DOCUMENT SUMMARY

This comprehensive review examines the effects of chronic exposure to stress hormones on the brain, behavior, and cognition across the entire lifespan, from the prenatal period to old age. The paper synthesizes findings from animal and human studies to show how the timing and duration of stress impact brain structures like the hippocampus, amygdala, and frontal cortex. A model is proposed to explain how stress exposure at different developmental stages can lead to different mental health and cognitive outcomes, integrating the neurotoxicity and vulnerability hypotheses.

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FORMATTED CONTENT

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.

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. 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 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. A single or repeated exposure of a pregnant female to **stress** or to **glucocorticoids** 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. In rats **prenatal stress** leads to long-term increases in **HPA axis** activity. 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**.

Glucocorticoids are important for normal brain maturation: they initiate terminal maturation, remodel axons and dendrites and affect cell survival; 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. 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. The **hippocampus** inhibits **HPA axis** activity, 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.

Exposure to **prenatal stress** has three major effects on adult behaviour: learning impairments, especially in aging rats; enhanced sensitivity to drugs of abuse; and increases in anxiety- and depression-related behaviours. The impaired learning is thought to result from the effects of **prenatal stress** on hippocampal function, whereas the effects on anxiety are thought to be mediated by **prenatal stress**-induced increases in CRH in the **amygdala**.

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. First, maternal **stress** or anxiety, depression and **glucocorticoid** treatment during pregnancy 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, 5 years and 10 years.

Disturbances in child development (both neurological and cognitive) and behaviour have been associated with maternal **stress** and maternal depression during pregnancy, and with fetal exposure to exogenous **glucocorticoids** in early pregnancy. 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.

Postnatal stress

Animal studies. Although in rodents the postnatal period is relatively hyporesponsive to **stress**, 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**. Protracted maternal separation also reduces pituitary CRH binding sites, and low levels of maternal care reduce **GR** levels in the **hippocampus**. 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.

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. 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.

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. 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, whereas a second possible mechanism is target tissue hypersensitivity to **glucocorticoids**.

Stress in adolescence

Animal studies. In adolescent rodents, HPA function is characterized by a prolonged activation in response to stressors compared with adulthood. In contrast to adult rats, which show a habituation of the **stress** response with repeated exposure to the same stressor, juvenile rats have a potentiated release of adrenocorticotropic hormone and **glucocorticoids** after repeated exposure to **stress**, suggesting that the **HPA axis** responses to acute and chronic **stress** depend on the developmental stage of the animal. 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.

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**. 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**. Various forms of psychopathology, including depression and anxiety, increase in prevalence in adolescence. 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.

Stress in adulthood

Animal studies. 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. Chronic **stress** or chronic exogenous administration of **glucocorticoids** in rodents causes dendritic atrophy in hippocampal CA3 pyramidal neurons. However, these changes take several weeks to develop and are reversed by 10 days after the cessation of the stressor. Pyramidal neurons in layers II/III of the **prefrontal cortex** also show dendritic retraction and a reduction in spine number in response to chronic **stress** in adulthood. Contrary to the reduction in hippocampal and frontal volumes, chronic **stress** in adult rodents leads to dendritic hypertrophy in the basolateral **amygdala**.

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. Most studies to date have shown that acute **glucocorticoid** elevations significantly increase memory for emotional information, whereas they impair the retrieval of neutral information.

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, whereas reduced basal **glucocorticoid** concentrations have been reported in patients with **PTSD**. Decreased hippocampal volume and function are landmark features of depression and **PTSD**.

Stress in aging

Animal studies. Approximately 30% of aged rats have basal **glucocorticoid** hypersecretion, which is correlated with memory impairments and reduced hippocampal volume. 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 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. These results have given rise to the **glucocorticoid cascade hypothesis**, which suggests that there is a relationship between cumulative exposure to high **glucocorticoid** levels and hippocampal atrophy.

Human studies. Aging, healthy humans exhibit higher mean diurnal levels of **cortisol** than younger individuals, and a longitudinal study has found that elevated plasma **glucocorticoid** levels over years in older adults negatively correlates with hippocampal volume and memory.

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).

The neurotoxicity and vulnerability hypotheses.

> The data obtained in adults and older animals and humans have led to the **neurotoxicity hypothesis**, 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. This hypothesis implies that a reduced hippocampal size is the end product of years or decades of **PTSD**, depressive symptoms or chronic **stress**.

> Data obtained in children, adolescents or adult animals and humans exposed to acute or early-life trauma have led to the **vulnerability hypothesis**. 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**.

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) during which specific regions of the developing brain are most susceptible to environmental influences, through a **neurotoxicity** process.

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**. 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 and humans 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.

The second factor that should be considered in future studies is exposure to **environmental toxins**. These agents... have been shown to affect the endocrine system in laboratory animals and in wildlife, and consequently have been called 'endocrine-disrupting chemicals'.

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 and **PTSD**.

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.