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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.

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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-

iod (Lupien et al., 1994, 1998). Similarly, a more recent prospective study reported an association between increased chronic stress over a 20-year period and smaller hippocampal volume and orbitofrontal cortex gray matter (Gianaros et al., 2007). Some reports do not support this evidence, as it has been shown that although cortisol levels are associated with reduced memory performance in a sample of healthy elderly men, an association with reduced hippocampal volume was absent (MacLullich et al., 2005).

2.2. Pathological aging

Given the intricate associations between cortisol, the hippocampus, and cognition as well as the importance of individual differences, a question that emerges is whether chronic exposure to high levels of GCs might contribute to pathological cognitive aging. Cognitive aging may be conceptualized as a spectrum; at one end of this spectrum are cognitively healthy older adults and at the other end are patients with dementia, Alzheimer's Disease (AD) being the most common type. The memory deficits characterizing AD are thought to result from the accumulation of amyloid-beta plaques and neurofibrillary tangles, resulting in loss of neurons and atrophy of the cerebral cortex and certain subcortical regions, namely the hippocampus. As the neuropathology spreads through the brain, other cognitive deficits arise. Since the formulation of the neurotoxicity hypothesis, many cross-sectional studies have confirmed the hypersecretion of basal cortisol in AD compared to healthy elderly (Arsenault-Lapierre, Chertkow, & Lupien, 2010; Davis et al., 1986; Giubilei et al., 2001; Peskind, Wilkinson, Petrie, Schellenberg, & Raskind, 2001; Spada et al., 2002).

Somewhere along the cognitive spectrum are individuals with Mild Cognitive Impairment (MCI). These individuals present at memory clinics with subjective memory deficits, corroborated by small deficits on neuropsychological tests, not sufficient to result in social or functional impairment, thus not fulfilling dementia criteria (Petersen et al., 1997). Studies show that they are at an increased risk to progress to AD (Petersen et al., 1997), but not all do. They also show hippocampal atrophy that falls between healthy older adults and AD patients (Grundman et al., 2004). A few studies have reported similar basal cortisol levels in MCI compared with healthy older adults (Csernansky et al., 2006; Kalmijn et al., 1998; Lee et al., 2008; Popp et al., 2009; Souza-Talarico, Chaves, Lupien, Nitrini, & Caramelli, 2010; Wolf, Convit, Thorn, & de Leon, 2002). However, looking at APOe4 carriers, who are also at risk of developing AD, Fiocco and colleagues (2008) have found higher cortisol levels in ApoE carriers when compared to normal healthy elderly. However, this effect was only found at the first year of this longitudinal study. Subsequent annual measures of cortisol did not reveal any group differences as a function of ApoE status, suggesting that the association between ApoE status and cortisol levels may be related to stress reactivity rather than to basal cortisol levels. Another study found that 15 min post-awakening cortisol levels is higher in the MCI group than in the healthy controls (Lind, Edman, Nordlund, Olsson, & Wallin, 2007). These contradicting results may be explained by the confounding effects of the season of collection. In fact, when controlling for season of collection, MCI individuals are found to secrete higher basal cortisol levels than healthy elderly (Arsenault-Lapierre et al., 2010). Altogether, these studies suggest a stepwise association between cortisol secretion and cognitive impairment, with AD patients secreting more cortisol than normal elderly and MCI individuals, and MCI individuals secreting more cortisol than normal elderly. Given that MCI individuals and AD patients do have smaller hippocampal volumes and that the hippocampus is an important regulator of the HPA axis, it is possible that higher cortisol secretion is mediated via an impaired negative feedback capacity from the hippocampus to the HPA axis (Csernansky et al., 2006).

Although cortisol seems to be implicated in AD to a certain extent, whether increased cortisol secretion is associated with dementia remains to be elucidated. To our knowledge, no study has prospectively looked at the association between baseline cortisol secretion and progression to dementia or AD. A few studies have looked at the association between cortisol levels at baseline and cognitive decline in elderly individuals, individuals at risk of AD, and AD patients. Most studies found that cortisol levels measured at baseline did not associate with cognitive decline in normal elderly (Comijs et al., 2010; Csernansky et al., 2006; Kalmijn et al., 1998; Kohler et al., 2010; Peavy et al., 2009) except for three studies (Beluche, Carriere, Ritchie, & Ancelin, 2010; Greendale, Kritz-Silverstein, Seeman, & Barrett-Connor, 2000; Li et al., 2006). The association in AD patients is less clear. Some have found an association, where higher cortisol levels are positively associated with increased cognitive decline (Huang et al., 2009; Umegaki et al., 2000; Weiner, Vobach, Olsson, Svetlik, & Risser, 1997). The association in MCI individuals or individuals at risk of AD is even more controversial. On one hand, Csernansky and colleagues (2006) and Swanwick and collaborators (1996) found a positive association between higher cortisol levels in individuals with a Clinical Dementia Rating scale of 0.5 and an increased cognitive decline. On the other hand, negative relationships have been also observed. One study found that lower morning cortisol levels are associated with increased cognitive decline in APOe4 carriers (Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2009) whereas another reported that higher cortisol levels are associated with slower cognitive decline (Peavy et al., 2009).

It is currently premature to make conclusions on the exact role cortisol has in predicting cognitive decline in individuals at risk of AD or even AD patients. If cortisol plays a role in AD pathology, it is far from being the sole contributor nor biomarker involved. With respect to aging in general, the term *allostatic load* (McEwen & Stellar, 1993) refers to the cumulative strain chronic stress exerts on neuroendocrine, immune, metabolic, and cardiovascular systems that ultimately renders individuals more susceptible to developing stress-related problems. This multi-systemic damage increases steadily as our bodies and minds age, then plateaus at around age 60 (Crimmins, Johnston, Hayward, & Seeman, 2003). This suggests that physiological dysregulations begin to emerge decades before manifest diseases occur in late life. Consequently, the field of stress research has turned its attention to earlier periods in the lifespan to further understand the role that stress hormones and inter-connected biomarkers might exert on disease trajectories.

3. Beyond aging: chronic stress at work and following trauma exposure

3.1. Depression and burnout in the workplace

Aging research centered upon the effects of chronic stress on neuroendocrine profiles and cognitive performance has propelled a complementary area of research that focuses on workplace stress (Taylor, Repetti, & Seeman, 1997). Compared to the aging field, research in this domain has been more compartmentalized where neuroendocrine and cognitive profiles have been studied separately in relation with the disorder.

While the cognitive functioning of distressed workers has received limited attention thus far, cognitive dysfunctions are nevertheless integral symptoms of numerous associated psychopathologies (e.g., cognitive theory of depression (Beck, 1963) or cognitive fatigue in burnout (Maslach, Schaufeli, & Leiter, 2001)). In addition

to potentially rendering individuals more vulnerable to problems later on in older adulthood, cognitive impairments in adulthood strongly interact with biological activities that modulate appraisals of past, present, and future stressful contexts.

Theories of occupational health often inherently assume information-processing deficits whereby the strain of chronic workplace distress overwhelms the psychological capacities of the individual and puts them at greater risk of psychiatric manifestations such as burnout and depression. For example, concepts and research on burnout have been vastly informed by a variety of cognitively oriented perspectives (for a review see Hodgkinson & Healey, 2008).

According to clinical observations, burnt out individuals purportedly complain more about difficulties in focusing on daily tasks (Maslach et al., 2001; Schaufeli & Enzmann, 1998). Based on the premise that burnout might be characterized by a deficit in executive control, van der Linder and colleagues (2005) showed that increased frequency of burnout symptoms are associated with increased frequency of cognitive failures in daily life, and increased inhibition errors and performance variability on attention task. Given that cognitive deficits are not exclusively manifested in clinical burnout but also in prodromal stages suggest that it might be detectable with cognitive screening (van der Linden, Keijsers, Eling, & van Schaijk, 2005). In the first comprehensive study of multiple cognitive domains (general cognitive abilities, attention, visuospatial functions, and memory functions), Sandstrom and colleagues (2005) found that female burnout patients had significantly decreased performance on nonverbal memory as well as delayed reaction on attention measures in contrast to a control group, although no differences were detected between the groups for verbal memory.

Likewise, depressed workers experience impairments in numerous work domains at an estimated loss of 5 h per week in the form of presenteeism (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003) and even greater costs in absenteeism (Goldberg & Steury, 2001). Note that the DSM-IV-TR criteria for a diagnosis of major depressive disorder include symptoms that are cognitive in nature (e.g., diminished ability to think or concentrate, or indecisiveness). Early research suggested that a positive association existed between memory impairment and the severity of depressive symptoms (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982; Henry, Weingartner, & Murphy, 1973; Sternberg & Jarvik, 1976; Stromgren, 1977). It is now widely accepted that depression corresponds to learning and episodic memory impairments (for an earlier review see Goodwin, 1997). In a matched-control study, a worsening of depressive illness was found to progressively impair cognitive functioning for memory tasks and visuo-motor speed, but not digit span (Austin et al., 1992). A more recent review suggests that depression is also associated with executive impairments in set-shifting tasks (Austin, Mitchell, & Goodwin, 2001).

In contrast to cognition, considerably more research has assessed neuroendocrine profiles in relation to workplace stress as they relate to divergent disease profiles that share similar symptomatologies. Although depression and burnout are two conditions that are qualitatively similar (Iacovides, Fountoulakis, Kaprinis, & Kaprinis, 2003; Nyklicek & Pop, 2005; Tennant, 2001), they are suspected to differ substantially in terms of stress hormone levels. For instance, the diurnal pattern of cortisol (e.g., awakening cortisol response (Pruessner et al., 1997)) in depression appears to be more hypercortisolemic in nature, while that found in burnout is a hypocortisolemic profile more akin to PTSD (Chida & Steptoe, 2009); however, this remains debatable. Hypocortisolism is indeed a phenomenon that occurs in approximately 20–25% of patients suffering from stress-related diseases like chronic fatigue syndrome, fibromyalgia, PTSD, burnout, and atypical depression to name a few (for a review see Fries, Hesse, Hellhammer, & Hellhammer, 2005). How these biological signatures correspond to cognitive impairments or declines has yet to be investigated.

Besides depression and burnout, numerous conditions related to chronic stress (e.g., chronic fatigue syndrome, PTSD, fibromyalgia) interact with features in the workplace that can amplify psychological and physical problems at that moment in the lifespan and perhaps thereafter. For instance, physical and psychological traumas are more likely to occur in certain occupations (i.e., military service, police force, firefighters) and augment one's risk of developing depression and/or PTSD later on (Bender & Farvolden, 2008). While speculative, it seems highly probable that such experiences in earlier life carry with them scars that accelerate senescence, highlighting the necessity to explore previous stressors and traumas in a person's life when studying the effects of chronic stress on age-related phenomena.

3.2. Post-traumatic stress disorder

PTSD is an anxiety disorder that can occur following exposure to a traumatic event. The lifetime prevalence in the population of adults living in the United States has been estimated at 8%. PTSD is characterized by symptoms of hyperarousal, avoidance and re-experience of the traumatic event such as in the case of flashbacks or nightmares. As it is the case with depression and burnout, few studies have looked at both cognitive and neuroendocrine measures with respect to this stress-related disorder.

PTSD individuals show different profiles of cognitive functioning. In general, they have an attentional bias towards trauma-related stimuli. For example, they are slower to name the color of trauma-related words in an emotional Stroop-task, but they do not exhibit differences in reaction times when naming the color of other words unrelated to the traumatic event (Bryant & Harvey, 1997; Foa, Feske, Murdock, Kozak, & McCarthy, 1991; McNally, English, & Lipke, 1993). Deficits have been reported in working memory tasks and other cognitive tasks sustained by frontal regions. Some studies have reported deficits in episodic memory (for a review on cognitive functions in PTSD see Isaac, Cushway, & Jones, 2006). However, these cognitive differences must be interpreted with caution. In fact, it is important to establish whether the memory deficits are direct consequence of PTSD symptomatology or whether they could be explained by the attention deficits or by the different hormonal status observed in PTSD.

In fact, it has been reported that PTSD patients have distinct neuroendocrine profiles. They present lower basal cortisol levels when compared to healthy controls and to individuals who have been exposed to trauma without developing PTSD. Conversely, some studies have reported hypercortisolemic profiles (for a recent review see Handwerger, 2009). With regards to stress reactivity, PTSD diagnosed individuals show increased reactivity when exposed to trauma-related stimuli (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003; Liberzon, Abelson, Flagel, Raz, & Young, 1999). Although it may be speculated that this marked reactivity is specific to trauma-related stimuli, it is not. Individuals with PTSD also display a more pronounced anticipation and reactivity to other cognitive stressors that are not associated with the trauma (Bremner et al., 2003; Liberzon et al., 1999). However, one study reported lower reactivity in PTSD patients when exposed to the cold pressor test (Santa Ana et al., 2006). It is possible that the nature of the stressor (psychological vs. physical) has an impact on the direction of the effect (higher vs. lower stress reactivity).

When assessing the functioning of the HPA axis, different pharmacological challenges have been used, notably the dexamethasone suppression test. Its purpose is to measure the feedback inhibition of the HPA axis. Dexamethasone is a synthetic form of

cortisol. Usually, it is administered late at night and cortisol levels are measured the morning following administration. Individuals diagnosed with PTSD have much lower levels of cortisol in the morning compared to healthy controls, suggesting greater negative feedback (for reviews see de Kloet et al., 2006; Handwerger, 2009). Contrary to people with depression who are hypo-suppressors (very high levels of cortisol in the morning following dexamethasone administration), PTSD individuals are hyper-suppressors. Recent studies have demonstrated that a hypersuppression profile is present not only in individuals diagnosed with PTSD but also in individuals who were exposed to a traumatic event without developing the disorder (de Kloet et al., 2007; Golier, Schmeidler, Legge, & Yehuda, 2006). Thus, according to these studies, exposure to the traumatic event rather than PTSD itself seems to be linked to a hypersuppression profile in response to the dexamethasone test.

Although a majority of individuals will be exposed to a traumatic event at some point in their life, about a quarter to a third will meet the criteria for a diagnosis of PTSD (McCarroll, Fagan, Hermsen, & Ursano, 1997; Yehuda, Southwick, & Giller, 1992). This suggests that some factors could render an individual more or less at risk of developing PTSD following trauma exposure. Keep in mind that the vast majority of studies have been performed after the trauma, thereby rendering it impossible to assume that the differences found between PTSD individuals and healthy controls results solely from trauma exposure and not from pre-existing vulnerabilities.

An important study performed by Gilbertson and colleagues (2002) demonstrated how some characteristics might be present before trauma exposure, thereby representing vulnerabilities rather than consequences. The authors investigated hippocampal volumes in war veterans with PTSD and compared them to other war veterans who did not develop the diagnosis, but were exposed to the traumatic event. Not surprisingly, they reported smaller hippocampal volumes in PTSD individuals compared to non-PTSD individuals, confirming previous studies with similar findings (Bremner et al., 1995, 1997; Gurvits et al., 1996; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). However, war veterans who were tested in that study each had a monozygotic twin (100% of shared genes) who did not go to war and was therefore not exposed to the traumatic event. If smaller hippocampal volume is a consequence of the neurotoxic effects of chronically elevated levels of GCs following a trauma, then the monozygotic twin who did not go to war should have had a larger hippocampal volume. Surprisingly, it was not the case. Twins had similar hippocampal volume even if one of them was not exposed to the traumatic event. This strongly supports the notion that smaller hippocampal volume is a pre-existing condition, rather than a consequence, that renders the individual more at risk of developing PTSD upon exposure to a traumatic event.

Overall, PTSD is characterized by increased reactivity to stressors and traumatic stimuli. Moreover, basal cortisol levels seem to follow a hypocortisolemic profile. Importantly, when the body's homeostasis is challenged with a dexamethasone administration, trauma-exposed people have hypersuppressive profiles. Regarding cognitive profiles, individuals diagnosed with PTSD exhibit certain deficits; however, results need to be interpreted with care. At the neuroanatomical level, differences have been reported both functionally and structurally. Perhaps the most striking finding is that smaller hippocampal volumes have been reported amidst initial belief that it was the neurotoxic consequence of dysregulated GCs on the hippocampus. However, relatively new findings strongly suggest that a smaller hippocampal volume represents a vulnerability to develop PTSD following a trauma and therefore not a consequence of the trauma (Lupien, McEwen, Gunnar, & Heim, 2009).

Nonetheless, it is important to note that these findings are rarely equivocal and a great deal of variability remains. This could be explained in various ways. Perhaps one important way is based on the fact that we study a common endpoint, namely PTSD, that actually stems from a different etiology than presumed. Although the final diagnosis is the same, the precipitating factors often differ. It is thus crucial to take into account factors such as age when the traumatic event was experienced, time elapsed since the traumatic event, type of trauma (e.g., vehicle accident vs. sexual abuse), chronicity of the trauma (single vs. multiple exposure to the traumatic event) and sex of the victim. Additionally, comorbidity is the rule rather than the exception in PTSD. Therefore, substance abuse and depression, which are common comorbid conditions, could also have an influence on the neuroendocrine and cognitive profiles of these individuals. This underlies the importance of taking an individualized approach when trying to understand the etiology of this and other disorders.

4. Beyond diagnostic criteria: the individual's history

As presented in the previous sections, chronic stress can markedly increase one's vulnerability of developing a host of different psychopathologies. Despite increasingly understood mechanisms that explain the path to disease, the capacity to predict which individual is more at risk for a particular disease remains elusive. This suggests that chronic stress might be an accelerator and/or amplifier of certain pre-existing vulnerabilities. Consequently, it is of crucial importance to take an individualized approach by considering one's vulnerabilities across the lifespan. The following section will explain how factors, such as sex, early life adversity, and genetics might act as protective or risk factors to develop certain stress-related diseases.

4.1. Sex and sex hormones

Being a woman or a man confers different vulnerability and/or resiliency factors to stress. For instance, women are more likely to develop autoimmune and affective disorders, while early mortality, substance abuse, antisocial and conduct disorders, as well as infectious diseases are more common in men (Blume, 1994; Fattore, Altea, & Fratta, 2008; Gleicher & Barad, 2007; Kessler & Wang, 2008; Kjelsberg & Friestad, 2009; May, 2007). Investigations of acute stress exposure in laboratory settings repeatedly demonstrate that men display a higher cortisol stress response compared to women (Kajantie & Phillips, 2006; Kudielka & Kirschbaum, 2005). On the other hand, the MacArthur studies provide evidence for age-specific sex differences in chronic stress biomarkers and its consequences (Juster, McEwen, & Lupien, 2009). For example, it was found that high cortisol levels are associated with memory impairments in women (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997), while elevated epinephrine levels relate to cognitive declines in men (Karlamangla, Singer, Chodosh, McEwen, & Seeman, 2005).

One key factor explaining sex differences stem from the two distinct endocrine milieus of women and men. It is thus important to take into account the different sex steroids (i.e., testosterone vs. estrogens and progestogens), their levels, dynamics (i.e., phase of the menstrual cycle, pregnancy, menopause), and previous or lifelong exposure (i.e., age at menarche/puberty, number of pregnancies, age at menopause, exogenous administration such as hormonal contraceptive and replacement therapy). Bidirectional interplays exist between the HPA axis and the hypothalamo–pituitary–gonadal (HPG) axis, from which sex hormones are the end products. While cortisol has inhibitory effects at all three levels of the HPG-axis, hypothalamic regulation of the HPA axis

is inhibited by testosterone (Terburg, Morgan, & van Honk, 2009). This might explain why the sexes differ vis-à-vis stress-related HPA activity.

In a variety of species, males have lower ACTH and GC levels in both basal and reactive conditions, which might be due to sex steroids such as testosterone and estrogen (Charney, 2004; Handa, Burgess, Kerr, & O'Keefe, 1994; Luine, Beck, Bowman, Frankfurt, & Maclusky, 2007; Young, 1998). Confirming this, gonadectomy increases ACTH and corticosterone responses to acute stress while 5-alpha-dihydrotestosterone (5α-DHT) replacement reverses this effect in male rats; however, this has not be scrutinized in studies of chronic stress (Handa et al., 1994). While evidence is scarce – particularly concerning progesterone – the mechanisms underlying the cross-talk between estrogen/progesterone and the HPA axis remains elusive. Preclinical and clinical evidence suggests that estrogen might dampen the HPA axis and potentially counteract the damaging actions of chronic stress on neural integrity and functioning (Kajantie & Phillips, 2006; McEwen, 2002). Data also suggest that estrogen actions are dependent on doses and exposure duration with low doses of estrogen suppressing the HPA axis responses and supraphysiological doses and prolonged treatment enhances the hormonal stress responses (Charney, 2004; Kajantie & Phillips, 2006; Young, Altemus, Parkison, & Shastry, 2001). Moreover, sex steroids are known to be neuroprotective factors influencing structural integrity of the hippocampus, amyloid beta formation, neuronal loss and neurogenesis (Behl, 2002; Lord, Buss, Lupien, & Pruessner, 2008; McEwen, 2002).

To better understand the differential impact of chronic stress in men and women and consequently the nature and origins of sex-related conditions, special attention must be directed toward the differential organizational and activational hormonal/physiological contexts and their interactions with the environment.

4.2. Early life adversity and risk for psychopathology

A topic that has recently received a great deal of attention is the importance and the impact of *early life adversity* (ELA) on general health in later adulthood. From physical to mental health problems, ELA has been linked with a host of negative health outcomes. Markedly, ELA encompasses numerous life events and circumstances ranging from poor parental care to physical abuse. These events or situations increase the child's exposure to stress and its adverse effects (for a recent review see Pechtel & Pizzagalli, 2011). During early childhood, a window of critical development, the adverse effects of chronic stress can affect neurodevelopment and program the individual's stress reactivity later in life (for reviews see Lupien et al., 2009; Panzer, 2008). For this reason, ELA may affect the individual's neural processes, increasing the risk for stress-related psychopathologies such as depression.

Rodent studies have developed various paradigms to investigate the impact of ELA on learning and memory. Chronic disruptive and fragmented contact with the dam has been utilized and is found to impair learning and memory functions in hippocampal-dependent tasks such as the Morris Water Maze (MWM) and object recognition in rodents 4–8 months of age (Rice, Sandman, Lenjavi, & Baram, 2008). As well, learning deficits in acquisition of the MWM have been observed in maternally separated rats (Huot, Plotsky, Lenox, & McNamara, 2002). Conversely, increase in neonatal handling and novelty exposure is shown to have enhancing effects on spatial memory in adult rats (Daskalakis, Kaperoni, Koros, de Kloet, & Kitraki, 2009). However, negative findings have been reported in terms of spatial learning and contextual fear memory, despite anatomical changes found in the dentate gyrus in maternally deprived female rats (Oomen et al., 2011).

Whilst investigating long-term effects of ELA in rodents, anatomical changes and HPA axis dysregulation have been observed. It is reported that early life stress induces permanent and harmful lifelong changes on the HPA axis (Meaney, Aitken, Bhatnagar, & Sapolsky, 1991). Maternal deprivation has also been shown to induce increased GC response to stressors, and decreased number of GC receptors in the hippocampus and frontal cortex (Meaney, 2001; Meaney, Aitken, Viau, Sharma, & Sarrieau, 1989; O'Donnell, Larocque, Seckl, & Meaney, 1994; Sarrieau, Sharma, & Meaney, 1988; Viau, Sharma, Plotsky, & Meaney, 1993). This is reflected in diminished negative feedback and a prolonged stress response. On the other hand, proper maternal care has been linked with dampened reactivity to stress and having a positive impact on the neurodevelopment in the offspring of rodents (Dent, Okimoto, Smith, & Levine, 2000; Meaney, 2001). Furthermore, handled pups show less of an age-related increase in basal cortisol, diminished stress reactivity and less hippocampal cell loss compared to non-handled rats (Meaney et al., 1991).

Human studies report deficits in learning and memory, primarily in extreme cases of ELA (i.e., physical and emotional abuse and/or neglect). A recent pilot study found impaired spatial working memory performance in subjects who experienced emotional abuse and physical neglect. The latter was also associated with deficits on pattern recognition memory (Majer, Nater, Lin, Capuron, & Reeves, 2010). In addition, Grassi-Oliveira and colleagues (2008) investigated patients with major depressive disorder who suffered childhood physical neglect and found impairment on immediate verbal memory recall.

Moreover, it is well established that ELA is a major risk factor for major depressive disorder (Brown & Harris, 1993; Faravelli et al., 1986; Kessler, Davis, & Kendler, 1997). A wide range of early life events or circumstances including loss of a parent (Bifulco, Brown, & Harris, 1987; Harris, Brown, & Bifulco, 1987), poor maternal care (Heider, Matschinger, Bernert, Alonso, & Angermeyer, 2006; Hill et al., 2000; Kendler, Sheth, Gardner, & Prescott, 2002) and parental neglect (Bifulco, Brown, Lillie, & Jarvis, 1997; Kilpatrick et al., 2003), have been associated with increased risk for depression in adulthood. Several studies show that these effects can also be observed as early as adolescence (Kilpatrick et al., 2003). Different mechanisms have been proposed to explain the link between ELA and depression later on in life.

Indeed, depression is reportedly associated with dysregulation of the HPA axis and a smaller hippocampal volume (Burke, Davis, Otte, & Mohr, 2005; Campbell, Marriott, Nahmias, & MacQueen, 2004; Gold & Chrousos, 2002). Not surprisingly, ELA has also been associated with physiological indicators of depression (Gunnar & Donzella, 2002; Plotsky & Meaney, 1993; Rao et al., 2010). The hippocampus, known for its role in learning and memory, is sensitive to chronic stress (Bannerman et al., 2004; Gould & Tanapat, 1999; Gould, Tanapat, Hastings, & Shors, 1999; McEwen, 2000; Sapolsky, 2000; Sapolsky, Uno, Rebert, & Finch, 1990). Being one of the regulators of the HPA axis, the hippocampus seems to be a highly plausible target for the effects of ELA at the neuronal level.

As animal studies have established the impact of ELA on hippocampal development, it is not surprising to observe smaller hippocampal volume in adults who were victims of maltreatment. Smaller bilateral hippocampal volume was observed in women exposed to childhood abuse and diagnosed with borderline personality disorder (Driessen et al., 2000). Smaller left hippocampal volume was observed in adults exposed to severe childhood physical and sexual abuse, accompanied with a diagnosis of PTSD or Dissociative Identity Disorder (Bremner et al., 1997; Stein et al., 1997). On the other hand, De Bellis and colleagues (1999) investigated maltreated children with PTSD diagnosis and did not observe any significant differences in hippocampal volumes.

Another notion that is becoming more and more important when hypothesizing about the potential neuroanatomical and cognitive consequences is the timing of ELA (Lupien et al., 2009). In fact, the amygdala, the prefrontal cortex and the hippocampus have different development trajectories (e.g., the hippocampus is fully developed by the age of 2 years, the development of the prefrontal cortex mostly takes place between the age of 8 and 14 years and the amygdala continues to develop until the late 20s). Thus, ELA during the first months of life will most likely affect the development of the hippocampus, but adversity at the age of 10 years will probably affect more the development of the prefrontal cortex and the amygdala. This notion of 'timing' is of great importance and might explain why findings are mixed with regards to ELA and certain brain structure volumes and/or functioning. For example, smaller medial prefrontal cortex has been reported in subjects who report childhood emotional maltreatment before the age of 16 years (van Harmelen et al., 2010).

In conclusion, it seems that ELA is associated with a host of negative health outcomes, namely vulnerability to depression and impaired hippocampal-dependent cognitive function. Although the precise mechanisms underlying these processes have not been fully identified at the molecular level, evidence points to HPA axis programming and its impact on brain anatomy and functioning. Emerging evidence show that ELA affects not only the functioning of the hippocampus, but also the prefrontal cortex and the amygdala (Stevenson, Spicer, Mason, & Marsden, 2009; van Harmelen et al., 2010). By further investigating how ELA might affect cognitive processes subserved by these regions, notably fear conditioning, fear extinction and emotion regulation, we will be one step ahead in understanding the association between ELA, neuroanatomy, cognition and psychopathology.

4.3. Genetics

In addition to biological (e.g., sex) and environmental (e.g., early life adversity) factors, one's genetic makeup may moderate or mediate the relationship between chronic stress and health outcomes. Although few studies have focused on genetics as a moderator/mediator in the relationship between chronic stress and mental health, research has shown how genetics is associated with stress and stress outcomes. Further, while many disorders have a genetic component, with moderate to high levels of heritability, much of the variation in the onset of disease can be explained by gene–environment interactions. Indeed, the study of genetics and the study of stress are not two separate entities, but are intertwined very closely to produce phenotypic variations.

Twin studies provide valuable insight into the proportion of phenotypic variation that is attributed to genetic and environmental factors among individuals. Although findings are mixed (Kirschbaum, Wust, Faig, & Hellhammer, 1992), quantitative genetic modeling has demonstrated significant heritability for stress reactivity (Steptoe, van Jaarsveld, Semmler, Plomin, & Wardle, 2009). A recent meta-analysis reported that the pooled heritability estimates range from 0.26 to 0.43 for reactivity to psychosocial stress (i.e., mental stressor) and 0.21–0.55 for reactivity to physical stress (i.e. cold pressor test) (Wu, Snieder, & de Geus, 2010). Twin studies have further shown that the association between salivary cortisol levels and prefrontal cortical thinning may be genetically regulated (Kremen et al., 2010). High-risk twins for affective disorder have been found to secrete higher levels of evening cortisol (Vinberg, Bennike, Kyvik, Andersen, & Kessing, 2008), display a tendency for higher levels of neuroticism (Vinberg, Mortensen, Kyvik, & Kessing, 2007), and show signs of discrete cognitive dysfunction (Christensen, Kyvik, & Kessing, 2006). Furthermore, heritability estimates have been reported for stress-related illnesses, notably for depression (Kendler, Gatz, Gardner, & Pedersen, 2006; Sullivan, Neale, & Kendler, 2000) and PTSD (Lyons et al., 1993; True et al., 1993). However, while estimates of heritability provide important information, the magnitude of heritability reveals nothing about the genetic structure of a particular endophenotype and the plausible number of genes that are involved.

Single nucleotide polymorphisms (SNPs), a one base pair change in DNA sequence with a frequency of 1%, is the most abundant type of variation in the human genome (Muller-Myhsok, 2005). Polymorphisms in the glucocorticoid receptor (GR) gene have a significant impact on the neuroendocrine system. Studies show that GR polymorphisms account for inter-individual variability in HPA activity, serum levels of HPA-axis markers, and GC sensitivity of target tissue to stress hormones, which ultimately determine vulnerability to disease (DeRijk, Schaaf, & de Kloet, 2002). The most common GR genes under investigation include the Bc*l*I and the ER22/23EK polymorphisms. While both genes are associated with increased risk for depression (Krishnamurthy et al., 2008; van Rossum et al., 2006; Zobel et al., 2008), their impact on the HPA system is remarkably different: carriers of the Bc*l*I gene display hypersensitivity to GCs (Huizenga et al., 1998; van Rossum et al., 2003, 2006), whereas ER22/23EK carriers show GC resistance (van Rossum et al., 2002). With regards to brain health, no association was found for either Bc*l*I or ER22/23EK on hippocampal volume (van Rossum et al., 2008; Zobel et al., 2008). However, in one prospective study with a mean follow-up of 5.8 years, it was found that carriers of the ER22/23EK gene are at lower risk of developing dementia, display fewer white matter lesions and perform better on a psychomotor speed task (van Rossum et al., 2008). As ER22/23EK carriers exhibit decreased sensitivity to GCs (van Rossum et al., 2002), it may be that ER22/23EK carriers are protected from the detrimental effect of chronic GC exposure with aging, which contributes to increased longevity in this group (van Rossum & Lamberts, 2004). Furthermore, although the ER22/23EK gene confers risk for the development of depression, it is reported that depressed patients who carry the ER22/23EK gene exhibit better treatment response and cognitive processing (van Rossum et al., 2006).

Apart from the GR gene, other biological systems have been assessed due to their involvement in the regulation of stress hormones. Genetic variants, including the serotonin transporter polymorphism (5-HTT: s/l) (Caspi et al., 2003), apolipoprotein E (APOE) (Fiocco et al., 2008, 2009), serotonin 2a receptor gene (5-HT2A: G/A) (Fiocco, Joober, Poirier, & Lupien, 2007), brain derived neurotrophic factor (BDNF: $Met^{66}Val$) (Vinberg et al., 2009), and the catechol-O-methyltransferase gene (COMT: $Met^{158}Val$) (Yavich, Forsberg, Karayiorgou, Gogos, & Mannisto, 2007) have provided valuable information on individual differences in markers and outcomes of stress.

The serotonin transporter gene (5-HTT), which is coded by a short or long allele, has been widely assessed in relation to depression (Dorado et al., 2007). The 5-HTT is involved in reuptake of serotonin, with the short allele associated with lower levels of serotonin uptake and lower transcriptional efficiency of the 5-HT transporter (Lesch & Gutknecht, 2005). It has been shown that carriers of the short allele tend to report greater perceived stress than carriers of the long allele (Otte, McCaffery, Ali, & Whooley, 2007), exhibit elevated MRI amygdala activation reactivity to threatening stimuli (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002), and display greater stress reactivity to psychosocial stress, with the greatest response in those homozygotic for the short allele (Gotlib, Joormann, Minor, & Hallmayer, 2008; Way & Taylor, 2010).

COMT catalyzes the degradation of catecholamines in the brain (Yavich et al., 2007) and is reportedly related to psychosis susceptibility (Craddock, Owen, & O'Donovan, 2006). The gene that

codes for COMT contains a functional common Val[158]Met polymorphism, with the Val allele exhibiting a three- to fourfold increase in enzyme activity compared to the Met allele (Chen et al., 2004). Recent studies show that, compared to Val/Val carriers, healthy adults with the Met/Met genotype report greater sensory and affective ratings of pain following a sustained pain challenge (Zubieta et al., 2003) and increased limbic and prefrontal activation following the presentation of unpleasant stimuli (Smolka et al., 2005). Furthermore, in a recent longitudinal study of non-demented elderly men and women, it was found that the Met allele is associated with greater cognitive decline over years compared to homozygotic carriers of the Val allele (Fiocco et al., 2010). While studies that focus on a single SNP have been marginal and somewhat inconsistent, COMT has been found to predict individual differences in neuroticism, risk for anxiety, and risk for major depressive disorder (Hettema et al., 2008). These studies suggest that the Met allele lowers physiological and psychological resilience against negative environmental challenges (i.e. chronic stress), which may increase the risk of stress-induced disease.

While the studies reported herein provide important information on inter-individual variations in stress sensitivity and disease susceptibility, a number of negative findings are also reported. One potential explanation for this is that genes do not act in isolation. In addition to gene–gene interactions, gene–sex (Kumsta et al., 2007) and gene–environment interactions (Bet et al., 2009) must be considered. For example, the pioneering work of Caspi and colleagues (Caspi et al., 2003) demonstrated a gene-by-environment interaction in a prospective-longitudinal study that assessed the relationship between the 5-HTT polymorphism and stressful life events on depressive symptomatology. However, it is important to note that these findings have not been replicated so far.

In addition to gene–environment interactions, environmental exposure has a tremendous impact on our development by influencing our physiology at its foundation, the DNA. Epigenetics examines changes in DNA that are produced by perturbations in the environment (e.g., early adversity) that alter the function, but not the structure, of a gene. Animal models show that changes incurred through epigenetics are stable and can at times be transmitted intergenerationally (Meaney & Szyf, 2005). For example, animal studies have shown that maternal care affect genetic expression, via DNA methylation, precisely acting on factors involved in GC receptor expression in the hippocampus (Fish et al., 2004; O'Donnell et al., 1994; Weaver, Diorio, Seckl, Szyf, & Meaney, 2004).

The epigenetic model in humans can be evaluated via epidemiologic studies. A twin study that examined the genetic and environmental contributions to cortisol reactivity in a cohort of 19-month-old twins from high and low family adversity found that high family adversity had a programming developmental effect on cortisol reactivity (Ouellet-Morin et al., 2008). Both genetic and environmental factors explained the variance in cortisol reactivity to a mild stressor in twins from low family adversity. However, in twins from high family adversity, only shared and unique environmental factors contributed to variance in cortisol reactivity. The authors suggested that infants who are exposed to an adverse environment undergo alterations of the stress-sensitive system that are over and above any genetic contribution alone. Whether the epigenetic programming effect of early adversity is on GC gene promotor expression in the hippocampus via DNA methylation remains unclear. However, a recent postmortem study (McGowan et al., 2009) that assessed the epigenetic regulation of GC receptor in suicide victims with or without a history of childhood abuse, reported differential neuron-specific GC receptor promotor in postmortem hippocampus. Abused suicide victims displayed decreased levels of GC receptor mRNA and increased cytosine methylation of the GC receptor promotor compared to non-abused suicide victims.

In conclusion, a growing body of research is attempting to explain how genes, environment, and their interaction, determine individual differences in stress sensitivity and risk for stress-related disease. Population neuroscience is an emerging field that incorporates genetics, cognitive neuroscience, and epidemiology, which may guide future research in examining and identifying complex environmental and genetic factors that contribute to individual differences in the neuronal and behavioral phenotypes that ensue (Paus, 2010). A number of longitudinal assessments are being implemented to elucidate the impact of genetic and environmental factors on human brain structures to understand normative brain aging and neuropsychiatric disorders.

5. Conclusion

Given that GCs have access to the brain and more particularly to brain regions responsible for memory, emotions and emotional regulation, it is not surprising that chronic exposure to elevated levels of GCs has an impact on cognition and the development of different psychopathologies. Ultimately, various factors will contribute to the development of different stress-related mental health diseases. Manifestations could occur during aging with cognitive impairments ranging from MCI to AD but could also occur earlier in life in the form of burnout, depression or PTSD during adulthood. Notwithstanding, these represent only a few models of human chronic stress.

One must keep in mind that stress influences the manner in which one perceives and appraises the next situation and consequently chronic stress can put into place a chronic loop from which it is difficult to escape. In order to prevent the development of certain diseases or to identify at-risk individuals early, it is crucial to view chronic stress from a developmental perspective. With this goal in mind, this review has addressed the importance of looking beyond the diagnosis and trying to understand the different protective and risk factors that each individual has and that can be conveyed by sex, early life experience and genetic factors. Taking a more individualized approach may foster increased understanding of stress-related pathologies, which in turn might eventually prevent the development of certain diseases.

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