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Review

Chronic stress, cognitive functioning and mental health

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ABSTRACT

This review aims to discuss the evidence supporting the link between chronic stress, cognitive function and mental health. Over the years, the associations between these concepts have been investigated in different populations. This review summarizes the findings that have emerged from older populations as well as from populations suffering from pathological aging, namely Mild Cognitive Impairment and Alzheimer's Disease. Although older adults are an interesting population to study in terms of chronic stress, other stress-related diseases can occur throughout the lifespan. The second section covers some of these stress-related diseases that have recently received a great deal of attention, namely burnout, depression, and post-traumatic stress disorder. Given that chronic stress contributes to the development of certain pathologies by accelerating and/or exacerbating pre-existing vulnerabilities that vary from one individual to the other, the final section summarizes data obtained on potential variables contributing to the association between chronic stress and cognition.

1. Introduction

Glucocorticoids (GCs) are a class of stress hormones released upon exposure to a stressful situation. GCs (primarily cortisol in humans and corticosterone in animals) are the end products of activation of the hypothalamic–pituitary–adrenal (HPA) axis. The activation of the HPA axis is first triggered by the release of corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus. This in turn provokes the release of adrenocorticotropin hormone (ACTH) from the anterior part of the pituitary gland. ACTH then travels into the bloodstream until it reaches its receptors on the adrenal glands, located just above the kidneys. GCs are finally released from the cortex of the adrenal glands. Because of their liposolubility, they have the capacity to cross the blood–brain barrier and bind to GC receptors in various brain regions (for a review see Herman & Cullinan, 1997).

Two types of GC receptors have been identified: the *mineralocorticoid receptor* (MR or Type I) and the *glucocorticoid receptor* (GR or Type II). Type I has a much higher affinity to GCs compared to Type II (Reul & de Kloet, 1985). While Type I is mainly distributed in the limbic system, Type II is present in subcortical and cortical structures, with a preferential distribution in the prefrontal cortex (Diorio, Viau, & Meaney, 1993; McEwen, De Kloet, & Rostene, 1986; McEwen, Weiss, & Schwartz, 1968; Meaney, Sapolsky, & McEwen, 1985; Sanchez, Young, Plotsky, & Insel, 2000; Sarrieau et al., 1988). Importantly, Type II receptors are also involved in the negative feedback mechanism that regulates the HPA axis. When GC levels increase, a portion of them binds at the level of the pituitary and the hypothalamus in order to maintain homeostasis. It has recently been demonstrated that glucocorticoids may act at the level of membrane receptors. Although they have been less documented than the MR and GR, the membrane receptors seem to be responsible for the rapidly GC-mediated effects (for a review see de Kloet, Karst, & Joels, 2008).

Albeit the negative feedback at the level of the pituitary and the hypothalamus, the HPA axis is regulated by three main structures: the hippocampus, the amygdala and the medial prefrontal cortex. The amygdala, known for its role in fear detection, is the only one of the three regulators that activates the HPA

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axis (Davis, 1992; Herman, Ostrander, Mueller, & Figueiredo, 2005). In contrast, the prefrontal cortex and the hippocampus play an inhibitory role on the HPA axis (Dunn & Orr, 1984; Herman et al., 2005; Rubin, Mandell, & Crandall, 1966). Of the three structures, the hippocampus is indubitably the most well defined regulator of the HPA axis due to its involvement in various well-documented mental health disorders such as depression, post-traumatic stress disorder (PTSD) and Alzheimer's Disease (AD) (Caetano et al., 2004; Shin, Rauch, & Pitman, 2006). Given that both types of GC receptors are found in this structure (Herman, 1993; Herman et al., 2005; Reul & de Kloet, 1985), the hippocampus is a key site for negative feedback regulation of the stress axis (Herman et al., 2005). Yet, the integrity of these three structures must be maintained in order for the HPA axis to function optimally.

Over the last decades, chronic exposure to GCs has been widely studied from different perspectives: some describe the neuroendocrine profiles of certain stress-related diseases, while others investigate the possible mechanisms explaining outcomes such as cognitive deficits or psychopathologies. To explore such a broad depth of knowledge, the review has three sections: the first section details findings that have emerged from the field of aging research, where high variability in cortisol secretion and cognitive performance has been reported. This section will explore literature that investigates whether chronic stress exposure can partly explain pathological aging, such as Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). Although some effects can be particularly striking in older adults, one must keep in mind that the chronicity implies that stressors have been present for a long period of time and thus, some consequences of chronic stress could be manifested earlier in life.

The second section explores other human models of chronic stress such as burnout, depression, and PTSD. Finally, despite the wealth of knowledge about different stress-related diseases and their associated neuroendocrine and cognitive profiles, the ability to predict disease outcome in the clinic remains limited. This may partly be explained by the fact that research commonly focuses on the disease endpoint with very little attention devoted to the individual's history. Indeed, throughout an individual's lifespan, different vulnerabilities and protective factors accumulate. Elucidating such factors may help increase the capacity to predict or, at least, detect at-risk individuals at an earlier stage before symptom manifestation. Factors such as sex, early life adversity and genetics have an important impact on the perception of what is stressful and consequently, on increased stress reactivity, cognition deficits and susceptibility to developing psychopathology. The third section of this review summarizes the importance of taking an individualized perspective when investigating psychopathologies.

2. Normal and pathological aging: could chronic stress be an important player?

2.1. Normal aging

Aging is characterized by variability in physiological functioning and cognitive performance. This variance is in part rooted in the HPA axis functioning and its impact on cognitive performance.

Elevated basal levels of GCs in aged rats do not represent a typical aging process and are observed in about 30% of the aging rodent population (Issa, Rowe, Gauthier, & Meaney, 1990). Further, it has been demonstrated that rats with memory impairments show increased HPA activity compared to their cognitively intact counterparts (Issa et al., 1990; Landfield, Waymire, & Lynch, 1978). One possible mechanism that could explain the memory deficits resulting from high levels of GCs is the integrity of the hippocampus, a brain structure well-known for its role in learning and memory (Squire, Knowlton, & Musen, 1993).

Given the high density of GC receptors in this brain structure, it is particularly vulnerable to the neurotoxic effects of GCs (McEwen et al., 1982, 1986; Seckl, Dickson, Yates, & Fink, 1991). In fact, chronic exposure to high levels of GCs has been associated with impaired cognitive performance, particularly on hippocampal-dependent tasks such as spatial memory (Borcel et al., 2008; Sandi et al., 2003). Mirroring the behavioral data, chronic exposure to elevated levels of GCs has been linked to hippocampal neuronal loss, dendritic atrophy and reduced hippocampal volume (Borcel et al., 2008; Issa et al., 1990; Kerr, Campbell, Applegate, Brodish, & Landfield, 1991; Landfield, Baskin, & Pitler, 1981; Sandi, 2004; Sandi et al., 2003; Sapolsky, Krey, & McEwen, 1985; Woolley, Gould, & Mcewen, 1990). It has also been associated with decreased neurogenesis in the dentate gyrus region of the hippocampus, one of the few brain regions that continue to generate neurons throughout adulthood (Gould & Tanapat, 1999; Sousa, Lukoyanov, Madeira, Almeida, & Paula-Barbosa, 2000). However, findings on widespread neuronal loss have not been replicated when using different methods for counting neurons, such as unbiased stereology as opposed to assumption-based counting techniques (Sapolsky, 1999; West, 1999).

Although age is an important risk factor for cognitive deficits and neuronal deterioration, it is not a direct predictor of impaired cognitive function. Indeed, when middle-aged rats are administered high levels of GCs for extended periods of time, the resulting deficits in memory performance are similar to those found in aged rats with high basal GC levels (Landfield et al., 1978). In contrast, decreasing GC secretion seems to be protective against spatial memory impairments in aging and has also been associated with increased neurogenesis (Montaron et al., 2006). Such results form the basis of the *'Glucocorticoid Cascade Hypothesis'* (Sapolsky, Krey, & McEwen, 1986) which is now known as the 'neurotoxicity hypothesis' (Lupien et al., 2007). This theory postulates that exposure to high levels of GCs for long periods of time can exert a deleterious effect on HPA-axis regulation that cumulatively impacts hippocampal volume and memory performance. Inter-individual vulnerability factors may increase the risk for heightened or dysfunctional stress reactivity and subsequent cognitive impairment (Sandi & Touyarot, 2006). For instance, it has been reported that rats that are high responders to novelty have an increased risk for later cognitive deficits and rapid decline (Dellu, Mayo, Vallee, Le Moal, & Simon, 1994; Sandi & Touyarot, 2006; Touyarot, Venero, & Sandi, 2004).

Human research on stress and memory tends to complement findings from the animal literature. Consistent with the data obtained in rodents, evidence shows that humans also have a wide range of inter-individual variability regarding GC secretion, cognitive performance and hippocampal volume and functioning (Christensen, 2001; Lupien et al., 2007; Nyberg, Persson, & Nilsson, 2002; Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001). A longitudinal study followed a sample of healthy older adults annually and had cortisol levels measured hourly during a 24-h period (Lupien et al., 1996). Results showed the presence of three subgroups in basal cortisol levels after 7-year follow-up: (1) increasing cortisol secretion over time, resulting in high cortisol levels at the end of the study (*Increasing*/*High group*); (2) increasing cortisol secretion over time, resulting in moderate cortisol levels at the end of the study (*Increasing*/*Moderate group*); and (3) decreasing cortisol secretion over time, resulting in moderate cortisol levels at the end of the study (*Decreasing*/*Moderate group*). The authors noted that the Increasing/High subgroup had memory impairments and smaller hippocampal volume when compared to older adults who had moderate cortisol levels at the end of the follow-up per-