect vasopressin released within the brain.

There are also indications that vasopressin plays a role in the regulation of aggression. In humans, a positive correlation between a life history of aggression and CSF levels of vasopressin was found in patients with personality disorders [42]. Moreover, intranasal vasopressin administration decreased perception of friendly faces and increased perception of anger and threat to neutral human facial expressions [295,296]. This biased perception of angry/threatening faces mediated by vasopressin might promote the expression of aggressive behaviors. In rodents, differences in the level of intermale aggression have been associated with large differences in the extrahypothalamic vasopressin system, including the number of vasopressin-immunoreactive cells in the BNST and the medial amygdala, vasopressin fiber density and vasopressin 1a receptor (V1aR) binding in the lateral septum [43,75,134,317,327,351]. Blockade of the V1aR, either centrally or locally in the anterior hypothalamus, reduced the display of intermale aggression in hamsters [79,80,83]. Studies in knockout mice suggest an additional role for the V1bR in the expression of aggression [334,335]. Recently, we were the first to demonstrate changes in extracellular vasopressin release within the lateral septum during the display of intermale aggression in rats using intracerebral microdialysis. These experiments were carried out with rats genetically selected for high (HAB) and low (LAB) anxiety-related behavior. HAB rats have a single nucleotide polymorphism in the promoter region of the vasopressin gene [225] resulting in higher vasopressin release within the PVN compared with LAB rats [148,340]. The difference in central release of vasopressin is key to the line difference in anxiety and might have additional implications for other related behaviors. For example, LAB rats were found to show a higher level of intermale aggression than HAB rats when exposed as residents to the resident–intruder test [318]. This high level of aggression in LAB rats was accompanied by a significant decrease in septal vasopressin release, whereas the lower level of aggression in HAB rats was rather accompanied by am increase in septal vasopressin release [16]. Surprisingly, pharmacological manipulation of the septal vasopressin system did not affect the level of aggression in LAB or HAB rats [16]. We, therefore, hypothesized that changes in septal AVP release are the result of the aggressive display, which in turn may influence behaviors that are relevant in the context of aggression, like social recognition or anxiety [319]. Further studies are recommended to measure and manipulate local extracellular activity of vasopressin and reveal its precise involvement in the regulation of aggression and other social behaviors.

3.2.1. Non-human primate models of social deprivation

Data on vasopressin in non-human primates, models of early life stress are limited. *Early social deprivation* of rhesus monkeys (monkeys were nursery-reared form birth) did not result in alterations

in plasma or CSF levels of vasopressin when compared with mother-reared monkeys [341]. However, CSF vasopressin levels correlated with fearful behaviors. In addition, socially-deprived monkeys had a higher expression of V1aR in the ventromedial hypothalamus, and in prefrontal and cingulate cortices, but lower V1aR expression in the corticomedial amygdala [130,268,342]. These brain regions have been implicated in aggressive behaviors, suggesting that changes in V1aR might influence the expression of aggression.

3.2.2. Rodent models of social deprivation

In male rats, exposure to *maternal separation* induced an increase in vasopressin mRNA and/or protein expression in several hypothalamic nuclei, including the PVN, SON and lateral hypothalamus at juvenile and adult age [315,321]. These changes in hypothalamic vasopressin activity were accompanied by an increase in aggressive behaviors in both juvenile and adult male rats [315,321]. Although a similar increase in vasopressin mRNA expression in the PVN was found in adult male mice exposed to maternal separation, this was accompanied by a decrease in intermale aggression [316]. Considering the well-known effects of maternal separation on a variety of non-social emotional behaviors (including increases in anxiety- and depression-like behaviors), it is postulated that maternal separation-induced alterations in vasopressin primarily influenced emotional regulation, which, in turn, resulted in species-specific differences in the expression of aggressive behaviors. However, a decrease in the number of vasopressin-immunoreactive cells in the PVN of maternally separated adult male rats has been reported as well [66]. Moreover, additional exposure to a chronic psychosocial stressor induced a decrease in vasopressin mRNA expression in the PVN in maternally separated male mice [320]. Remarkably, no effects of maternal separation on hypothalamic vasopressin were observed in female rats or mice [66,316], despite its effects on maternal aggression [316]. Overall, these findings point to a high plasticity of the hypothalamic vasopressin system in male rodents exposed to maternal separation.

In other rodent models of early life stress, data on vasopressin are restricted. One study reported that *post-weaning social isolation* of rats had no effect on vasopressin content in the PVN or median eminence [267]. Effects of *post-weaning social deprivation* of guinea pigs on central vasopressin are unknown. *Early social subjugation* of male golden hamsters was found to decrease vasopressin protein levels within the anterior hypothalamus [64]. A reduction in vasopressin levels might be interpreted as reduced vasopressin activity within the anterior hypothalamus, and hence a reduction in aggression. Conversely, if vasopressin activity in the anterior hypothalamus is required for the appropriate regulation of aggression, reduced vasopressin activity might be associated with inappropriate expression of aggression. Future studies are required using more delicate techniques like intracerebral microdialysis to assess vasopressin physiological activity more accurately.

The dual role of vasopressin in modulating pro-social behaviors, like social attachment, and anti-social behaviors, like aggression, as well as anxiety and stress coping, makes this neuropeptide a unique candidate in mediating alterations in social behaviors upon early life stress. Large variations in the vasopressin system across and within species have been associated with variations in social attachment and aggression [328], which underlines the high degree of plasticity of the vasopressin system. Clearly, further studies are warranted to test the hypothesis that early life stress induces alterations in aggressive and other social behaviors via changes in the central vasopressin system.

3.3. Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) is essential for the regulation of emotional and social behaviors, in particular aggression [186]. It is therefore not a surprise that dysregulation of the brain 5-HT system is involved in the pathophysiology of depression and aggression [10,41,180,188,247,311]. The 5-HT system is highly conserved in vertebrate evolution and similarities in 5-HT mechanisms allow to make some generalizations about the role of the 5-HT system in specific behaviors and related disorders. 5-HT is produced in brain stem raphe nuclei, which send 5-HT projections to numerous brain regions. During the postnatal period, 5-HT acts as a neurotrophic factor modulating the development of the central nervous system [97]. Several studies in humans and animals demonstrated that excessive aggressive and violent behaviors are associated with low 5-HT function [41,180,220,336], suggesting that 5-HT inhibits aggression. However, application of 5-HT1A or 1B receptor agonists reduce aggressive behavior, and was associated with a decrease in brain 5-HT release [59,234]. Furthermore, the display of aggressive behavior is associated with an increase in 5-HT neuronal activity [307,308]. These paradoxical findings can be united by proposing that an acute increase in 5-HT activity is required for the display of normal and adaptive levels of aggression (e.g. display of adult dominance behavior) while a chronically reduced 5-HT activity might be associated with inappropriate, escalated or abnormal forms of adult aggression.

Alterations in the 5-HT system have been reported in humans exposed to child maltreatment. Administration of the 5-HT precursor L-5-hydroxytryptophan, which stimulates the release of prolactin, induced a higher prolactin response in maltreated depressed children compared with control groups [145], suggesting increased activity of the 5-HT system. Prolactin secretion after L-5-hydroxytryptophan infusion was also positively correlated with indices of aggressive behavior. Similarly, adverse rearing circumstances associated with high aggressive behavior were positively correlated with the prolactin response to the 5-HT releasing agent fenfluramine in young boys [240]. In contrast, inverse correlations of child maltreatment and 5-HT activity were found in adulthood. For example, in borderline personality disorder patients, previous exposure to child abuse was associated with a blunted prolactin response to application of the 5-HT1/2 receptor agonist m-CPP [249]. These patients further showed high levels of aggressive and impulsive behaviors. Moreover, childhood emotional neglect was associated with lower CSF levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in adults [254]. CSF concentrations of 5-HIAA are presumed to reflect central 5-HT activity, and alterations in 5-HIAA concentrations are thought to underlie changes in 5-HT turnover or metabolism. These studies suggest a relation between child maltreatment, high aggression, and age-dependent 5-HT functioning, with a shift from an increased to a decreased 5-HT activity during maturation.

3.3.1. Non-human primate models of social deprivation

Immature female rhesus monkeys exposed to *infant abuse and neglect* had lower CSF 5-HIAA concentrations than controls [199–201]. This effect was highly stable across the first 3 years of life, suggesting that it is long-lasting. However, adult female rhesus monkeys exposed to infant abuse and neglect had significantly higher CSF concentrations of 5-HIAA than controls [198]. Interestingly, low 5-HIAA concentrations at infant age and high 5-HIAA concentrations at adult age were both associated with anti-social behavior patterns, including a high frequency of maternal aggression, infant rejection, and a low frequency of contacts received from other individuals, in adult females exposed to infant abuse and neglect [198,199]. The causes of these developmental alterations in 5-HT metabolism are unclear at present, but may involve a differential activation of the cytokine signaling pathway, p38 MAPK, during maturation. Adult rhesus monkeys exposed to early maternal rejection showed an increase in p38 activity, which may influence 5-HT metabolism by stimulating 5-HT transporter activ-

ity and/or altering the availability of tryptophan, the primary precursor of 5-HT [271]. Thus, naturally occurring variations in maternal care in non-human primates are associated with differences in 5-HT function, which, in turn, might have predisposed female rhesus monkeys to the display of aggressive and anti-social behaviors. Whether the same is true for male rhesus monkeys is unknown at present.

Bonnet macaques reared under *variable foraging-demand* conditions showed a diminished behavioral response to acute administration of the 5-HT1/2 receptor agonist, m-CPP, a putative anxiety-provoking agent [253]. Furthermore, higher CSF 5-HIAA concentrations were found in bonnet macaques being reared under variable foraging-demand conditions [45,204]. The hyposensitivity to m-CPP challenge and higher 5-HIAA concentrations may point to an increased 5-HT turnover and less sensitive postsynaptic 5-HT1/2 receptors. A direct link between these alterations and changes in aggressive behavior is unknown thus far.

Peer-reared monkeys had significantly lower CSF 5-HIAA levels than their non-separated peers at infant and adult age, which was associated with impulsive–aggressive behavior [123,124,283]. Conflicting results have also been reported [38,40,119,120], which are likely due to the use of a control group consisting of infants reared by their mother only, which, by itself, is a socially-deprived rearing condition [see [149]]. Additional studies demonstrate that low CSF 5-HIAA concentrations was predictive for excessive and unrestrained aggression, risk taking, and even premature death among free-ranging male rhesus monkeys [121,122]. Furthermore, decreases of 5-HT transporter binding were found in a wide range of brain areas (including the raphe, hypothalamus, anterior cingulate gyrus, and amygdala and hippocampus) of peer-reared compared with non-separated rhesus monkeys [133]. Together, permanent separation from the mother affects the development of the 5-HT system and suggest that decreased 5-HT activity in certain brain regions may be a crucial predisposing mechanism involved in the development of excessive aggressive behaviors in maternally deprived monkeys.

Summarizing these findings in non-human primates, variable foraging-demand rearing was associated with high CSF 5-HIAA concentrations and reduced male aggression, whereas peer-rearing was associated with low CSF 5-HIAA concentrations and excessive and inappropriate male aggression. This implies a negative association between CSF 5-HIAA concentrations and the expression of male aggressive behaviors. In contrast to male aggression, maternal aggression was positively associated with CSF 5-HIAA concentrations in female monkeys exposed to infant abuse and neglect. These results indicate that different forms of early social deprivation may alter the 5-HT system in different ways resulting in opposing effects on male aggression and that there might be sex-specific effects of early social deprivation on 5-HT and aggression.

3.3.2. Rodent models of social deprivation

In adult male rats, *maternal separation* induced a decrease in 5-HT activity of the raphe nucleus in response to application of the alpha1-adrenergic agonist phenylephrine to dorsal raphe slices [96] or systemic application of the selective 5-HT re-uptake inhibitor citalopram [8]. The effect of citalopram might be mediated by decreased activation of the 5-HT transporter and/or increased activation of local inhibitory 5-HT1A autoreceptors in maternally separated rats. However, no alterations were found in mRNA expression or binding sites of the 5-HT transporter nor in 5-HT1A or 1B receptors in the raphe nuclei upon maternal separation [8,96]. This contrasts with another study reporting decreased 5-HT transporter mRNA expression [167]. However, maternal separation was found to increase 5-HT turnover in the brain stem [232], which might underlie, in part, the enhanced negative feedback of 5-HT raphe neurons in response to citalopram. Additionally, postsynaptic 5-HT1A receptors located in the prefrontal cortex mediate a negative feedback regulation on 5-HT cell firing in raphe nuclei [202]. In this respect, it is of interest that maternally separated adult male rats showed decreased 5-HT concentrations in the prefrontal cortex and hippocampus [167,205], although others did not report changes in 5-HT concentrations in these brain regions [53,232]. Recently, we found a significant decrease in 5-HT immunoreactivity in the anterior hypothalamus, which correlated negatively with the display of intermale aggression in maternally separated rats [315]. Finally, chronic antidepressant treatment with either paroxetine or desipramine was found to reduce anxiety and depression-like behaviors in maternally separated rats [131,187], further suggesting maternal separation-induced alterations in central 5-HT activity. Whether these treatments induce a similar reversal of aggressive behaviors is unknown so far.

Post-weaning social isolation of rodents has been commonly associated with alterations in 5-HT parameters in a wide variety of brain regions. In the hippocampus, a decrease in 5-HT innervation was found in socially-isolated rats [337]. This is in line with a diminished 5-HT response to a single systemic injection of parachloroamphetamine (stimulating 5-HT release) or an acute non-social stressor [223], and lack of an increase in local 5-HT release in response to a novel environment [20] in post-weaning socially-isolated rats. However, other studies reported a higher KCl-stimulated, Ca^{2+}-dependent release of 5-HT [135] and impaired presynaptic 5-HT1B receptor activity [224] in the hippocampus of post-weaning isolated rats. Postsynaptic 5-HT1A receptor binding in the hippocampus was increased in socially-isolated rats [243], although the in vitro electrophysiological activity of postsynaptic 5-HT1A receptors in CA1 hippocampal neurons was not altered [224]. Nevertheless, an increased '5-HT behavioral syndrome' response to 5-HT1A receptor or 5-HT2 receptor agonists was found in post-weaning isolated rats [347], suggesting increased postsynaptic 5-HT1A and 5-HT2 receptor responsiveness. This is in line with the increased anxiogenic response to the 5-HT1/2 receptor agonist, m-CPP, in socially isolated compared with socially-reared male rats exposed to the elevated plus maze [86]. Thus, most studies suggest that post-weaning social isolation decreased extracellular 5-HT responsiveness in the hippocampus. Increased postsynaptic 5-HT1A receptor binding/sensitivity and decreased pre-synaptic 5-HT1B receptor activity might be compensatory mechanisms for low hippocampal 5-HT reactivity in post-weaning socially-isolated rats.

In the nucleus accumbens, a brain region that integrates information from limbic and cortical regions, linking reward and motivation to goal-directed behaviors, a decrease in basal 5-HT turnover was found in post-weaning socially-isolated rats [112], which was likely due to decreased 5-HIAA concentrations [139], rather than changes in 5-HT release [127]. Post-weaning social isolation of rats did not alter the 5-HT efflux in the nucleus accumbens in response to a systemic cocaine challenge [127], but increased extracellular 5-HT release in the nucleus accumbens in response to a footshock and the footshock-context only [91,92]. Thus, isolation rearing appears to increase pre-synaptic serotonergic function in the nucleus accumbens. Moreover, a significant increase in the KCl-stimulated 5-HT release was found within the nucleus accumbens of post-weaning isolated rats [135]. These findings may point to a facilitation of 5-HT release in the nucleus accumbens upon stress exposure.

In the prefrontal cortex, basal 5-HT release and turnover were not altered [52,139], but an attenuated amphetamine-induced 5-HT release was found [52] in isolated rats. This is in line with a lack of a KCl-stimulated release of 5-HT in the prefrontal cortex of socially-isolated rats [20], although two other studies reported a significant increase in KCl-stimulated release of 5-HT [48,135]. Isolation rearing reduced 5-HT1A, 1B, 2A, and 2C receptor mRNA

expression in the prefrontal cortex of mice [19], whereas it reduced 5-HT1A receptor binding in the prelimbic cortex, but increased 5-HT1A and 2A receptor binding in motor and cingulate cortices of rats [243].

In the dorsal raphe nucleus, heightened 5-HT1A autoreceptor inhibition of 5-HT neuronal function was reported in isolation-reared CB57BL/6 J mice [1], suggesting decreased 5-HT postsynaptic (re)activity. Another study reported no changes in 5-HT1A receptor mRNA expression, but decreased 5-HT1B, 2A, and 2C receptor mRNA expression in midbrain tissue samples upon post-weaning social isolation of C57Bl/6 J mice [19]. It is however not clear whether these changes in 5-HT1B receptor mRNA expression can be attributed to autoreceptors in the dorsal raphe or to post-synaptic heteroreceptors in adjacent areas.

Effects of *post-weaning social deprivation* on 5-HT system in guinea pigs are unknown so far, and only one study reported that *post-weaning social subjugation* increased 5-HT immunoreactivity in the anterior hypothalamus and lateral septum and was associated with inappropriate aggression in adult hamsters [64].

Taken together, findings from rodent models reveal that alterations in the 5-HT system upon early social deprivation are highly complex, brain-region specific, occur at multiple levels and are not always consistent (see Table 1). Up to now, only two rodent studies investigated the link between early social deprivation, 5-HT and aggressive behaviors. In maternally separated rats, low 5-HT immunoreactivity in the anterior hypothalamus correlated with high intermale aggression [315]. Hamsters exposed to post-weaning social subjugation showed enhanced 5-HT immunoreactivity in the anterior hypothalamus and lateral septum, which was associated with abnormal patterns of aggression [64]. At this point, changes in 5-HT immunoreactivity are difficult to interpret as, for example, high 5-HT immunoreactivity may reflect higher extracellular 5-HT release or may reflect lower extracellular 5-HT release due to higher storage in pre-synaptic terminals. Clearly, additional studies are required to confirm these and other indices of the 5-HT system and their role in aggression in animal models of early life stress. Moreover, age-dependent changes in the central 5-HT system were reported in humans exposed to child maltreatment and in monkeys exposed to infant abuse and neglect. Further studies will have to reveal the function of age-dependent changes in the 5-HT system in the development of aggression in animal models of early social stress.

4. Genetic and epigenetic factors modulating the effects of early social deprivation

4.1. Genetic modulation

Recent findings in humans and primates that the genetic background plays an important role in the susceptibility for, or in turn, protection against, early life stress-induced aggressive behaviors [for review, see [47]]. These studies examined the interaction between early adverse experience and gene polymorphisms in two key 5-HT metabolizing enzymes, namely monoamine oxidase A (MAO-A; involved in the degradation of 5-HT) and 5-HT transporter (involved in 5-HT re-uptake into pre-synaptic neurons).

Regarding the role of MAO-A in aggression, a longitudinal study demonstrated that men exposed to child maltreatment and possessing the genotype associated with low levels of MAO-A expression were more likely to develop anti-social problems than those with the genotype associated with high levels of MAO-A expression [33]. Subsequent studies provided further evidence for the importance of MAO-A genotype in the impact of child maltreatment on risk for developing aggressive and anti-social behaviors [e.g. [152], although some studies were unable to detect a genetic–environmental interaction with MAO-A genotype for maltreatment [e.g. [352]. These mixed findings are likely attributed to sample size (meta-analysis seems critical for evaluating gene–environment interactions) and differences in the selection of subjects. Moreover, extreme levels of child maltreatment may overshadow the effects of MAO-A genotype on aggression [331]. Interestingly, a similar MAO-A promoter polymorphism variant was found in rhesus macaques, in which the low-activity MAO-A allele was associated with higher aggression scores. However, additional exposure to early social deprivation (peer-rearing) did not interact with low MAO-A activity to increase aggression [229]. In fact, peer-reared monkeys with low MAO-A activity showed low aggression. Yet, the two tests that were used in the study were designed to measure naturally occurring aggressive interactions and food competition-related aggression. These behaviors represent adaptive dominance behaviors rather than the inappropriate forms of aggression observed in peer-reared monkeys. The existence of MAO-A promoter polymorphisms in both humans and rhesus monkeys suggests that varieties in functional MAO-A expression underlie aggression-related behavioral traits, which are sensitive to early social experiences. As MAO-A is capable of degrading 5-HT as well as noradrenaline and dopamine, alterations in MAO-A enzymatic activity may not be limited to alterations in 5-HT activity. This would be of interest to investigate in follow-up studies.

A functional polymorphism in the promotor region of the 5-HT transporter gene (5-HTTLPR) is associated with two variants, namely a short (S) and a long (L) allele variant. The S allele reduces 5-HT transporter function by restricting its transcriptional activity [171] and has been, although inconsistently, associated with anxiety and depression [177]. Importantly, adults exposed to child maltreatment and carrying one or two copies of the S allele were more likely to develop depression than adult subjects carrying two copies of the L allele [34,146]. Moreover, humans with a history of child maltreatment and carrying the S allele of the 5-HTTLPR are at increased risk of showing alcohol abuse and suicidal behavior [147,255]. These latter findings are relevant as alcohol abuse and suicidal behavior are often interconnected with aggression [154], suggesting a role for 5-HT transporter polymorphisms in aggressive traits. Thus far, first evidence for this may be provided by studies with non-human primates. In rhesus monkeys, an analogous length variation in the 5-HT transporter gene (rh5-HTTLPR) resulting in a similar reduction in transcription efficiency was found and interacted with early social experience to affect central 5-HT functioning. Here, peer-reared monkeys carrying the S allele showed significantly lower CSF concentrations of 5-HIAA, less engagement in infant play-fighting, and higher levels of adolescent aggression compared with peer-reared monkeys that did not carry the S allele [13,17]. Interestingly, the S allele in socially-reared monkeys did not affect 5-HIAA concentrations. These data confirm the association between low 5-HIAA and high aggression in peer-reared monkeys [15,123,124,283]. Thus, 5-HT transporter promotor polymorphisms may contribute to the functional expression of an aggressive phenotype in peer-reared monkeys by changes in 5-HT activity.

Peer-reared rhesus macaques carrying the S allele showed further signs of behavioral despair and had higher ACTH concentrations in response to social separation [14,287] and had a higher alcohol sensitivity if they carried the S allele [12] when compared with peer-reared macaques carrying the L allele. The latter finding shows parallels with alcohol use in humans carrying the S allele and exposed to child maltreatment [147]. Thus, a polymorphism in the 5-HT transporter gene not only reduced basal 5-HT functioning, but also increased neuroendocrine and behavioral stress responsiveness as a consequence of early social stress.

In rodents, the role of genetic variation in determining the effects of chronic early social deprivation are limited and mainly concentrated on comparisons of strains or lines. For example, effects of maternal separation on emotion and HPA axis were found to depend on genetic selection for high and low anxiety. Maternal separation increased anxiety in rats selectively bred for low anxiety (LAB), whereas maternal separation reduced anxiety and HPA axis responsiveness in rats selectively bred for high anxiety (HAB) [227]. As HAB and LAB rats show differences in intermale aggression and corresponding alterations in HPA axis reactivity and septal vasopressin release [16,317,318], we are currently investigating the effects of maternal separation on the development of aggression in these rat lines. Exposure to maternal separation in an animal model of depression, the Flinders Sensitive Line (FSL) rats, and their controls, the Flinders Resistant Line (FRL) rats, resulted in an increase in depression-like behaviors in FSL rats only [71]. Treatment with a escitalopram, a selective serotonin re-uptake inhibitor, decreased depression-like behaviors in FSL rats only. Post-weaning social isolation of male rats induced a strain-independent increase in locomotor activity in the open field. However, a more rigid behavioral repertoire was found in Lewis rats, a strain normally characterized by the lowest susceptibility for stress [238]. These results demonstrate that the long-term effects of early life adverse experience in rodents may depend on the genetic background of the individual.

In summary, human, primate, and rodent studies demonstrate the importance of genetic background in the effects of early life stress. Polymorphisms in the MAO-A and 5-HT transporter genes the development of aggressive behaviors, likely by affecting a variety of other systems, like the HPA axis. These findings may also help to explain individual differences in their responses to early life stress. More longitudinal studies from childhood into adulthood are needed to clarify how the early social environment and genetic background interact to generate an aggressive and violent individual. Further research should be promoted, especially by utilizing animal models of early life stress and investigating gene–environment interactions using candidate genes for aggressive traits.

4.2. Epigenetic modulation

In addition to the genetic make-up of the individual, epigenetic processes may influence the outcome of early adverse experience. Epigenetic mechanisms determine which genes are expressed and involve chemical modifications to chromatin (complex of DNA and histone and non-histone proteins) including DNA methylation. Recent data suggest that these chemical modifications are highly responsive to environmental stimuli [150]. The potent role of epigenetic programming of behavioral and neuroendocrine stress responses through variations in maternal care have been elegantly demonstrated by Meaney and colleagues using rat dams with naturally occurring differences in the quality of nurturing behaviors. Offspring of rat dams displaying low maternal care (low level of licking and grooming and arched back nursing) are more anxious, have an attenuated corticosterone response to stress and a decreased expression of GR mRNA and protein in the hippocampus compared with offspring of rat dams displaying high maternal care [28,181]. The decreased expression of GR mRNA is induced by an increased methylation of the nerve growth factor-inducible protein A (NGFI-A) transcription factor response element located within the GR promoter [329]. Methylation of the GR promotor prevented binding of NGFI-A, thereby reducing GR gene transcription, an effect that was found to persist into adulthood. Importantly, the epigenetic methylation of the GR promotor in the offspring of low care mothers could be reversed by cross-fostering or by central infusion of pharmacological agents altering DNA methylation, and was accompanied by an increase in GR mRNA expression in the hippocampus and a decrease in HPA response to stress to the level seen in offspring of high care mothers [329,330]. This suggests a causal relation between epigenetic programming of GR expression and the maternal effect on HPA stress responsiveness in the offspring. These findings further suggest that, even in the adult brain, patterns of DNA methylation are reversible. This is a promising observation with regard to the development of potential drugs targeting specific epigenetic processes and thereby restoring early life stress-induced pathophysiological changes in the brain and hence in behavior.

The epigenetic programming of the GR promoter by maternal care is a critical example of how the early social environment may influence neuroendocrine, neurobiological and behavioral functioning at the level of the genome. The importance of differences in maternal care in modulating the offspring's behavior has been demonstrated by several studies using cross-fostering [e.g. [7,353]], although the role of genetic background should not be disregarded [306]. It is tempting to speculate that alterations in aggressive behaviors in animal models of early social deprivation are, in part, mediated by epigenetically-induced alterations in neuroendocrine or neurobiological functioning. This might, for example, explain the intergenerational transmission of infant abuse and neglect in non-human primates, which was found to occur via early experience rather than genetic inheritance [197]. Intergenerational transmission of child abuse has also been described in humans [68,228]. Interestingly, preliminary data suggest the occurrence of epigenetic programming in humans exposed to childhood abuse. Here, decreased levels of the glucocorticoid receptor and decreased NGFI-A transcription factor binding to a neuron-specific glucocorticoid receptor promoter were found in postmortem hippocampus of suicide victims exposed to childhood abuse [211]. Future studies are needed to investigate the contribution and the generality of epigenetic processes mediating alterations in aggressive behaviors upon exposure to early life stress. Increased knowledge of early epigenetic programming is expected to contribute to effective interventions preventing the development of abnormal aggression [299].

5. Conclusions and future directions

The early social environment shapes emotional and cognitive development and thereby determines adult social functioning (see Fig. 3). Disturbed social relations during childhood and adolescence are a risk factor for the development of aggression-related psychopathologies. The high incidence of child and adolescent maltreatment (about 1.5 million verified cases of child maltreatment are reported annually in the USA) warrants the need for research aimed at understanding the biological mechanisms underlying the development of aggressive behaviors upon exposure to early adversities. Data from research on primates and rodents indisputably demonstrate that exposure to early life stress (i.e. disruption of early maternal care or early social interactions with peers) increases the risk for the development of excessive and inappropriate aggression and underscores findings in humans exposed to child maltreatment. Underlying mechanisms likely include alterations in HPA axis (low as well as high activity), and in vasopressin and 5-HT (generally low activity) functioning (see Table 1).

The question now arises, what can we learn from these animal models of early life stress in the near future? There are several important points that emerge from the above discussed studies and that should be given attention in further studies:

5.1. Aggression should be placed in a broader context

Aggression is a highly complex behavior and its expression is mainly controlled and regulated by emotional and cognitive pro-

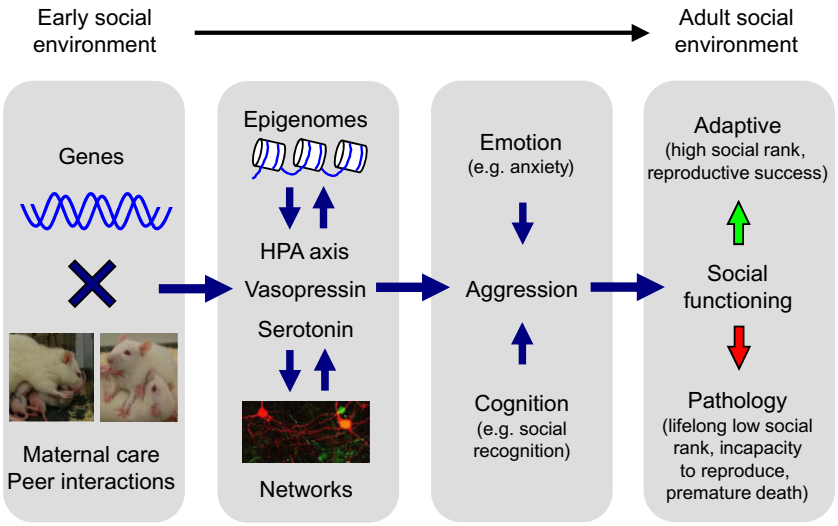

Fig. 3. Genetic background × early social environment determine the development of the brain by influencing epigenomic processes, HPA axis and vasopressin and serotonin systems, and neural networks. This, in turn, shapes the development and expression of aggressive behaviors, which is influenced by emotional and cognitive brain systems and ultimately determines adult social functioning. Depending on the adult social environment, the expression of aggressive behavior formed by the early social environment in interaction with the genetic make-up of the individual, can be adaptive (such as high social rank and reproductive success) or turn into a pathology (such as lifelong low social rank and incapacity to reproduce, exclusion from troop, premature death).

cesses [54,285]. Hence, alterations in aggressive behaviors in humans, primates and rodents exposed to early life stress are likely embedded in alterations in emotional and cognitive behaviors [168]. Moreover, aggression in humans and animals can be divided into two major subtypes (i.e. offensive and defensive aggression), which have different neuroendocrine and neurobiological underpinnings. While studies in rodents exploit tests that primarily measure offensive aggression, studies in primates predominantly measure defensive aggression. To improve our understanding of the link between early life stress and aggression, it is desirable to study aggressive behaviors in a broader framework, in which aggression is tested in different settings (to enable to discriminate between different subtypes of aggression) and in which parameters of emotion (e.g. anxiety) and cognition (e.g. social information processing) are tested in parallel.

5.2. Developmental regulation of aggression

The success and survival of an individual living in social groups largely depends on its social skills and competence, and includes the appropriate use of aggression. The discussed primate and rodent studies provide clear evidence that deprivation of maternal care as well as deprivation of physical interactions with peers hampers the normal development of aggressive control. This suggest that a species-normative early social environment is required to learn how and when to use aggression, which applies not only for animals, but for humans as well [298]. Developmental data in humans and animals exposed to early life stress is still limited, especially in linking aggression in childhood with aggression in adolescence and adulthood. Therefore, to understand the effects of early life stress on aggression, more attention should be given to changes across development in the function and morphology of aggressive behavior and the reorganization of neuroendocrine and neurobiological systems involved in aggression.

5.3. Neuroendocrine correlates of aggression

Despite numerous primate and rodent studies describing alterations in neuroendocrine parameters upon exposure to early life stress, there are less studies that correlate early life stress-induced changes in aggression with neuroendocrine (re)activity. The notion that high as well as chronically low HPA axis functioning can be associated with excessive aggression, should stimulate further research to disentangle these opposing mechanisms in terms of aggressive functioning. Despite the high complexity of the neuronal effects of glucocorticoids, there has been substantial progress over the last decade in the understanding of molecular mechanisms regulating glucocorticoid-signaling. This includes the discovery of membrane-located receptors, which would explain rapid and non-genomic effects of glucocorticoids in the brain [143], new insights in the differential recruitment of co-activators and co-repressors that may account for brain region and cell-specific effects of glucocorticoids on gene transcription [305], and the detection of epigenetically-induced long-lasting changes in the transcription of glucocorticoid receptors [211,329]. These new insights in central glucocorticoid actions should be incorporated in future studies that aim to unravel the function of the HPA axis in early life stress-induced changes in social and emotional behaviors, including aggression.

5.4. Correlation between aggression and vasopressin system

Preliminary studies suggest a role for the central vasopressin system in early life stress-induced alterations in aggressive behaviors. The vasopressin system is highly conserved, is involved in stress coping, is unique in its ability to modulate pro- and anti-social behaviors, and shows a high degree of plasticity and variability among individuals. Thus, vasopressin is an attractive candidate to further investigate its role in regulating aggression and social behaviors upon exposure to early life stress.

5.5. Correlation between aggression and 5-HT system

The 5-HT system is among the best studied systems with respect to genetic and environmental control of aggressive behavior. Most studies suggest a link between low 5-HT functioning and excessive and abnormal aggression in primate and rodent models of early life stress. However, there has been less attention to the role of 5-HT in different subtypes of aggression. Moreover, 5-HT has been implicated in both aggression and anxiety, two key behaviors that are altered in humans and animals exposed to early life stress. Unraveling the role of 5-HT in different forms of aggres-

sion as well as its role in the integration of aggression and anxiety are two major tasks for future studies.

5.6. The pathway from genes to behavior under the influence of early social experiences

A major challenge in the field of early life stress would be to connect alterations in genetic and molecular pathways to alterations in neuroendocrine and neurobiological circuits, which ultimately result in alterations in aggression and related behaviors. This requires the use of advanced techniques and a multiple-level-of-analysis approach in order to investigate neurodevelopmental processes and functional interactions between components of the HPA axis and vasopressin and 5-HT systems. As aggression causes major public health and social problems, further investigation into the (epi)genetic, neuroendocrine and neurobiological mechanisms underlying excessive and inappropriate aggression in socially-deprived animals is required and could make a valuable contribution to the management, treatment and prevention of aggression-related psychopathologies associated with child maltreatment.

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