

## PSYCHOPHYSIOLOGICAL CORRELATES OF COGNITIVE DEFICITS IN FAMILY CAREGIVERS OF PATIENTS WITH ALZHEIMER DISEASE

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**Abstract—Background:** The progressive loss of memory and autonomy of Alzheimer's Disease (AD) patients, together with their characteristic behavioral and psychological symptoms, subjects their family caregivers to chronic stress. Several studies indicate that these caregivers are predisposed to cognitive impairments, but the physiological correlates of these alterations remain to be elucidated.

**Objective:** Analyze the effects of chronic stress of family caregivers of AD patients on cognition, cortisol/DHEA ratios and BDNF levels and investigate the relation between these variables.

**Experimental procedure:** Seventeen family caregivers (64.83 ± 3.64 years) of patients with AD and eighteen non-caregivers (58.29 ± 3.16 years) completed stress, depression and anxiety inventories. Exclusion criteria were current neurological disorders, major unstable medical illnesses, use of medications that could interfere with cognitive or

HPA axis function and dementia. Attention, working memory and executive function were assessed with Digit Span and Trail Making tests, and declarative memory was analyzed with the Logical Memory test. Saliva was collected at 8 AM and 10 PM and its cortisol and DHEA levels determined by radioimmunoassay. Serum BDNF levels were measured by sandwich-ELISA. Results were analyzed with independent samples *t* test, covariance analysis and linear regressions. The statistical significance was set at  $p < 0.05$  and all *p* values were adjusted with Holm's Method.

**Results:** Caregivers showed more stress, depression and anxiety symptoms than non-caregivers, as well as significantly worse performances on attention, working memory and executive function tests. Caregivers also had higher cortisol/DHEA ratios and lower BDNF levels than non-caregivers. Cortisol/DHEA ratios, especially at 10 PM, were negatively related with all cognitive tasks in which caregivers showed impaired performance. On the other hand, the only cognitive task that related with the BDNF level was digit span.

**Conclusions:** This study showed that caregivers' cognitive impairment is related with alterations on cortisol/DHEA ratios, and that chronic stress experienced by these subjects has the potential to alter their BDNF levels.

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**Key words:** caregivers, chronic stress, cognitive deficits, cortisol, DHEA, BDNF.

### INTRODUCTION

The world population has been experiencing significant aging—the process that results in rising proportions of older persons in the total population—since the mid-twentieth century (DESA United Nations, 2002) and, consequently, a greater incidence and prevalence of aging-related dementias, like Alzheimer Disease (AD) (review in Thies and Bleiler, 2013). AD is characterized by a progressive decline in cognitive and functional abilities, demanding a growing need of care as the patient's clinical condition worsens (Hazzan et al., 2014). This caregiving task is mostly done by the patients' relatives, especially their spouses or children (Ferrara et al., 2008). Several studies argue that these caregivers suffer from chronic stress (Vitaliano, 2010; Vitaliano et al., 2011).

Although acute stress has physiological benefits to the organism, chronic stress may promote severe and broad health dysfunctions (McEwen, 2000, 2004; Lupien et al., 2009). The effect of chronic stress on cognition, as well as its cellular and molecular correlates, has been the

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**Abbreviations:** AD, Alzheimer's Disease; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CAR, cortisol awakening response; CNS, central nervous system; DHEA, dehydroepiandrosterone; GRs, glucocorticoid receptors; HPA, Hypothalamus–Pituitary–Adrenal; ISSL, Lipp Stress Symptoms Inventory for Adults; MAOI, monoamine oxidase inhibitor; MMSE, Mini Mental Status Examination; SSRI, selective serotonin reuptake inhibitor; WAIS III, Wechsler Adult Intelligence Scale.

subject of several studies (Bremner, 1999; McEwen, 2000; Sandi, 2004; Hanson et al., 2011; Nooshin et al., 2011). Most of these researches indicate that chronic stress may imply a number of changes on important brain structures responsible for cognitive aspects, such as the prefrontal cortex and hippocampus (Yamada and Nabeshima, 2003; Kozisek et al., 2008). Executive function, attention, working and declarative memories are among the most affected cognitive domains (Bremner, 1999; Sandi, 2004; Lindauer et al., 2006; Holmes and Wellman, 2009). Attention, working memory and executive function, responsible for information assortment and processing, are mediated by the prefrontal cortex (Holmes and Wellman, 2009) and deficits on these cognitive domains were already verified in caregivers of dementia patients (Vitaliano et al., 2005; Oken et al., 2011). Hippocampus-dependent declarative memory impairment (Braver et al., 2001; Glisky et al., 2001; Buwalda et al., 2005; Huang et al., 2005; Artola et al., 2006; Joëls and Krugers, 2007) is also reported in studies of caregivers with chronic physical and emotional burden (de Vugt et al., 2006; Palma et al., 2011).

The main hypothesis for the cognitive impairment of chronically stressed individuals is the Hypothalamus–Pituitary–Adrenal (HPA) axis dysfunction, which results in increased cortisol levels. This hypercortisolemia has adverse effects on morphological and physiological aspects of structures related with cognitive functions (Conrad, 2008). These effects seem to be largely mediated by the lower affinity glucocorticoid receptors (GRs), which become heavily occupied with corticosteroids in response to stress (Kim and Diamond, 2002). One consequence of such deleterious effects is the impairment of long-term potentiation induction (Kim and Diamond, 2002; Artola et al., 2006), a central nervous system (CNS) mechanism for memory maintenance (Buwalda et al., 2005; Huang et al., 2005; Joëls and Krugers, 2007; Kumar, 2011). Moreover, the extended exposure to high levels of glucocorticoids is considered neurotoxic, since these hormones can disturb different neurotransmitter systems, synaptic plasticity, neurogenesis and lead to neuronal death, dysfunctions that were already related with cognitive impairment (McEwen, 2000; Datson et al., 2008; Henckens et al., 2012).

Previous studies with caregivers show that they have high cortisol levels and/or disturbances on the circadian secretion pattern of this glucocorticoid (Oken et al., 2011; Palma et al., 2011). In healthy subjects, besides the elevation of the cortisol levels during stress, there is also the release of dehydroepiandrosterone (DHEA), an antiglucocorticoid (Young et al., 2002; Dong and Zheng, 2012) able to reduce GR levels (Gallagher et al., 2007) and promote neuronal survival and repair by stimulating an increase in neurotrophin levels (Shoae-Hassani et al., 2011). However, in caregivers of dementia patients, there is a decrease in DHEA levels (Jeckel et al., 2010). Thus, the ratio between cortisol and DHEA would be a more reliable evaluation of the effects of stress on CNS than the individual analysis of one or another hormone (Kaminska et al., 2000; Maninger et al., 2009). Until the present time, only one study examined the cortisol/DHEA

ratio in family caregivers of AD patients (Jeckel et al., 2010) and none analyzed the relation between their cortisol/DHEA ratios and cognitive parameters.

Besides alterations of cortisol and DHEA levels, some studies showed that the expression of neurotrophins involved with synaptic plasticity and neuronal survival and repair, such as the brain-derived neurotrophic factor (BDNF), is greatly reduced during chronic stress (Vinberg et al., 2009; Issa et al., 2010). This decrease in BDNF levels might be related with the glucocorticoid increase (Kawashima et al., 2010; Jeanneteau and Chao, 2013; Pluchino et al., 2013; Suri and Vaidya, 2013). Moreover, a large body of evidence established a link between BDNF reduction and impaired neuronal plasticity and survival (Calabrese et al., 2009, 2013). Studies with patients of neurodegenerative diseases imply that BDNF can be important for the maintenance of a normal cognitive function (Diniz and Teixeira, 2011; Laske et al., 2011; Carlino et al., 2013). However, to date, no study has examined levels of this neurotrophin in caregivers, despite the existing evidences of their cognitive impairment (de Vugt et al., 2006; Oken et al., 2011) and physiologic alterations that predispose to BDNF decline (Pluchino et al., 2013; Suri and Vaidya, 2013).

This study aims to contribute to the understanding of the neurophysiological correlates of the cognitive impairments of familial caregivers of AD patients. Therefore, we tested the following hypotheses (I) that the cognitive performance of caregivers would be susceptible to the effects of chronic stress; (II) that cortisol/DHEA ratios would be higher and the BDNF levels would be lower in caregivers; (III) that cognitive results would be negatively related with the cortisol/DHEA ratios and positively related with BDNF levels.

## EXPERIMENTAL PROCEDURES

### Participants

Seventeen family caregivers ( $64.83 \pm 3.64$  years old; 13 women) of patients with AD were recruited from the Brazilian Alzheimer Association – Porto Alegre, RS, Brazil. To be included, caregivers had to be providing care for 8 h/day, for at least a year, at the time of the study. A control group, composed by eighteen non-caregivers ( $58.29 \pm 3.16$  years old, 14 women) recruited in the community, was also included in the study. Exclusion criteria comprised previous or current neurological disorders, major unstable medical illnesses, use of medications that could interfere with cognitive or HPA axis function, hormone replacement therapy, previous or current use of illegal psychoactive drugs and scores on Mini Mental Status Examination (MMSE) (Folstein et al., 1975) indicative of dementia. Cutoff values for the Brazilian version of MMSE were  $< 18$  for middle educational level (4–8 years of education) and  $< 26$  for high educational level (more than 8 years of education) (Bertolucci et al., 1994). Symptoms of depression and anxiety were assessed for all participants with the Brazilian adapted and validated version (Cunha, 2001) of Beck Depression Inventory (BDI) and Beck Anxiety Inventory

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