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Increased morning salivary cortisol levels in older adults with nonamnestic and multidomain mild cognitive impairment

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Summary Exposure to elevated glucocorticoid levels has a detrimental impact on cognitive function. In the present study, elderly individuals were classified according to their cognitive status to (i) cognitively healthy; (ii) amnestic; (iii) nonamnestic; or (iv) multidomain, with an extensive cognitive profiling. Salivary cortisol samples were taken at awakening, evening and night. We report that, compared to cognitively normal control individuals, subjects with nonamnestic or multidomain mild cognitive impairment profiles show increased salivary cortisol levels, immediately after awakening, but not in the evening or at night. Importantly, individuals with amnestic mild cognitive impairment did not show this increase in salivary cortisol levels. We also found that higher morning cortisol levels were associated with a lower global cognitive state, as well as poorer score in executive function and visuoconstructive praxes, verbal fluency, and a worse free immediate recall of items from a word list. These findings open new avenues to the use of salivary cortisol levels as a possible biomarker for nonamnestic and multidomain mild cognitive impairment in elderly subjects.

1. Introduction

Cortisol (corticosterone in rodents) is the main glucocorticoid hormone released into the bloodstream after activation of the hypothalamic—pituitary—adrenal (HPA) axis. Cortisol level fluctuates daily, with high levels at awakening and low levels at night (Hucklebridge et al., 2005). Due to its permeability into the blood—brain barrier cortisol modulates neural function. Among the well-known actions of glucocorticoids in the brain are the restraint of the HPA axis, and suppression of hippocampal glucose and blood flow (de Leon et al., 1997; Endo et al., 1997; de Quervain et al., 2003). Moreover, experimental animal studies have demonstrated that glucocorticoids can affect brain morphology and cognitive function (Magariños and McEwen, 1995; Sousa et al.,

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2000; Dias-Ferreira et al., 2009; for review see Herbert et al., 2006; McEwen, 2008). In humans, when cortisol is constantly elevated, such as in Cushing's syndrome or in certain cases of major depression, some brain structures (*e.g.* hippocampus) show shrinkage (Rubinow et al., 1984; Starkman et al., 1999; Campbell et al., 2004), and cognitive function is compromised (for review see Sapolsky, 2000; Pereira et al., 2010).

In the last decade, there is an increasing interest in using free plasma cortisol levels (reflected by salivary cortisol levels) as a possible indicator of age-related mild cognitive impairment (MCI). MCI is a subtle but measurable functional deficit in daily tasks with lower cognitive scores than normal subjects (Petersen, 2004). Pioneer epidemiological studies in elderly people revealed an association between high cortisol levels and cognitive dysfunction in elderly subjects (Lupien et al., 1994, 1998). In addition, other studies have reported alterations in the activity of the hypothalamic–pituitary–adrenal (HPA) axis, with increase in cortisol levels (Lupien et al., 1994; Ferrari et al., 1995; Van Cauter et al., 1996; Li et al., 2006) or flattened diurnal rhythm (van Coevorden et al., 1991; Van Cauter et al., 1996; Deuschle et al., 1997; Luz et al., 2003). Later studies investigating the association between salivary cortisol levels and cognitive decline at aging have shown a mixed pattern of findings. While some reported an inverse correlation between cortisol levels and memory performance at aging (MacLullich et al., 2005; Lee et al., 2007; Lind et al., 2007; Suhr et al., 2008; Souza-Talarico et al., 2010; Evans et al., 2011), others authors found such a correlation only in MCI subjects, but not in cognitively unimpaired elderly individuals (Wolf et al., 2002).

MCI is a heterogeneous cognitive state that, in some cases, can progress to Alzheimer's disease or another dementia. Using an extensive neuropsychological test battery MCI can be identified as amnestic, when isolated mild memory impairment is present (Ganguli et al., 2004; Petersen, 2004), nonamnestic, with isolated mild impairments in cognitive domains apart from memory occur (*e.g.* language, praxes), and multidomain, with impairments in memory and other cognitive domains (Petersen, 2004). Interestingly, the diagnosis of MCI and the likelihood of progression to AD varies among the different subtypes of this disorder (for review see Petersen and Negash, 2008).

Different subtypes of MCI have been associated with morphological and functional changes in certain brain structures, such as the anterior hippocampus in amnestic subtype or the prefrontal cortex in nonamnestic subjects (de Leon et al., 1989; Hämäläinen et al., 2007; Nobili et al., 2008; Pa et al., 2009; Qiu et al., 2009). Given that these brain structures modulate HPA activity, their malfunctioning may affect circadian cortisol secretion (McEwen, 2008). Therefore, we hypothesized that MCI may be associated with distinct cortisol diurnal patterns.

The aim of the present work was to evaluate whether free cortisol levels differ in elderly patients with different subtypes of MCI amnestic, nonamnestic and multidomain, compared with age-matched cognitively healthy subjects. For this purpose, we extensively examined cognitive function in a cohort of elderly individuals and evaluated salivary cortisol levels in the same population. In addition, we decided to investigate whether there was an association between cortisol and cognitive performance.

2. Materials and methods

2.1. Participants

Our sample (N = 56 participants) was recruited from a larger sample of 247 participants of an ongoing longitudinal study focused on determining the prevalence and stability of the different MCI subtypes (Peraita et al., 2011). The participants were recruited in the Autonomous Community of Madrid (ACM, Spain). The larger sample of participants was originally a mixed sample with individuals presenting mild cognitive impairment and also with unimpaired subjects. For the present study, we first excluded those people that were not independent in daily activities or that fulfilled one of the exclusion criteria (see below). After taking into consideration the excluding criteria and the use of antidepressant and/or corticosteroid medication, the initial sample of participants from a longitudinal study was significantly reduced to 132 subjects. Afterwards, 34% of participants did not sign the written consent to supply the salivary samples, so they were not included in this study. Finally, 22% of the selected subjects did not collect one of the 3 salivary samples or collected them at different time points of the day than requested and rejected to repeat the sampling procedure. As a result, we had salivary samples from subjects with MCI: 10 amnestic, 15 nonamnestic and 11 multidomain, and 31 cognitively healthy controls. Then, one researcher of our group selected 20 control subjects that matched in age, gender and years of education to the 3 groups of MCI before salivary cortisol measurements were done.

The study was approved by the Ethic and Research Committee at the UNED, and all participants provided written consent to perform the neuropsychological test battery and supply the salivary samples.

2.1.1. Inclusion criteria

Individuals aged between 65 and 90 years living in 2 towns of the ACM who volunteered to participate in the study, and were interested in having an assessment of their cognitive processes, either because they expressed subjective complaints about the functioning of these processes or simply because they were interesting in having information on these processes. They were to be informed about their cognitive processes at the end of the study, and could not have fulfilled any of the exclusion criteria (see below).

2.1.2. Exclusion criteria

(a) Neurodegenerative disease, (b) diagnosed with severe cognitive impairment, (c) disabling chronic disease, (d) psychiatric disorder, (e) marked neurological abnormality, such as aphasia, agraphia, alexia, and/or apraxia, (f) a severe sensory deficit, (g) depression, (h) diabetes or (i) cerebrovascular accident. These criteria were confirmed by a neurologist. Participants taking antidepressant medication were also excluded from the study since antidepressants can normalize HPA dysregulation (Holsboer and Barden, 1996). In addition, participants were also excluded if they were currently using corticosteroids, since these drugs suppress the synthesis of cortisol in the adrenal gland.