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Memory performance is related to the cortisol awakening response in older people, but not to the diurnal cortisol slope

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ABSTRACT

There are large individual differences in age-related cognitive decline. Hypothalamic-pituitary-adrenal axis (HPA-axis) functioning has been suggested as one of the mechanisms underlying these differences. This study aimed to investigate the relationships between the diurnal cortisol cycle, measured as the cortisol awakening response (CAR), and the diurnal cortisol slope (DCS) and the memory performance of healthy older people. To do so, we assessed the verbal, visual, and working memory performance of 64 participants (32 men) from 57 to 76 years old who also provided 14 saliva samples on two consecutive weekdays to determine their diurnal cortisol cycle. The CAR was linearly and negatively associated with verbal (significantly) and visual (marginally) memory domains, but not with working memory. Sex did not moderate these relationships. Furthermore, no associations were found between the DCS and any of the three memory domains assessed. Our results indicate that the two components of the diurnal cortisol cycle have different relationships with memory performance, with the CAR being more relevant than DCS in understanding the link from HPA-axis activity and regulation to different types of memory. These results suggest that the CAR is related to memory domains dependent on hippocampal functioning (i.e., declarative memory), but not to those that are more dependent on prefrontal cortex functioning (i.e., working memory).

1. Introduction

Cognitive decline stands out among the main negative changes associated with aging. However, there is great variability in the way people experience these age-related changes (Christensen et al., 1999). While some people maintain their cognitive abilities intact or show few changes, others experience important cognitive problems such as dementia. It has been suggested that hypothalamus-pituitary-adrenal axis (HPA-axis) functioning can explain these differences, at least in part. Along these lines, HPA-axis dysregulation has been related to poorer cognitive performance (Lupien et al., 2007, 2009). The HPA-axis would exert its effects on cognitive performance through the action of cortisol, the main glucocorticoid in humans, which binds to receptors (i.e., mineralocorticoid and glucocorticoid receptors) especially distributed in the hippocampus, prefrontal cortex and amygdala (Lupien and Lepage, 2001; Lupien et al., 2009; Roozendaal, 2000). Different mechanisms might underlie the negative effect of an HPA-axis dysregulation on cognitive performance. Several studies have shown that both long-term high and low cortisol levels may produce neurogenesis suppression, dendritic atrophy, synaptic and spine loss, a synaptic transmission reduction, and loss of neuronal integrity, especially in the hippocampus and prefrontal cortex, affecting cognitive performance (Berger et al., 2006; Lupien et al., 2005, 2009; Sloviter et al., 1993; Stienstra et al., 1998; Wossink et al., 2001). In addition, a dysregulation of the HPA-axis has been related to different physical and psychiatric disorders that could explain, at least in part, the inter-individual differences in cognitive performance. Thus, some authors have proposed that a dysregulation of the HPA-axis may be the key to the pathophysiology behind depression in later life and/or the diagnosis of metabolic syndrome, producing a negative effect on cognitive performance (Kuehl et al., 2015; Lupien et al., 2009; Pariante and Lightman, 2008). In this vein, memory is one of the main cognitive processes that have been related to HPA-axis functioning because these brain structures are key brain areas for learning and memory processes (for review see: Lupien et al., 2007).

Most studies on the relationship between HPA-axis functioning and memory performance have been carried out in acute stress situations, and only a few have studied the diurnal cortisol cycle. It is worth noting that the dynamic nature of the cortisol cycle makes

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the study of HPA-axis functioning difficult. In non-stress conditions, the secretion of cortisol follows a circadian pattern characterized by higher cortisol levels in the morning and lower cortisol levels during the last hours of the day. Generally, two components are distinguished in the diurnal cortisol cycle: (i) the cortisol awakening response (CAR; a sharp rise in cortisol that occurs from 30 to 45 min after awakening), and (ii) a steeper decrease in cortisol levels secreted throughout the rest of the day (Adam and Kumari, 2009). It seems that the regulatory mechanism underlying the CAR is independent from the rest of the diurnal cycle (Edwards et al., 2001). Given that these are considered two independent components of HPA-axis activity, some authors have indicated that they deserve to be analyzed independently (Fries et al., 2009; Clow et al., 2010a,b). However, most of the cross-sectional studies investigating the relationship between the HPA-axis functioning and cognitive performance in healthy older people have not jointly considered both of the discrete components of the diurnal HPA-axis activity. In addition, results have been obtained by analyzing a limited and different number of samples and memory tests (MacLullich et al., 2005; Li et al., 2006; Kuningas et al., 2007; Lee et al., 2007, 2008; Comijs et al., 2010; Seeman et al., 1997; Souza-Talarico et al., 2010; Pulopulos et al., 2014). Moreover, the relationship between memory and cortisol has been studied employing different indices, such as the awakening cortisol (O'Hara et al., 2007; Singh-Manoux et al., 2014), the area under the curve with respect to the ground, AUCg (Almela et al., 2012; Franz et al., 2011), mean cortisol levels (Abercrombie et al., 2004; Evans et al., 2011; Singh-Manoux et al., 2014) and bedtime cortisol (Singh-Manoux et al., 2014). However, to our knowledge, only a few studies have investigated the specific contribution of the two dynamic components of the diurnal cortisol cycle (i.e., CAR and cortisol secreted the rest of the day) to memory performance in older people.

Regarding the CAR, most of the studies failed to find a clear association with memory performance (Evans et al., 2011, 2012; Franz et al., 2011; Singh-Manoux et al., 2014; Stawski et al., 2011). For instance, Evans et al. (2012) showed that, in 50 older individuals (60–91 years old), the CAR was positively related to executive function, but not to memory performance (Evans et al., 2012). Along these lines, it has been also observed that the CAR was not related to episodic memory, working memory (Stawski et al., 2011) or short-term verbal memory (Singh-Manoux et al., 2014). Studying only older men (51–60 years old), Franz et al. (2011) did not find significant relationships between the CAR and visual spatial memory and working memory when they controlled for several covariates. By contrast, we found a significant but different relationship between the CAR and memory performance depending on the type of memory studied. Thus, while a higher CAR was negatively related to verbal memory in both men and women, it was positively related to spatial working memory, but only in men (Almela et al., 2012).

For the cortisol secreted during the rest of the day, different measures and indices have been used. One of those most frequently employed is the diurnal cortisol slope DCS, cortisol index, which indicates the decline in cortisol levels during the day, frequently calculated by regressing cortisol values on each sample collection time (Sephton et al., 2000). Poor memory performance has been related to both a steeper (O'Hara et al., 2007) and a flatter DCS (Abercrombie et al., 2004; Gerritsen et al., 2011). Finally, a lack of significant relationships has also been found (Beluche et al., 2010; Stawski et al., 2011; Singh-Manoux et al., 2014; Fiocco et al., 2006). When other indices were employed, mixed results were also reported. For example, the average diurnal cortisol decline was positively related to overall cognitive performance, executive function and verbal fluency tasks (Evans et al., 2011), while the cortisol AUCg (an index of total hormonal output throughout the day) was negatively related to visual spatial memory, executive functions, and processing speed (Franz et al., 2011). Therefore, in light of the inconclusive results, the need to obtain more evidence about this issue seems clear.

It is worth noting that, among the studies that have investigated the specific contribution of the CAR and the cortisol secreted during the rest of the day to differences in the cognitive performance in healthy older people, most of them only assessed one type of memory: visual (Beluche et al., 2010), verbal (Abercrombie et al., 2004; Evans et al., 2011, 2012; Gerritsen et al., 2011; O'Hara et al., 2007; Singh-Manoux et al., 2014) or working and declarative memory (Almela et al., 2012; Fiocco et al., 2006; Stawski et al., 2011). To our knowledge, only Franz et al. (2011) used several memory tasks (two tests for verbal and one test for spatial working memory) and short and delayed recall (two tests for verbal and one test for visual memory). However, this study with a younger sample of only men focused on a more limited age range (51–59 years old) compared to the other studies, which could explain the lack of association between cortisol and most of the memory tasks used. Therefore, more research is needed to investigate whether the two components of the HPA-axis activity may be related to different types of memory tasks in healthy older people.

With all this in mind, the aim of the present study was to investigate whether the components of the cortisol diurnal cycle (i.e., the CAR and the DCS) were related to declarative and working memory assessed with several tasks in older men and women. To do so, we assessed the performance on different memory tests of 64 older people who provided fourteen saliva samples on two consecutive weekdays, in order to obtain the CAR and the DCS. Based on previous results (Almela et al., 2012) and findings about the relationship between general life stress and increased CAR (Chida and Steptoe, 2009), as well as the well-known effect of long-term stress on memory (Lupien et al., 2005, 2009), we expected a CAR of increased magnitude to be associated with poorer performance on memory tasks that are dependent on hippocampal functioning, and at the same time, with better performance on memory tasks that are dependent on prefrontal cortex functioning (Almela et al., 2012; Evans et al., 2012). Moreover, we hypothesized that a flatter DCS would be associated with poorer memory performance (Abercrombie et al., 2004; Evans et al., 2011; Franz et al., 2011; Gerritsen et al., 2011). Finally, because some results suggest that sex moderates the relationship between CAR and working memory (Almela et al., 2012), especially stress-induced cortisol and memory performance (Seeman et al., 1997; Wolf et al., 1998; Almela et al., 2011), we also investigated possible sex differences.

2. Methods

2.1. Participants

The sample was composed of 64 participants (32 men and 32 women) from 57 to 76 years old (Men: $M = 64.47$, $SD = 4.295$; Women: $M = 64.84$, $SD = 3.886$). There were no sex differences in age or educational level (both $p > 0.586$), but men had a higher body mass index (Men: $M = 28.35$, $SD = 3.79$; Women: $M = 25.73$, $SD = 4.18$, $p = 0.011$) and reported slightly higher subjective socioeconomic status (SES) than women (Men: $M = 6.63$, $SD = 1.24$; Women: $M = 5.97$, $SD = 1.09$, $p = 0.028$). SES was measured using the MacArthur Scale of Subjective Social Status (Adler et al., 2000). In this scale, participants rated themselves on a scale ranging from 1 (people with the lowest education, income and worst jobs) to 10 points (people with the best education, income and jobs) according to their subjective socioeconomic status.

Participants belonged to a study program at the University of Valencia for people over 55 years of age. They completed a general questionnaire to check whether they met the study prerequisites. The criteria for exclusion were as follows: smoking