Effects of stress throughout the lifespan on the brain, behaviour and cognition

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Abstract | Chronic exposure to stress hormones, whether it occurs during the prenatal period, infancy, childhood, adolescence, adulthood or aging, has an impact on brain structures involved in cognition and mental health. However, the specific effects on the brain, behaviour and cognition emerge as a function of the timing and the duration of the exposure, and some also depend on the interaction between gene effects and previous exposure to environmental adversity. Advances in animal and human studies have made it possible to synthesize these findings, and in this Review a model is developed to explain why different disorders emerge in individuals exposed to stress at different times in their lives.

Programming
When an environmental factor that acts during a sensitive developmental period affects the structure and function of tissues, leading to effects that persist throughout life.

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Every day, parents observe the growing behavioural repertoires of their infants and young children, and the corresponding changes in cognitive and emotional functions. These changes are thought to relate to normal brain development, particularly the development of the hippocampus, the amygdala and the frontal lobes, and the complex circuitry that connects these brain regions. At the other end of the age spectrum, we observe changes in cognition that accompany aging in our parents. These changes are related to both normal and pathological brain processes associated with aging.

Studies in animals and humans have shown that during both early childhood and old age the brain is particularly sensitive to stress, probably because it undergoes such important changes during these periods. Furthermore, research now relates exposure to early-life stress with increased reactivity to stress and cognitive deficits in adulthood, indicating that the effects of stress at different periods of life interact.

Stress triggers the activation of the hypothalamus-pituitary-adrenal (HPA) axis, culminating in the production of glucocorticoids by the adrenals (FIG. 1). Receptors for these steroids are expressed throughout the brain; they can act as transcription factors and so regulate gene expression. Thus, glucocorticoids can have potentially long-lasting effects on the functioning of the brain regions that regulate their release.

This Review describes the effects of stress during prenatal life, infancy, adolescence, adulthood and old age on the brain, behaviour and cognition, using data from animal (BOX 1) and human studies. Here, we propose a model that integrates the effects of stress across the lifespan, along with future directions for stress research.

Prenatal stress

Animal studies. In animals, exposure to stress early in life has 'programming' effects on the HPA axis and the brain[1]. A single or repeated exposure of a pregnant female to stress[2] or to glucocorticoids[3] increases maternal glucocorticoid secretion. A portion of these glucocorticoids passes through the placenta to reach the fetus, increasing fetal HPA axis activity and modifying brain development[4]. In rats prenatal stress leads to long-term increases in HPA axis activity[5]. Controlling glucocorticoid levels in stressed dams by adrenalectomy and hormone replacement prevents these effects, indicating that elevations in maternal glucocorticoids mediate the prenatal programming of the HPA axis[6].

Glucocorticoids are important for normal brain maturation: they initiate terminal maturation, remodel axons and dendrites and affect cell survival[7]; both suppressed and elevated glucocorticoid levels impair brain development and functioning. For example, administration of synthetic glucocorticoids to pregnant rats delays the maturation of neurons, myelination, glia and vasculature in the offspring, significantly altering neuronal structure and synapse formation and inhibiting neurogenesis[4]. Furthermore, juvenile and adult rats exposed to prenatal stress have decreased numbers of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the hippocampus, possibly because of epigenetic effects on gene transcription[8]. The hippocampus

Mineralocorticoid receptor
A receptor that is activated by mineralocorticoids, such as aldosterone and deoxycorticosterone, as well as glucocorticoids, such as cortisol and cortisone. It also responds to progestins.

Glucocorticoid receptor
A receptor that is activated by cortisol, corticosterone and other glucocorticoids and is expressed in almost every cell in the body. It regulates genes controlling development, metabolism and the immune response.

inhibits HPA axis activity (FIG. 1), and a prenatal stress-induced reduction in hippocampal MRs and GRs could decrease this inhibition, with a resulting increase in basal and/or stress-induced glucocorticoid secretion. In rhesus monkeys, prenatal treatment with the synthetic GR agonist dexamethasone causes a dose-dependent degeneration of hippocampal neurons, leading to a reduced hippocampal volume at 20 months of age[9].

Effects on other brain regions are also apparent. Rats exposed to stress during the last week of gestation have significantly decreased dendritic spine density in the anterior cingulate gyrus and orbitofrontal cortex[10]. Furthermore, prenatal exposure to glucocorticoids leads to increased adult corticotropin-releasing hormone (CRH) levels in the central nucleus of the amygdala, a key region in the regulation of fear and anxiety[11].

Exposure to prenatal stress has three major effects on adult behaviour: learning impairments, especially in aging rats[12]; enhanced sensitivity to drugs of abuse[13]; and increases in anxiety- and depression-related behaviours[14]. The impaired learning is thought to result from the effects of prenatal stress on hippocampal function[15], whereas the effects on anxiety are thought to be mediated by prenatal stress-induced increases in CRH in the amygdala[11]. Prenatal glucocorticoid exposure affects the developing dopaminergic system, which is involved in reward- or drug-seeking behaviour[16], and it has been suggested that the increased sensitivity to drugs of abuse is related to the interaction between prenatal stress, glucocorticoids and dopaminergic neurons[16].

Human studies. In agreement with animal data, findings from retrospective studies on children whose mothers experienced psychological stress or adverse events or received exogenous glucocorticoids during pregnancy suggest that there are long-term neurodevelopmental effects[17]. First, maternal stress or anxiety[18], depression[19] and glucocorticoid treatment during pregnancy[17] have been linked with lower birthweight or smaller size (for gestational age) of the baby. More importantly, maternal stress, depression and anxiety have been associated with increased basal HPA axis activity in the offspring at different ages, including 6 months[20], 5 years[21] and 10 years[22].

Disturbances in child development (both neurological and cognitive) and behaviour have been associated with maternal stress[23] and maternal depression during pregnancy[24], and with fetal exposure to exogenous glucocorticoids in early pregnancy[25]. These behavioural alterations include unsociable and inconsiderate behaviours, attention deficit hyperactivity disorder and sleep disturbances as well as some psychiatric disorders, including depressive symptoms, drug abuse and mood and anxiety disorders. Very few studies have measured

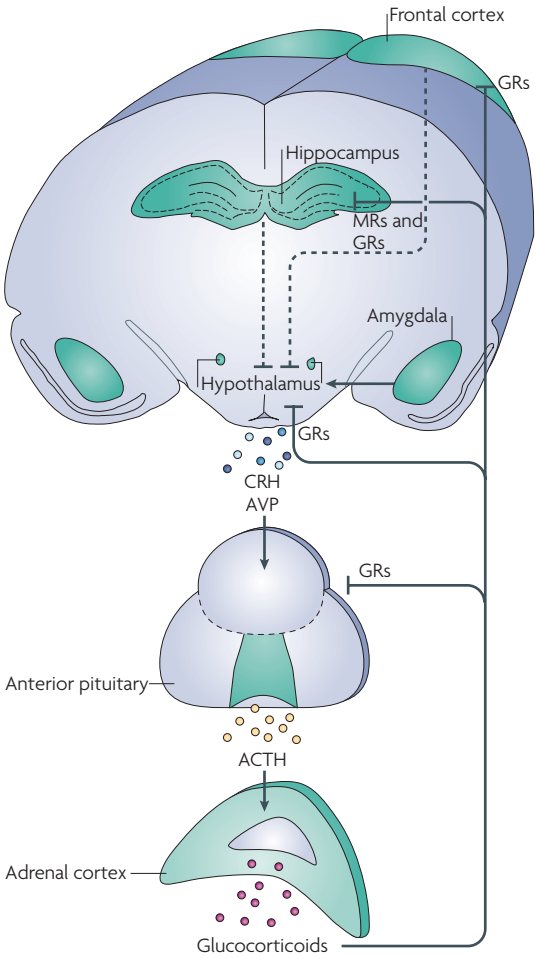

Figure 1 | **The stress system.** When the brain detects a threat, a coordinated physiological response involving autonomic, neuroendocrine, metabolic and immune system components is activated. A key system in the stress response that has been extensively studied is the hypothalamus-pituitary-adrenal (HPA) axis. Neurons in the medial parvocellular region of the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). This triggers the subsequent secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, leading to the production of glucocorticoids by the adrenal cortex. In addition, the adrenal medulla releases catecholamines (adrenaline and noradrenaline) (not shown). The responsiveness of the HPA axis to stress is in part determined by the ability of glucocorticoids to regulate ACTH and CRH release by binding to two corticosteroid receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). Following activation of the system, and once the perceived stressor has subsided, feedback loops are triggered at various levels of the system (that is, from the adrenal gland to the hypothalamus and other brain regions such as the hippocampus and the frontal cortex) in order to shut the HPA axis down and return to a set homeostatic point. By contrast, the amygdala, which is involved in fear processing[142], activates the HPA axis in order to set in motion the stress response that is necessary to deal with the challenge. Not shown are the other major systems and factors that respond to stress, including the autonomic nervous system, the inflammatory cytokines and the metabolic hormones. All of these are affected by HPA activity and, in turn, affect HPA function, and they are also implicated in the pathophysiological changes that occur in response to chronic stress, from early experiences into adult life.

changes in the brain as a function of prenatal stress in humans. However, a recent study showed that low birthweight combined with lower levels of maternal care was associated with reduced hippocampal volume in adulthood[26]. This finding is consistent with evidence that effects of prenatal stress in humans are often moderated by the quality of postnatal care, which in turn is consistent with the protracted postnatal development of the human brain.

Postnatal stress

Animal studies. Although in rodents the postnatal period is relatively hyporesponsive to stress (BOX 2), one of the most potent stressors for pups is separation from the dam. Long separation periods (3 h or more each day) activate the pups' HPA axis, as evidenced by increased plasma levels of adrenocorticotropic hormone and glucocorticoids[27]. Protracted maternal separation also reduces pituitary CRH binding sites[28], and low levels of maternal care reduce GR levels in the hippocampus[29].

The effects of maternal deprivation extend beyond the HPA axis. Early prolonged maternal separation in rats increases the density of CRH binding sites in the prefrontal cortex, amygdala, hypothalamus, hippocampus and cerebellum, as measured post-infancy[28]. In the hippocampus CRH mediates stress-related loss of branches and spines[30], and in the amygdala and hypothalamus elevated CRH levels are associated with increased anxiety and HPA axis activity, respectively[31]. Thus, the increase in CRH-binding sites induced by maternal separation might have negative effects over time. The long-term effects of prolonged separation depend on the age of the pup and the duration of the deprivation, with the effects noted above generally being greater when these separations occur earlier in infancy and last for longer durations[32].

Although the rodent work provides a rich framework for conceptualizing the impact of early-life stress, the fact that the rodent brain is much less developed at birth than the primate brain makes translation of the findings to humans somewhat challenging (BOX 3). Non-human primates have more human-like brain maturation at birth and patterns of parent–offspring relations, and so provide an important bridge in the translation of the rodent findings. Studies in monkeys have shown that repeated, unpredictable separations from the mother[33], unpredictable maternal feedings[34] or spontaneous maternal abusive behaviour[35] increases CRH concentrations in the cerebrospinal fluid and alters the diurnal activity of the HPA axis for months or even years after the period of adversity: cortisol levels are lower than normal early in the morning (around wake-up) and slightly higher than normal later in the day, an effect that seems to reverse over time in the absence of continued, ongoing psychosocial stress[35]. These diurnal effects have not been noted in rodents, but the effects on higher brain regions seem to be comparable to the rodent findings and include heightened fear behaviour[36], exaggerated startle responses[33], hippocampal changes such as an increase in the intensity of non-phosphorylated neurofilament protein immunoreactivity in the dentate gyrus granule cell layer[37], and atypical development of prefrontal regions involved in emotion and behaviour control[38].

Human studies. A human equivalent of the rodent maternal separation paradigms might be studies of children who attend full-day, out-of-home day care centres. Studies have reported that glucocorticoid levels rise in these children over the day, more so in toddlers than in older preschool-aged children[39,40]. However, it is important to note that the elevated glucocorticoid levels observed are less pronounced than those observed in rodents and monkeys exposed to maternal separation. Moreover, although age accounts for most of the variation in the rise in glucocorticoid levels by late afternoon, the quality of care is also important, with less supportive care producing larger increases, especially for children who are more emotionally negative and behaviourally disorganized[39]. So far, there is no evidence that the elevated glucocorticoid levels associated with being in day care affect development; however, children who are exposed to poor care for long hours early in development have an increased risk of behaviour problems later in development[41].

Parent–child interactions and the psychological state of the mother also influence the child's HPA axis activity. Beginning early in the first year, when the HPA system of the infant is quite labile, sensitive parenting is associated with either smaller increases in or less prolonged activations of the HPA axis to everyday perturbations[42]. Maternal depression often interferes with sensitive and supportive care of the infant and young child; there is increasing evidence that offspring of depressed mothers,

Box 1 | **Models to study stress in animals and humans**

The hypothalamus-pituitary-adrenal axis can be activated by a wide variety of stressors. Some of the most potent are psychological or processive stressors (that is, stressors that involve higher-order sensory cognitive processing), as opposed to physiological or systemic stressors. Many psychological stressors are anticipatory in nature — that is, they are based on expectation as the result of learning and memory (for example, conditioned stimuli in animals and the anticipation of threats, real or implied, in humans) or on species-specific predispositions (for example, avoidance of open space in rodents or the threat of social rejection and negative social evaluations in humans).

Animal studies allow the development of experimental protocols in which animals are submitted to acute and/or chronic stress and the resulting effects on brain and behaviour are studied. Experimental stressful 'early-life' manipulations in animals can be broadly split into prenatal and postnatal manipulations. Prenatal manipulations involve maternal stress, exposing the mother to synthetic glucocorticoids or maternal nutrient restriction. Postnatal manipulations include depriving the animal of maternal contact, modifying maternal behaviour and exposing the animal to synthetic glucocorticoids. In these protocols, the cause–effects relationship between stress and its impact on the brain can be demonstrated. By contrast, and because of ethical issues, the cause–effects impact of stress on the brain cannot be studied in humans, and most human studies are correlational by nature. However, there are some 'experiments of nature' that can be used to inform scientists about the effects of chronic exposure to early adversity on brain development and of adulthood and late-life stress effects on the brain. Intrauterine under-growth and low birth weight are considered indices of prenatal stress (including malnutrition) in humans. In terms of postnatal stress, low socio-economic status, maltreatment and war are considered adverse events. In adults and older adults, studies of chronic caregivers (spouses of patients with brain degenerative disorders, parents of chronically sick children and health-care professionals) provide a human model of the impact of chronic stress on the brain, behaviour and cognition.

Box 2 | **The stress hyporesponsive period: from animals to humans**

Despite there being clear evidence that corticotropin-releasing hormone-containing neurons are present in the fetal rat[139], in rodents noxious stimuli evoke only a subnormal hypothalamus-pituitary-adrenal (HPA) axis response during the first 2 weeks of life[140]. During this so-called stress hyporesponsive period (SHRP), baseline plasma glucocorticoid levels are lower than normal and are only minimally increased by exposure to a noxious stressor[140]. The SHRP is due to a rapid regression of the HPA axis after birth[140] and may have evolved in rodents to protect the rapidly developing brain from the impact of elevated glucocorticoids.

Evidence is accumulating that in children there may be a comparable hyporesponsive period that emerges in infancy and extends throughout most of childhood[141]. At birth, glucocorticoid levels increase sharply in response to various stressors, such as a physical examination or a heel lance. However, over the course of the first year the HPA axis becomes more insensitive to stressors. No study has assessed the exact period over which this human SHRP may occur, but in adolescents glucocorticoid levels can become elevated in response to a psychosocial stressor[141], which suggests that the SHRP could extend throughout childhood.

In rodents the SHRP is maintained primarily by maternal care (that is, the presence of the dam seems to suppress HPA axis activity); indeed, maternal separation is a potent inducer of a stress response, even during the SHRP. Similarly, in humans the apparent hyporesponsivity of the HPA axis might reflect the fact that during the first year of life the HPA axis comes under strong social regulation or parental buffering[141]. Here again, stressors that involve a lack of parental care or social contact can induce a stress response in children.

especially those who were clinically depressed in the child's early years, are at risk of heightened activity of the HPA axis[43] or of developing depression during adolescence (controlling for maternal depression during adolescence)[44]. However, it should be noted that it can be difficult to exclude potentially confounding genetic factors in such studies. Furthermore, preschool-aged children of depressed mothers exhibit electroencephalographic alterations in frontal lobe activity that correlate with diminished empathy and other behavioural problems[45].

In contrast to findings of elevated glucocorticoid levels in conditions of low parental care, studies in human children exposed to severe deprivation (for example, in orphanages or other institutions), neglect or abuse report lower basal levels of glucocorticoids, similar to what has been observed in primates[39]. One proposed mechanism for the development of hypocortisolism is downregulation of the HPA axis at the level of the pituitary in response to chronic CRH drive from the hypothalamus[46], whereas a second possible mechanism is target tissue hypersensitivity to glucocorticoids[47]. Importantly, this hypocortisolism in humans in response to severe stress may not be permanent: sensitive and supportive care of fostered children normalizes their basal glucocorticoid levels after only 10 weeks[48]. Another important finding comes from a recent study which showed that exposure to early adversity is associated with epigenetic regulation of the GR receptor, as measured in the post-mortem brains of suicide victims[49].

Stress in adolescence

Animal studies. In rodents the period of adolescence has three stages: a prepubescent or early adolescent period from day 21 to 34, a mid-adolescent period from day 34 to 46 and a late adolescent period from day 46 to 59 (REF. 50). In humans, adolescence is often considered to demarcate the period of sexual maturation (that is, starting with menarche in girls).

Although adolescence is a time of significant brain development, particularly in the frontal lobe[51], there has been relatively little research on stress during this period in rodents. In adolescent rodents, HPA function is characterized by a prolonged activation in response to stressors compared with adulthood. Moreover, prepubertal rats have a delayed rise of glucocorticoid levels and prolonged glucocorticoid release in response to several types of stressors compared with adult rats[52], owing to incomplete maturation of negative-feedback systems[53].

In contrast to adult rats, which show a habituation of the stress response with repeated exposure to the same stressor[54], juvenile rats have a potentiated release of adrenocorticotropic hormone and glucocorticoids after repeated exposure to stress[55], suggesting that the HPA axis responses to acute and chronic stress depend on the developmental stage of the animal. Compared with exposure to stress in adulthood alone, exposure to stress as both a juvenile and an adult increases basal anxiety levels in the adult[56]. Moreover, exposure to juvenile stress results in greater HPA axis activation than a double exposure to stress during adulthood[56], and this effect is long-lasting. These results suggest that repeated stress in adolescence leads to greater exposure of the brain to glucocorticoids than similar experiences in adulthood.

The fact that the adolescent brain undergoes vigorous maturation and the fact that, in rats, the hippocampus continues to grow until adulthood suggest that the adolescent brain may be more susceptible to stressors and the concomitant exposure to high levels of glucocorticoids than the adult brain. Consistent with this hypothesis are findings that increased glucocorticoid levels before but not after puberty alter the expression of genes for NMDA (*N*-methyl-D-aspartate) receptor subunits in the hippocampus[57]. In addition, chronic, variable stress during the peripubertal juvenile period results in reduced hippocampal volume in adulthood, which is accompanied by impairments in Morris water maze navigation and delayed shutdown of the HPA response to acute stress[58]. These differences became evident only in adulthood[58], suggesting that stress in adolescence reduces hippocampal growth. Finally, the effects of juvenile stress are long-lasting: adult rats exposed to juvenile stress exhibit reduced exploratory behaviour and poor avoidance learning[59]. Moreover, stress in adolescence increases susceptibility to drugs of abuse during the adolescent period[60] and in adulthood[61].

Human studies. Interestingly, studies in human adolescents also suggest that the adolescent period is associated with heightened basal and stress-induced activity of the HPA axis[62]. This could be related to the dramatic changes in sex steroid levels during this period, as these steroids influence HPA axis activity[50]. However, studies of stress in adolescent rats cannot be translated directly to humans because the brain areas that are undergoing development during adolescence differ between rats and humans: although the rodent hippocampus continues to

develop well into adulthood, in humans it is fully developed by 2 years of age[63]. The frontal cortex and amygdala continue to develop in both species, but humans have larger ontogenic bouts of development in frontal regions than do rodents (BOX 3).

There are indications that the adolescent human brain might be especially sensitive to the effects of elevated levels of glucocorticoids and, by extension, to stress. Recent studies on the ontogeny of MR and GR expression show that GR mRNA levels in the prefrontal cortex are high in adolescence and late adulthood compared with in infancy, young adulthood and senescence[64]. This suggests that the cognitive and emotional processes that are regulated by these brain areas might be sensitive to GR-mediated regulation by glucocorticoids in an age-dependent manner. Various forms of psychopathology, including depression and anxiety, increase in prevalence in adolescence[65,66]. Periods of heightened stress often precede the first episodes of these disorders, raising the possibility that heightened HPA reactivity during adolescence increases sensitivity to the onset of stress-related mental disorders.

Adolescence is also a period in which the long-lasting effects of earlier exposures to stress become evident. Adolescents who grew up in poor economic conditions have higher baseline glucocorticoid levels[67], as do adolescents whose mothers were depressed in the early postnatal period[44]. High early-morning glucocorticoid levels that vary markedly from day to day during the transition to adolescence are not associated with depressive symptoms at that time, but they predict increased risk for depression by age 16 (REF. 44).

Although early-life stress impairs hippocampal development in rodents, there is currently little evidence of comparable effects in humans. Children exposed to physical or sexual abuse early in life do not exhibit reduced hippocampal volume (relative to whole-brain size) as adolescents, although adults with these histories do show volume reductions[68]. This finding holds even when the abused children have been selected for chronic post-traumatic stress disorder (PTSD), and even though in some cases they exhibit overall reductions in brain volume[69]. By contrast, alterations in grey matter volume and the neuronal integrity of the frontal cortex, and reduced size of the anterior cingulate cortex, have been reported in adolescents exposed to early (and continued) adversity[70]. Together, these results suggest that in humans the frontal cortex, which continues to develop during adolescence, might be particularly vulnerable to the effects of stress during adolescence. By contrast, the hippocampus, which develops mainly in the first years of life, might be less affected by exposure to adversity in adolescence.

Stress in adulthood

Animal studies. Studies on adult stress in rodents have delineated the effects of acute versus chronic stress on brain and behaviour. The impact of acute stressors depends on the level of glucocorticoid elevations, with small increases resulting in enhanced hippocampus-mediated learning and memory, and larger, prolonged elevations impairing hippocampal function[71]. The inverted-U-shaped effects of acute glucocorticoid elevations might serve adaptive purposes by increasing vigilance and learning processes during acute challenges.

The mechanism that underlies the acute biphasic actions of glucocorticoids on cognition involves the adrenergic system in the basolateral nucleus of the amygdala. By enhancing noradrenergic function in the amygdala, glucocorticoids have a permissive effect on the priming of long-term potentiation in the dentate gyrus by the basolateral nucleus[72]. This modulation of noradrenergic function by glucocorticoids has been linked to the enhanced memory for emotional events that occur under stress[73].

Chronic stress or chronic exogenous administration of glucocorticoids in rodents causes dendritic atrophy in hippocampal CA3 pyramidal neurons[74]. However, these changes take several weeks to develop and are reversed by 10 days after the cessation of the stressor[75]. Chronic stress in adult rats also inhibits neurogenesis in the dentate gyrus[76] and causes hippocampal volume loss[77]. Importantly, this volume decrease is not associated with reduced neuron numbers and is not limited to the dentate gyrus[78], suggesting that reduced neurogenesis might not be the only contributing factor. The morphological changes that take place in the hippocampus after chronic stress have been related to changes in spatial learning[79], which are reversed following 21 days of withdrawal from stress[80]. Here, it is interesting to note that in contrast to the effects of chronic or severe stress on the brain and behaviour earlier in life, which are long-lasting, effects of adulthood stress — even chronic stress — are reversed after a few weeks of non-stress. These differences between the effects of early and adulthood

Box 3 | **Stress effects on the brain: timing is crucial**

In animals that give birth to relatively mature young (for example, primates, sheep and guinea pigs), maximal brain growth and most of the neuroendocrine maturation occurs *in utero*. However, in rats, rabbits and mice the mother gives birth to immature young and most of the neuroendocrine development occurs in the postnatal period[17]. In humans the hypothalamus-pituitary-adrenal axis is highly responsive at birth, but brain development is not finished. The volume of the hippocampal formation increases sharply until the age of 2 years, whereas amygdala volume continues to increase slowly until the late 20s[63]. By contrast, the development of the frontal cortex in humans takes place mostly between 8 and 14 years of age[63]. The late increase in prefrontal volumes is consistent with data showing that this region develops latest in terms of myelination and synaptic density in humans[136].

Prenatal and postnatal stress can both thus have contrasting effects in different species because perinatal manipulations will affect different stages of development as a function of the species studied. Consequently, stress in the first week of the rodent's life is often developmentally equated with stress during the last trimester of human gestation.

Significant decreases in brain volume have been reported in aged animals and humans, although most of the studies performed are cross-sectional. In men the volume of the hippocampus starts to decrease by the second decade of life, whereas in women this decrease is delayed until around 40 years of age, possibly owing to the protective effects of oestrogen[137]. By contrast, amygdala volume decreases around the sixth decade of life in humans[63]. In the frontal cortex, different subregions are differentially affected by aging. For example, aging is associated with shrinking of the dorsolateral and inferior frontal cortices, but no age effects have been reported for the anterior cingulate cortex, the frontal pole or the precentral gyrus[138].

stress might be related to differences in the severity of stressors to which pups and adult rats are exposed or in the development of the hippocampus at the time of exposure.

Pyramidal neurons in layers II/III of the prefrontal cortex also show dendritic retraction and a reduction in spine number[81] in response to chronic stress in adulthood — this can be observed 24 h after a single forced-swim stress[82] — but remodelling occurs after cessation of the stressor[83]. In accordance with these findings, glucocorticoid hypersecretion is associated with reduced volume of at least the right anterior cingulate cortex in rodents[84]. Contrary to the reduction in hippocampal and frontal volumes, chronic stress in adult rodents leads to dendritic hypertrophy in the basolateral amygdala[85]. Moreover, a recent study showed that even a single acute administration of glucocorticoids caused dendritic hypertrophy in this area 12 days later[86]. The dendritic hypertrophy was correlated with anxiety in both the acute[86] and the chronic[85] administration paradigms.

Human studies. In humans, studies of the effects of acute stress confirm animal studies and report the presence of an inverted-U-shaped relationship between glucocorticoid levels and cognitive performance[87]. However, contrary to animal studies, in which most laboratory tests for learning and memory involve a fear and/or an emotional process[88], tests of learning and memory in humans can differentiate the effects of glucocorticoids on the processing of neutral versus emotional information. Most studies to date have shown that acute glucocorticoid elevations significantly increase memory for emotional information, whereas they impair the retrieval of neutral information[89].

Only a few reports suggest that there is an association between exposure to chronic stress and reduced hippocampal volume in individuals not suffering from mental health disorders (for a review see REF. 90). However, a recent study reported that low self-esteem, a potent predictor of increased reactivity to stress in humans[91], is associated with reduced hippocampal volume[92].

Most of the studies of chronic-stress effects on the adult human brain have concentrated either on stress-related psychopathologies or on the impact of early-life stress on adult psychopathology. A large number of studies have reported elevated basal glucocorticoid levels in individuals with some forms of depression[93], whereas reduced basal glucocorticoid concentrations have been reported in patients with PTSD[94], although this finding has been controversial[95]. Given that low glucocorticoid concentrations seem to develop in early childhood in response to neglect or trauma, it is possible that low cortisol predicts vulnerability to developing PTSD in response to trauma in adulthood.

Studies of adults who suffered childhood abuse also reveal hyper-reactivity of the HPA axis in abused, depressed individuals[96] and hypoactivity in those with PTSD[94]. The changes in abused, depressed adults have been associated with CRH-induced 'escape' of glucocorticoid secretion from suppression by treatment with dexamethasone[97], suggesting that the glucocorticoid feedback of the HPA axis is impaired under conditions of increased hypothalamic drive. Thus, a decreased capacity of glucocorticoids to inhibit the HPA axis when it is stimulated could further accentuate CNS responses to stressors. In agreement with this suggestion, increased cerebrospinal fluid CRH levels have been reported in individuals who reported childhood stress[98] and childhood abuse[99].

Decreased hippocampal volume and function are landmark features of depression and PTSD[100,101]. One cross-sectional study[102] found that a smaller hippocampus in women with major depression was associated with experiences of childhood trauma, whereas depressed women without such trauma had hippocampal volumes similar to healthy controls. This supports the notion that certain brain changes in patients with depression or PTSD could represent markers of vulnerability for the disorder rather than markers of the disorder itself. This finding is in line with results from a twin study of Vietnam veterans[103] which showed that decreased hippocampal volume is not a consequence of combat exposure or PTSD: decreased volume was also present in unexposed co-twins, and thus it might be a pre-existing risk factor for PTSD that could be genetic or rooted early in life.

Stress in aging

Animal studies. Approximately 30% of aged rats have basal glucocorticoid hypersecretion, which is correlated with memory impairments and reduced hippocampal volume[104]. If a middle-aged rat is exposed for a long period to high levels of exogenous glucocorticoids, it will develop memory impairments and hippocampal atrophy[105] similar to those observed in these 30% of aged rats. Conversely, artificially keeping glucocorticoid levels low in middle-aged rats prevents the emergence of both memory deficits and hippocampal atrophy in old age[106]. Several groups have also found that chronic stress in aged rats can accelerate the appearance of biomarkers of hippocampal aging (for example, frequency potentiation and synaptic excitability thresholds) and that excess endogenous or exogenous glucocorticoids induce hippocampal dendritic atrophy and inhibit neurogenesis[107]. Finally, in aged monkeys[108] chronic glucocorticoid treatment can increase amyloid-β pathology, similar to that reported in Alzheimer's disease.

These results have given rise to the glucocorticoid cascade hypothesis[109], which suggests that there is a relationship between cumulative exposure to high glucocorticoid levels and hippocampal atrophy. It was recently renamed the neurotoxicity hypothesis[103], because the proposed explanation for this relationship is that prolonged exposure to stress hormones reduces the ability of neurons to resist insults, thus increasing the rate at which they are damaged by other toxic challenges or ordinary attrition[109]. Glucocorticoids might have a similar neurotoxic effect in the prefrontal cortex. A study demonstrated an enhanced elevation of extracellular glutamate levels post-stress in the hippocampus and medial prefrontal cortex of aged rats compared with young rats[110].

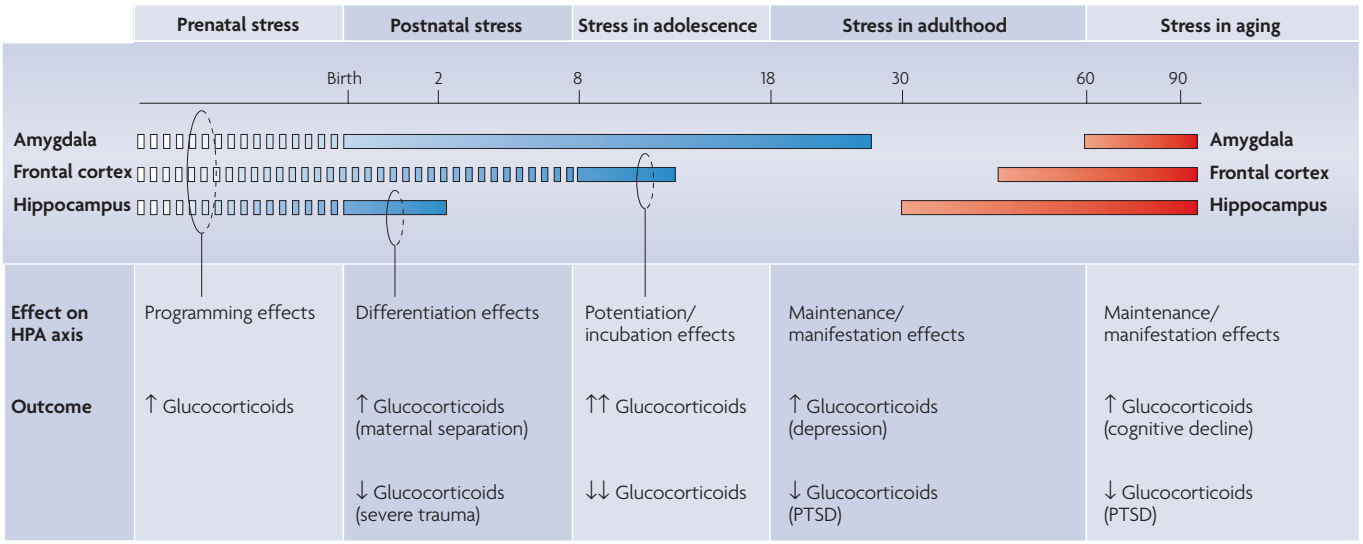

Figure 2 | **The life cycle model of stress.** How the effects of chronic or repeated exposure to stress (or a single exposure to severe stress) at different stages in life depend on the brain areas that are developing or declining at the time of the exposure. Stress in the prenatal period affects the development of many of the brain regions that are involved in regulating the hypothalamus-pituitary-adrenal (HPA) axis — that is, the hippocampus, the frontal cortex and the amygdala (programming effects). Postnatal stress has varying effects: exposure to maternal separation during childhood leads to increased secretion of glucocorticoids, whereas exposure to severe abuse is associated with decreased levels of glucocorticoids. Thus, glucocorticoid production during childhood differentiates as a function of the environment (differentiation effects). From the prenatal period onwards, all developing brain areas are sensitive to the effects of stress hormones (broken blue bars); however, some areas undergo rapid growth during a particular period (solid blue bars). From birth to 2 years of age the hippocampus is developing; it might therefore be the brain area that is most vulnerable to the effects of stress at this time. By contrast, exposure to stress from birth to late childhood might lead to changes in amygdala volume, as this brain region continues to develop until the late 20s. During adolescence the hippocampus is fully organized, the amygdala is still developing and there is an important increase in frontal volume. Consequently, stress exposure during this period should have major effects on the frontal cortex. Studies show that adolescents are highly vulnerable to stress, possibly because of a protracted glucocorticoid response to stress that persists into adulthood (potentiation/incubation effects). In adulthood and during aging the brain regions that undergo the most rapid decline as a result of aging (red bars) are highly vulnerable to the effects of stress hormones. Stress during these periods can lead to the manifestation of incubated effects of early adversity on the brain (manifestation effects) or to maintenance of chronic effects of stress (maintenance effects). PTSD, post-traumatic stress disorder.

Increased glutamate levels after stress, and perhaps other neurotoxic insults, might thus increase the vulnerability of the aging brain to neuronal damage.

Human studies. Aging, healthy humans exhibit higher mean diurnal levels of cortisol than younger individuals[111], and a longitudinal study has found that elevated plasma glucocorticoid levels over years in older adults negatively correlates with hippocampal volume and memory[112]. Given that aged individuals with Alzheimer's disease present both memory impairments and hippocampal atrophy, studies have assessed basal glucocorticoid levels in this population and found that they are higher than in controls[113]. In addition, chronic glucocorticoid treatment has been shown to worsen cognition in people with Alzheimer's disease[114].

The frontal lobe also seems to be sensitive to glucocorticoid effects during human aging. Using a novel *in vitro* post-mortem tracing method on human brain slices, Dai *et al.*[115] found an inverted-U-shaped effect of glucocorticoids on axonal transport in prefrontal neurons with, in most cases, a stimulating effect at low concentrations and a depressing effect at high concentrations. Given that axonal transport plays a crucial part in neuronal survival and function, these results suggest that glucocorticoids potentially have negative effects on prefrontal cortex neurons' survival and/or function.

A model of stress effects throughout life

The data obtained in animals and humans suggest that chronic or repeated exposure to stress has enduring effects on the brain, through activation of the HPA axis and the release of glucocorticoids, with the highest impact on those structures that are developing at the time of the stress exposure (in young individuals) and those that are undergoing age-related changes (in adult and aged individuals). Stress in the prenatal period affects the development of many of the brain regions that have a role in regulating the HPA axis — that is, the hippocampus, the frontal cortex and the amygdala (programming effects (FIG. 2)). During childhood the hippocampus — which continues to develop after birth — might be the brain region that is most vulnerable to the effects of chronic stress, possibly through a process of increased CRH drive in the hippocampus[116]. Because it modulates HPA axis activity, altered functioning of the hippocampus

might cause glucocorticoid hyposecretion in cases of severe abuse, or increased basal cortisol levels in cases of maternal deprivation (differentiation effects (FIG. 2)). By contrast, in adolescence the frontal cortex, which undergoes major development at this stage, may be most vulnerable to the effects of stress, possibly leading to a protracted glucocorticoid response to stress that persists into adulthood (potentiation/incubation effects (FIG. 2)). In adulthood and old age the brain regions that undergo the most rapid decline as a result of aging are highly vulnerable to the effects of stress hormones. For example, in the hippocampus glucocorticoids affect neurogenesis, neuronal survival rate and dendritic arborization (manifestation/maintenance effects (FIG. 2)).

The neurotoxicity and vulnerability hypotheses. The data obtained in adults and older animals and humans have led to the neurotoxicity hypothesis[109], which suggests that prolonged exposure to glucocorticoids reduces the ability of neurons to resist insults, increasing the rate at which they are damaged by other toxic challenges or ordinary attrition[109]. This hypothesis implies that a reduced hippocampal size is the end product of years or decades of PTSD, depressive symptoms or chronic stress. Although the neurotoxicity hypothesis has been confirmed by various animal and human studies, it does not explain the hyposecretion of glucocorticoids that occurs in patients suffering from PTSD, who also present reduced hippocampal volume.

Data obtained in children, adolescents or adult animals and humans exposed to acute or early-life trauma have led to the vulnerability hypothesis[103]. In contrast to the neurotoxicity hypothesis, the vulnerability hypothesis suggests that reduced hippocampal volume in adulthood is not a consequence of chronic exposure to PTSD, depression or chronic stress, but is a pre-existing risk factor for stress-related disorders that is induced by genetics and/or early exposure to stress[117]. Unlike the neurotoxicity hypothesis, the vulnerability hypothesis can explain glucocorticoid hyposecretion in patients with PTSD. Indeed, studies in children facing significant adversity, such as abuse, report the development of glucocorticoid hyposecretion[39], which might last until adulthood and confer vulnerability to developing PTSD as a result of trauma.

We think that the two hypotheses are not mutually exclusive when viewed from a developmental perspective. Indeed, the data summarized in this Review suggest that there might be early windows of vulnerability (or sensitive periods[68]) during which specific regions of the developing brain are most susceptible to environmental influences, through a neurotoxicity process. Exposure to stress and/or adversity during these key vulnerable periods might slow the development of those brain regions for the duration of the adversity. When measured in adulthood, the reduced volumes of these brain regions could be a strong marker of the time of exposure to early adversity rather than of the effects of specific traumas on various brain regions. These windows of vulnerability could also be used to predict the nature of the psychopathology that will result from exposure to stress at different ages. Exposure to adversity at the time of hippocampal development could lead to hippocampus-dependent emotional disorders, which would be different from disorders arising from exposure to adversity at times of frontal cortex development. Two recent studies support this hypothesis. The first reported that women who experienced trauma before the age of 12 years had increased risk for major depression, whereas women who experienced trauma between 12 and 18 years of age more frequently developed PTSD[118]. The second study reported that repeated episodes of sexual abuse were associated with reduced hippocampal volume if the abuse occurred early in childhood, but with reduced prefrontal cortex volume if the abuse occurred during adolescence[119]. These results suggest that, similar to what has been observed in animals[120], there may be distinct structural, neuropsychological and neuropsychiatric sequelae of early abuse, depending in part on the age or developmental stage of the brain when the insult occurred.

Besides slowing down the development of the brain during the time of adversity, leading to reduced brain volumes in adulthood, stress in early life could modify the developmental trajectory of the brain. The potential immediate benefit of such modifications is that they might increase acute survival probability, but they could have negative long-term effects. During childhood and adolescence the brain undergoes a period of overproduction and pruning of synapses[121]. One of the brain regions that shows the slowest development over the lifespan is the amygdala (BOX 3). It is interesting to note that contrary to the hippocampus and the frontal lobe — which show volume reduction as a result of chronic stress — the amygdala increases in volume under chronic stress, owing to increased dendritic arborization. Given that the amygdala plays a significant part in the detection of fear and threat, it is possible that throughout evolution increases in amygdala volume in response to stress might have improved the detection of threatening information and so increased survival probability. If this is indeed the case, young children exposed to adversity should also have increased amygdala volume, but no study has yet examined this important question.

This acute effect of adversity on brain organization could have negative long-term consequences. Stress at key periods of synaptic organization could modify the trajectories of connections, leading to an incubation period, such that the effects of stress would not be apparent at the time of adversity but would emerge later, when the synaptic organization has been completed. Studies showing protracted effects of early-life stress that emerge at puberty support this suggestion[44]. Furthermore, although depression is the most extensively documented outcome of exposure to chronic sexual abuse in adults, it is not a common occurrence in children suffering abuse. Indeed, the average time from the onset of abuse to the emergence of clinical depression is 11.5 years, with the first major episode occurring during adolescence[122]. It is thus conceivable that in susceptible individuals exposure to early adversity during a window of vulnerability sets into motion a series of events that lead to a heterotypic reorganization of synaptic development, resulting in a protracted expression of depression or PTSD.

This same process could also explain the development of resilience in face of adversity. Environmental enrichment in rodents is a potent inducer of changes in neurogenesis and/or dendritic arborization in the hippocampus, and has been documented to lead to increases in hippocampal volume[123]. In children facing early adversity, forms of environmental enrichment, such as support from a family member, enriched day care or school environment or social support from members of the community, could induce a similar heterotypic reorganization of synaptic development, programming of neurotrophic factors or changes in gene expression that could lead to resilience later in life. If this is the case, it could be suggested that any type of intervention performed during the early years could not only have a tremendous effect in preventing the deleterious impact of chronic stress and/or early abuse on the developing brain, but could also help to prevent effects on the brain of chronic stress occurring in adulthood or during aging.

Conclusions and future directions

Although studies on stress have provided a wealth of data delineating the effects of acute and chronic stress on the developing brain, much remains to be done to fully understand how the brain develops pathology or resilience in the face of adversity. We believe that three main factors should receive special consideration in future studies on stress in both animals and humans.

The first factor is sex and gender. Sex refers to the biological differences between males and females, whereas gender refers to the different roles (gender role and gender identity) that men and women may have during their lifetime. Both sex and gender might have potent influences on stress reactivity in humans of all ages. However, most studies of the effects of stress on the brain, behaviour and cognition have tested only male animals or humans. This is a major issue considering that studies in both animals[50] and humans[124] report sex differences in response to stress, and considering the gender gap ratio (two girls for one boy) that emerges in early adolescence for the risk of depression[125]. To this day, a consistent finding in the endocrine literature is that the risk of depression in adolescent girls increases with decreasing age at menarche[126]. An increased sensitivity of girls to environmental and/or family adversity, along with interactions between glucocorticoids and gonadal steroids, could be a potential explanation for the increased risk of depressive disorders in females. Recent results showing an earlier age at menarche in girls exposed to early adversity[127] support this suggestion.

The second factor that should be considered in future studies is exposure to environmental toxins. Today, children in many cities are chronically exposed, at background levels, to a range of common toxins that are environmentally persistent and that tend to be lipophilic and bioaccumulate, such as lead and bisphenol A[128]. These agents reach humans mainly through food and food additives, and they can be transferred to the fetus through the placenta and to infants through maternal milk[129]. They have been shown to affect the endocrine system in laboratory animals and in wildlife, and consequently have been called 'endocrine-disrupting chemicals' (REF. 130). A recent study showed that prenatal and postnatal exposure to lead is associated with increased glucocorticoid responses to acute stress in children[131]. Also, perinatal exposure to endocrine-disrupting chemicals is associated with an earlier age at menarche among girls[132]. Taken together, these results suggest that both the timing of sexual maturation and stress reactivity may be sensitive to relatively low levels of endocrine-disrupting chemicals in the environment.

The third factor that should receive greater attention is circadian rhythmicity. Sleep deprivation, shift work and jet lag all disrupt normal biological rhythms and have major impacts on health. Interestingly, circadian disorganization is often observed in stress-related disorders such as depression[133] and PTSD[134]. The discovery of the molecular clock that is responsible for the generation of circadian rhythms[135] provides new insights into how rhythm abnormalities might lead to greater vulnerability to stress at various ages. Most studies performed in animals and humans do not measure the circadian fluctuations in glucocorticoid levels, but rather concentrate on specific time points across the day. Although such measurements are easier, they do not provide the full spectrum of circadian variations, which could inform us about specific changes in circadian organization in response to chronic stress across the lifespan. Consequently, studies assessing multiple time points for glucocorticoid secretion across a whole day or several days are needed in order to document the complex relationships that exist between reactivity to stress and circadian (dis)organization.

Animal and human studies have provided a wealth of results showing the negative effects of chronic exposure to stress and/or adversity on the developing brain. However, stress is not and should not be considered as a negative concept only. Stress is a physiological response that is necessary for the survival of the species. The stress response that today can have negative consequences for brain development and mental health may have conferred the necessary tools to our ancestors in prehistorical times for surviving in the presence of predators. Studies of modern individuals who have developed resilience by facing significant adversity should inform us about the physiological and psychological mechanisms at the basis of vulnerability or resilience to stress. Understanding these mechanisms, which are possibly rooted in genes and modulated by the family environment, is extremely important if one wants to provide interventions early enough to individuals who are the most likely to respond to them. This article has reviewed the potential for early intervention to prevent the deleterious effects of stress on the brain, behaviour and cognition. After more than 30 years of research on the negative effects of stress on the brain, it is now time to turn our attention to the potential positive impact of early interventions on brain development. These results could help us to develop social policies that treat the problem of early-life stress at its root — that is, in the family home.

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FURTHER INFORMATION
Sonia J. Lupien's homepage: http://www.humanstress.ca
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