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Effects of Stress on Memory: Relevance for Human Aging

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Synonyms

Changes in stress vulnerability during aging: Focus on the brain; Effects of stress on memory: Relevance for human aging; HPA axis alterations during aging: Impact on cognition

Introduction

Is aging associated with a more pronounced susceptibility to stress? Do older people respond differently to stress, and if so, how does this influence their cognitive performance? Might chronic stress be one of the reasons for the large interindividual variance observed in cognitive aging? The present chapter aims to answer these and related questions. A neuroendocrine perspective is taken, focusing on stress hormones and their action in the human brain. The response patterns of young people are described before age-related changes are discussed. Acute and chronic stress effects are then compared with each other, and finally, some possible lines of intervention are characterized.

Definition of Stress

A common definition is that stress occurs when a person perceives a challenge to his or her internal or external balance (homeostasis; De Kloet et al. 2005). Thus, a discrepancy between what "should be" and "what is" induces stress. A stressor can be physical (e.g., cold, hunger) or psychological (e.g., work overload, mobbing, neighborhood violence, marital problems), as well as acute or chronic. The subjective evaluation of the stressor and of available coping resources determines its impact on the individual (Lazarus 1993). Something perceived as a threat by one person might be perceived as an exciting challenge by another. There is thus substantial interindividual variability in the vulnerability to stress. As humans are social animals, a threat to the social self (social evaluative threat), in combination with uncontrollability of the situation, is especially potent in prompting stress (Dickerson and Kemeny 2004). As further outlined below, genetic susceptibilities, when combined with early adversity, render an individual more vulnerable in adulthood.

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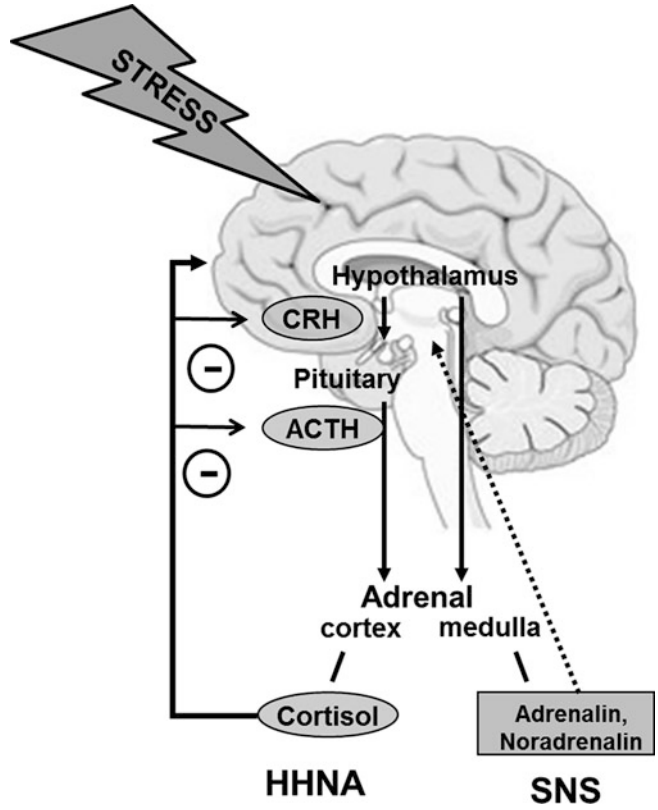


Effects of Stress on Memory: Relevance for Human Aging, Fig. 1 Stress activates two neurohormonal systems: the rapidly acting sympathetic nervous system (*SNS*) and the slightly slower hypothalamic-pituitary-adrenal (*HPA*) axis. Activation of the hypothalamus stimulates the SNS to secrete (nor)epinephrine from the adrenal medulla. These catecholamines cannot easily pass the blood-brain barrier but can exert excitatory actions in the brain by stimulating the vagus nerve (hence the *dotted line*). The hypothalamus releases corticotropin-releasing hormone (*CRH*), which stimulates the secretion of adrenocorticotropin (*ACTH*) from the anterior pituitary gland into the blood stream. ACTH stimulates the adrenal cortex to release glucocorticoids (GCs, mostly cortisol in humans), which can easily pass the blood-brain barrier and modulate brain functions involved in learning and memory (see text). GCs exert negative feedback effects (indicated by the *minus* symbol) on the hypothalamus and the pituitary gland, leading to reduced activity of the HPA axis in the aftermath of stress

The Two Stress Systems: HPA and SNS

Stress leads to neuroendocrine responses aimed at facilitating adaptation. In this context, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) play the most important roles. SNS activity leads to the rapid release of (nor)epinephrine from the adrenal medulla, which constitutes the first response wave. Activity of the HPA axis on the other hand leads to the release of glucocorticoids (GCs; cortisol in humans, corticosterone in most laboratory rodents) from the adrenal cortex. This response is slower and constitutes the second response wave (De Kloet et al. 2005). The two systems are illustrated in Fig. 1.

GCs are lipophilic hormones that can enter the brain, where they influence regions involved in cognitive functions (e.g., amygdala, hippocampus, and prefrontal cortex). These effects are mediated by the two receptors for the hormone: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which differ in their affinity for GCs and in their localization. While MR activation leads to enhanced neuronal excitability, GR activation causes a delayed

suppression or normalization of the neuronal network (Joels et al. 2008). Their activation furthermore leads to an altered expression of responsive genes. In addition, GCs can exert more rapid non-genomic effects which, in part, are mediated by membrane-bound MRs (Joels et al. 2008).

After acute stress, the HPA axis' negative feedback leads to GC levels returning to baseline values within hours (De Kloet et al. 2005; Dickerson and Kemeny 2004). In periods of chronic stress on the other hand, persistent alterations of the HPA axis can occur, leading to continuingly elevated cortisol levels. However, elevated cortisol concentrations, as typically observed in major depression, are not always the consequence of chronic stress (Wolf 2008). For example, reduced cortisol levels occur in several stress-associated somatoform disorders (Fries et al. 2005) as well as in post-traumatic stress disorder (Wolf 2008).

Age-Associated Changes in HPA Axis Activity/Reactivity

Since HPA axis alterations are a close correlate of or even a determining factor in the onset of different diseases, the assessment of the integrity and functioning of HPA axis regulation is of major interest in older individuals in particular.

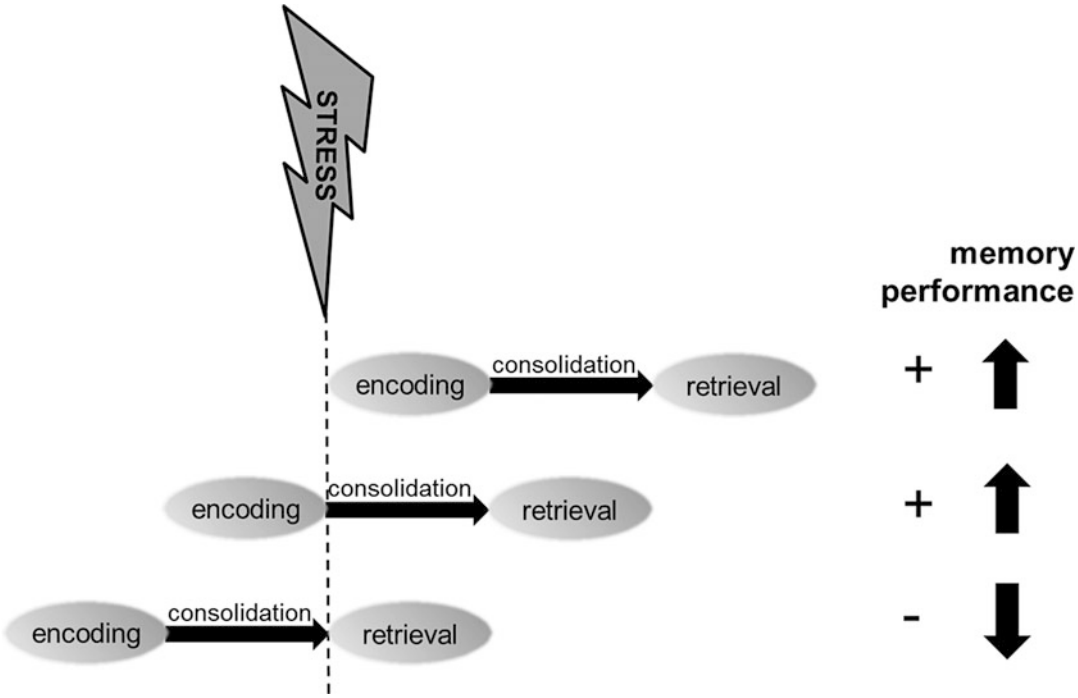
Aging is accompanied by several distinct alterations affecting basal HPA activity as well as the system's response to stress or pharmacological manipulations (Lupien et al. 2009). Regarding the circadian profile, several studies have revealed an increase in nocturnal nadir levels with age, meaning that older people are exposed to higher levels of cortisol during the night (Wolf and Kudielka 2008). A somewhat different picture has emerged for the cortisol awakening response (CAR), which occurs directly after awakening and is associated with a robust increase in cortisol concentrations during the first 30 min after waking up. During aging, this response appears to become more blunted, a phenomenon which has been linked to atrophy of the hippocampus (Pruessner et al. 2010), a structure critically involved in the supra-hypothalamic control of the HPA axis and, at the same time, a structure of vital importance for episodic memory (see below).

Longitudinal studies indicate that not all older participants show an increase in basal cortisol levels over the years. A substantial interindividual variance exists, ranging from increasing or stable to even decreasing levels (Lupien et al. 2009). To summarize, the existing data point to altered basal cortisol concentrations during the nocturnal trough, while cortisol levels remain mainly unchanged or show only slight changes over the course of the day (Wolf and Kudielka 2008).

During the past decades, several studies have investigated the reactivity of the HPA axis using psychosocial laboratory stressors such as the Trier Social Stress Test. In this test, participants have to deliver a speech in front of an emotionally cold, nonresponsive committee. In addition, a difficult mental calculation task has to be performed. Based on observations made in rodents, older participants were expected to show a more pronounced and/or more prolonged stress response. Indeed, this is what several well-conducted studies observed, even though findings are not unequivocal (Wolf and Kudielka 2008), especially concerning some of the sex differences observed.

A different approach involves pharmacological stimulation of the HPA axis using, for example, CRH (with or without pretreatment with dexamethasone). The majority of these studies have found evidence for an enhanced HPA reactivity with aging, accompanied by an impaired negative feedback. Interestingly, these alterations appear to be more pronounced in older women (Otte et al. 2005).

The factors causing the HPA axis hyperactivity observed during aging in some individuals remain poorly understood. Possible candidates are early adversity or chronic stress (Lupien et al. 2009). However, metabolic alterations associated with glucose intolerance or type 2 diabetes (Convit 2005) should also be considered. Alternatively, degenerative processes in the central nervous system might be the starting point of the age-associated HPA axis alterations, since it



Effects of Stress on Memory: Relevance for Human Aging, Fig. 2 Memory phase-dependent effects of stress on long-term memory. Immediate pre- or post-learning stress enhances memory consolidation, thus leading to enhanced memory retrieval hours, days, or weeks later. In contrast, stress shortly before memory retrieval impairs long-term memory by temporarily blocking the accessibility of the memory trace

is known that degeneration of supra-thalamic control centers of the HPA axis (e.g., the hippocampus) leads to HPA axis hyperactivity. Of course, these explanations are not exclusive and might interact at multiple levels.

Stress and Cognition: Acute Effects

Stress affects the central processing of incoming information at multiple levels. Early influences on perception and attention have been documented, as well as later effects on working memory and long-term memory. The present chapter will focus on the influence of stress on long-term memory because it is the area which has been best characterized in young adults and at least partially investigated with respect to aging.

Long-term memory can be subdivided into declarative or explicit and non-declarative or procedural (implicit) memory. Based on its content, declarative memory can be further subdivided into episodic memory (recall of a specific event which can be located in space and time) and semantic memory (our knowledge of the world). The medial temporal lobe is critical for declarative memory, with the hippocampus being especially important for episodic memory (Wolf 2009).

Long-term memory can further be subdivided into different memory phases, namely, acquisition (or initial learning), consolidation (or storage), and retrieval (or recall). The literature regarding the effects of stress on episodic memory was initially somewhat divergent and confusing, with groups reporting both enhancing and impairing effects of GCs on this form of memory. However, it has become apparent that this is largely due to the fact that the different memory phases outlined above are modulated by GCs in an opposing fashion (Wolf 2009).

GCs enhance memory consolidation, this process representing the adaptive and beneficial side of the action of GCs in the central nervous system (see Fig. 2). It has been conceptualized as the beneficial effects of "stress within the learning context," or "intrinsic stress." The terminology used emphasizes the fact that a stressful episode is remembered better, an effect which is mediated by the action of stress-released GCs on the hippocampal formation and which is very well documented in rodents. Studies have shown that an adrenergic activation in the basolateral amygdala (BLA) appears to be a prerequisite for the modulating effects of GCs on other brain regions (e.g., the hippocampus). Lesions in the BLA as well as beta-blockade abolish the enhancing effects of post-training GC administration (Roozendaal et al. 2009).

Comparable effects have been observed in humans: Immediate post-learning stress has repeatedly been linked to enhanced memory consolidation. Similar evidence comes from pharmacological studies, while neuroimaging studies have provided further evidence for a stress-induced modulation of amygdala and hippocampal activity (Wolf 2009). Pre-learning stress or cortisol studies have led to a somewhat less consistent picture. In this case, the exact timing of the stressor, the emotionality of the learning material, and the relation of the learning material to the stressor appear to be important modulatory factors (Wolf 2009).

While an enhanced memory consolidation is adaptive and beneficial, this process appears to occur at the cost of impaired retrieval (see Fig. 2). Using a 24 h delay interval, researchers were able to show that stress or GC treatment shortly before retrieval testing impairs memory retrieval in rats in a water maze. Further studies have revealed that, once again, an intact BLA and its adrenergic activation appear to be necessary for the occurrence of this negative GC effect (Roozendaal et al. 2009). Roozendaal has summarized these findings as indicative of stress putting the brain into a consolidation mode, accompanied by impaired retrieval. Such a reduction in retrieval might facilitate consolidation by reducing interference (Wolf 2009).

In humans, multiple studies have been able to demonstrate a stress-induced retrieval impairment using different stressors and different memory paradigms. Similar impairment has been induced using pharmacological cortisol elevations (Wolf 2009). Interestingly, the beneficial effects on consolidation and the impairing effects on retrieval in humans are more pronounced for emotionally arousing material. This observation fits the mentioned observation in animals that GCs can only exert effects on memory in the presence of adrenergic activity in the amygdala. This arousal can result from specifics of the learning material and/or specifics of the testing conditions.

In a meta-analysis, time of day appeared as an additional modulatory factor. Studies in which cortisol was administered before initial acquisition observed impairing effects on memory when conducted in the morning, a time of high endogenous cortisol levels in humans. In contrast, studies in the evening were more likely to observe beneficial effects (Het et al. 2005). This supports the idea of an inverted U-shaped function between cortisol levels and memory in humans, with levels too low as well as levels too high at the time of acquisition being associated with impairments, especially when retrieval is tested while cortisol levels are still elevated (Het et al. 2005).

In sum, studies in animals and humans converge on the idea that GCs acutely enhance memory consolidation while impairing memory retrieval (see Fig. 2). Within this framework, emotional arousal and a nonlinear dose-response relationship are important modulatory variables (Wolf 2009).

Age-Associated Changes in Acute Stress Effects

Few studies have investigated age-associated changes in the impact of stress or stress hormones on memory. Findings thus have to be considered as somewhat preliminary. A pharmacological study observed a cortisol-induced memory retrieval impairment in both young and old

participants (Wolf 2009). Stress studies have revealed a somewhat different picture, with older adults less impaired by the stressor. At the same time, stressed older adults appeared to be more susceptible to distraction. Interesting correlational findings have been provided by a neuroimaging study. In young participants, increasing cortisol concentrations were associated with more neural activity in several memory-relevant brain regions. In older participants, the opposite pattern was observed: Here, increasing cortisol concentrations were linked to less brain activity in the hippocampus.

In sum, the currently available literature indicates that the memory of older participants is in some cases differently affected by acute stress (Wolf and Kudielka 2008). Importantly, enhanced and reduced stress responsivities have been reported. It is therefore likely that the impact of acute stress on aging is specific for certain processes and brain regions.

Stress and Cognition: Chronic Effects

The following paragraphs will focus on the impact of chronic stress on cognition in aging. First, the long-term consequences of early life stress will be summarized. These changes have an impact throughout the lifespan leading up to old age. Next, the impact of chronic stress on memory in adulthood is reviewed, before specific age-associated changes in the chronic stress effects associated with aging are highlighted.

Long-Term Consequences of Early Life Stress

Several studies support the notion that early stress exposure is associated with accelerated neurodegenerative processes and early onset of memory decline in the course of aging (Lupien et al. 2009). Neurodevelopmental impairments in association with early stress exposure may be one of the factors explaining such cognitive disadvantages at an older age. Changes in stress susceptibility programmed early on in life might account for such deficits (Schlotz and Phillips 2009). There is evidence for pre- and postnatal stress exposure being associated with a chronically increased reactivity of the HPA axis, potentially resulting from a reduced expression of central glucocorticoid receptors (Meaney 2001). Animal models show increased corticosterone concentrations and lower GR density in the hippocampus in the offspring of stressed mothers. Also, postnatal maternal separation and poorer maternal care have been associated with reduced GR gene expression in the hippocampus, which, in turn, is associated with reduced feedback sensitivity of the HPA axis. Recently, a mechanism has been discovered in rodents that explains how environmental stimuli can impact gene expression. Permanent alterations of GR gene expression result from methylation/demethylation of specific GR promoters, a process associated, among others, with variations in maternal care (Meaney 2001). Initial evidence suggests that the human GR gene is also subject to early life programming (Schlotz and Phillips 2009). Moreover, elevated cortisol concentrations have, for example, been reported in association with reduced birth weight or preterm birth.

In the following, the consequences of chronic stress exposure throughout life on cognitive functioning will be described. It will become apparent that individuals with an increased stress susceptibility (reflecting genetic susceptibilities and/or early adversity) are especially vulnerable to stress-induced cognitive impairments in adulthood and aging (Lupien et al. 2009).

Chronic Stress During Adulthood: Effects on Cognition

Animal research provides insights into the structural alterations caused by chronic stress. One main finding is that the integrity of the hippocampus and the medial prefrontal cortex is compromised, while, in parallel, the amygdala (the “fear center” of the brain) and parts of the striatum (the “habit center” of the brain) become hyperactive (Roozendaal et al. 2009). In the hippocampus, chronic stress leads to a retraction of

dendrites (dendritic atrophy), and similar effects occur in the medial PFC (Lupien et al. 2009). This atrophy is reversible after stress termination, pointing to substantial neuroplasticity. In addition, stress leads to reduced neurogenesis in the dentate gyrus and the mPFC. Even though the function of these newborn neurons is discussed controversially, impairment of memory and learning resulting from reduced neurogenesis is likely. At the behavioral level, impaired performance in hippocampal-dependent spatial memory tasks and impaired PFC-dependent set-shifting capabilities can be observed (Roozendaal et al. 2009).

In contrast to the hippocampus and the PFC, the amygdala becomes hypertrophic in conditions of chronic stress. Increases in dendritic arborization and spine density take place (Roozendaal et al. 2009). Moreover, activity of the CRF system in the amygdala, which is involved in anxiety, is enhanced. Chronically stressed animals show enhanced fear conditioning and are characterized by a more habitual and less goal-directed response style. Thus, the balance between brain regions involved in cognition is altered by chronic stress (Lupien et al. 2009). While "analytic" cognitive functions mediated by the hippocampus and PFC are impaired, "affective" fear-related amygdala functioning and habit-related striatal functioning are enhanced (Wolf 2008).

In humans, exposure to chronic stress (e.g., shift workers, airplane personnel, soldiers) is associated with cognitive deficits in several domains such as working memory and declarative memory (Lupien et al. 2009; Wolf 2008). These observed cognitive deficits can, in part, be explained by GC overexposure in the presence of chronic stress, a finding supported by studies administering GCs for days to weeks, resulting in cognitive impairments. Further evidence comes from studies with patients receiving GC therapy. Whether the negative effects on memory reflect acute or chronic effects is sometimes hard to disentangle, and at least one study showed a rapid reversal of the deficits after discontinuation of the GC treatment. Data from patients with Cushing's disease point in the same direction, with cognitive impairments and hippocampal volume reductions reported. Hippocampal atrophy might be reversible once successful treatment has occurred. This would be in line with the remaining plasticity of this structure observed in animal studies (Wolf 2008).

Chronic Stress or Rising Cortisol Levels During Aging: Effects on Cognition

In older laboratory rodents, an increase in basal corticosterone levels and a less efficient negative feedback of the HPA axis can be detected. Studies have reported that enhanced HPA activity is associated with poorer memory in those animals (Lupien et al. 2009).

As reviewed above, increases in basal cortisol levels occur during human aging. In addition, pharmacological or behavioral challenge studies observe an increased HPA response. Moreover, HPA-negative feedback in older subjects is less efficient. These alterations might reflect age-associated diseases, stress exposure over the lifespan, genetic vulnerabilities, the long-term consequences of exposure to early life adversity, or a combination of the above (Lupien et al. 2009). In older adults, correlations between elevated or rising cortisol levels and cognitive impairments have been reported (Lupien et al. 2009). The association between rising cortisol levels and atrophy of the hippocampus is not sufficiently understood, and the current empirical situation is heterogeneous. Similar associations with other GC-sensitive brain regions (e.g., PFC) have received less attention so far.

Evidence for HPA hyperactivity has been observed in patients with Alzheimer's dementia (AD). This could reflect the damage to HPA feedback centers in the brain, but it might also be causally involved in disease progression (Wolf and Kudielka 2008). Work in animals has documented that HPA hyperactivity can influence amyloid metabolism as well as tau phosphorylation, the two hallmarks of AD pathology. In human patients, treatment with prednisone resulted in exaggerated memory loss. Moreover, a genetic susceptibility to AD

could be linked to the gene encoding 11beta-HSD, which influences local GC metabolism. In addition, at the self-report level, evidence exists that enhanced stress susceptibility is associated with a greater risk of dementia (Wolf and Kudielka 2008).

Another condition associated with HPA hyperactivity is the metabolic syndrome, as well as type 2 diabetes. There are close links between the stress system and the glucoregulatory system. Several authors have suggested that chronic stress facilitates the occurrence of the metabolic syndrome by influencing visceral fat deposition, impairing insulin sensitivity, or by changing eating habits toward unhealthier (comfort) food. Alternatively, the negative impact of glucose intolerance on the brain might lead to HPA hyperactivity and, in turn, elevated cortisol levels (Convit 2005).

Intervention Strategies

In laboratory animals, stress-induced dendritic atrophy and reduced neurogenesis can be prevented with antidepressants and anticonvulsants. Also, treatment with a glucocorticoid receptor antagonist is effective in preventing such stress-induced changes in neurophysiology. Similarly, memory impairments can be prevented with these drugs (Wolf 2008).

In humans, chronic stress without an associated psychopathology could be alleviated by psychological stress intervention strategies. Possible examples are stress inoculation training and mindfulness-based stress reduction training. In addition, social support is an effective stress-buffering factor.

Pharmacological treatment with beta-blockers can prevent the effects of acute GC elevations on memory retrieval. It remains to be shown whether similar approaches are effective in conditions of chronic stress. In addition, GR antagonists and/or CRF antagonists might be candidate drugs. Moreover, drugs that influence the local GC metabolism in the brain could also be effective. Depression is often associated with HPA hyperactivity. Successful treatment with antidepressants leads to a normalized HPA axis. One study observed that treatment with a selective serotonin reuptake inhibitor (SSRI) improved memory performance and reduced cortisol levels. More direct interventions targeting the HPA axis have been tested in laboratory animals, and clinical trials are on the way. In this context, CRF antagonists and GR antagonists appear promising. In sum, reinstating appropriate HPA signaling appears to be a promising treatment approach both in chronically stressed animals and in human patients suffering from stress-related psychiatric disorders (De Kloet et al. 2007).

Intervention strategies specifically designed for older people could be developed based on the following findings. In rodents, behavioral (e.g., neonatal handling) and pharmacological (adrenalectomy with low-dose corticosterone replacement) intervention strategies, leading to stable HPA activity throughout life, prevent age-associated cognitive decline. Similarly, a pharmacological reduction of active GC concentrations in the hippocampus (inhibition of 11beta-HSD synthesis) is efficient in preventing memory impairments in aging mice. In humans, a pilot study showed that the 11beta-HSD inhibitor carbenoxolone improved some aspects of memory in older men and in older patients with type 2 diabetes (Wyrwoll et al. 2010). Future studies are needed to better investigate possible side effects of long-term treatment with these kinds of drugs. Regarding treatment of the metabolic syndrome, lifestyle modifications are often successful if started early enough. In addition, pharmacological approaches are available. They should be able to prevent or reduce memory impairment and hippocampal atrophy associated with diabetes and the metabolic syndrome (Convit 2005).

Summary and Outlook

This chapter illustrates that chronic stress has a negative impact on cognition throughout life. A lifespan approach in research on stress and cognition emphasizes the long-lasting effects of

exposure to early life adversity. Genetic risk factors, in combination with early life adversity, render an individual more susceptible to stress and stress-associated diseases during aging.

By reducing early adversity, it would thus be possible to support the development of a more resilient phenotype less susceptible to stress-associated cognitive disturbances in later life. Importantly, a previously unappreciated amount of neuroplasticity remains in adulthood, allowing an optimistic view of the potential to successfully treat stress-associated neurophysiological changes in the future. These interventions should aim at reinstating appropriate HPA signaling and will thus rely upon a thorough diagnostic neuroendocrine workup of the phenotype.

Taken together, considerable progress has been made in understanding the impact of acute and chronic stress on the human brain. This knowledge has substantial relevance for aging, since age-associated changes in HPA (re)activity have been found to occur, and the sensitivity of the brain to stress appears to be altered in aging. Preventing or diminishing the age-associated increase in HPA activity appears to be a promising future research avenue to foster successful (mental) aging (Lupien et al. 2009; Wolf and Kudielka 2008).

Cross-References

- Cognitive Changes, Normal and Age-Related
- Cognitive Plasticity
- Depression
- Emotion-Cognition Interactions
- Memory: Autobiographical
- Memory: Episodic
- Memory: Training Methods and Benefits
- Mild Cognitive Impairment
- Process and Systems Views of Aging and Memory
- PTSD and Trauma
- Stress and Well-Being: Its Relationship to Work and Retirement for Older Workers
- Working Memory

References

Convit, A. (2005). Links between cognitive impairment in insulin resistance: An explanatory model. *Neurobiology of Aging, 26*(Suppl 1), 31–35.

De Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Review Neuroscience, 6*, 463–475.

De Kloet, E. R., Derijk, R. H., & Meijer, O. C. (2007). Therapy Insight: Is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nature Clinical Practice Endocrinology & Metabolism, 3*, 168–179.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*, 355–391.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*, 1010–1016.

Het, S., Ramlow, G., & Wolf, O. T. (2005). A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology, 30*, 771–784.

Joels, M., Karst, H., DeRijk, R., & De Kloet, E. R. (2008). The coming out of the brain mineralocorticoid receptor. *Trends in Neurosciences, 31*, 1–7.

Lazarus, R. S. (1993). Coping theory and research: Past, present, and future. *Psychosomatic Medicine, 55*, 234–247.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews in the Neurosciences, 10*, 434–445.

Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 1161–1192.

Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., & Mohr, D. C. (2005). A meta-analysis of cortisol response to challenge in human aging: Importance of gender. *Psychoneuroendocrinology, 30*, 80–91.

Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., et al. (2010). Stress regulation in the central nervous system: Evidence from structural and functional neuroimaging studies in human populations. *Psychoneuroendocrinology, 35*, 179–191.

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews in the Neurosciences, 10*, 423–433.

Schlotz, W., & Phillips, D. I. (2009). Fetal origins of mental health: Evidence and mechanisms. *Brain, Behavior, and Immunity, 23*, 905–916.

Wolf, O. T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica, 127*, 513–531.

Wolf, O. T. (2009). Stress and memory in humans: Twelve years of progress? *Brain Research, 1293*, 142–154.

Wolf, O. T., & Kudielka, B. M. (2008). Stress, health and ageing: A focus on postmenopausal women. *Menopause International, 14*, 129–133.

Wyrwoll, C. S., Holmes, M. C., & Seckl, J. R. (2010). 11beta-Hydroxysteroid dehydrogenases and the brain: From zero to hero, a decade of progress. *Frontiers in Neuroendocrinology, 32*, 265–286.