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# Acute stress impairs recall after interference in older people, but not in young people

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ABSTRACT

Stress has been associated with negative changes observed during the aging process. However, very little research has been carried out on the role of age in acute stress effects on memory. We aimed to explore the role of age and sex in the relationship between hypothalamus–pituitary–adrenal axis (HPA-axis) and sympathetic nervous system (SNS) reactivity to psychosocial stress and short-term declarative memory performance. To do so, sixty-seven participants divided into two age groups (each group with a similar number of men and women) were exposed to the Trier Social Stress Test (TSST) and a control condition in a crossover design. Memory performance was assessed by the Rey Auditory Verbal Learning Test (RAVLT). As expected, worse memory performance was associated with age; but more interestingly, the stressor impaired recall after interference only in the older group. In addition, this effect was negatively correlated with the alpha-amylase over cortisol ratio, which has recently been suggested as a good marker of stress system dysregulation. However, we failed to find sex differences in memory performance. These results show that age moderates stress-induced effects on declarative memory, and they point out the importance of studying both of the physiological systems involved in the stress response together.



## Introduction

Stress has been suggested as a main factor related to negative changes observed during the aging process. However, little is known about the role of age in acute stress effects on memory performance. Given that there are data suggesting age differences in the reactivity to stress, the need to obtain evidence to fill this gap in the literature seems clear.

Stress, particularly, provokes the activation of two systems: (i) the sympathetic nervous system (SNS) and (ii) the hypothalamus–pituitary–adrenal axis (HPA-axis). The fast SNS response includes the release of the catecholamines (adrenaline and noradrenaline), which are responsible for different physiological changes preparing the organism for a "fight-or-flight" response. Minutes after the onset of the stressor, HPA-axis activation occurs and, consequently, large amounts of glucocorticoids are secreted in the adrenal cortex. There are numerous glucocorticoid receptors in the brain areas involved in the memory process, such as the hippocampus, the frontal lobe and the amygdala (Lupien and Lepage, 2001; Lupien et al., 2009; Roozendaal, 2000), which also play an important role in the regulation of the HPA-axis (Herman et al., 2005; Lupien and Lepage, 2001). Thus, cortisol, the main glucocorticoid hormone in humans, would have important effects on memory, although the direction of these effects remains unclear. They can differ depending on several factors, some related to the task (such as the type of memory or the nature of the material, neutral or emotional) and others associated with characteristics of the individual (including age and sex). In addition, it has been well established that SNS activation can also affect memory performance through the influence of cathecolamines on the limbic brain structures. According to Roozendaal et al. (2009), the noradrenergic activation of the amygdala and the interactions between the amygdala and hippocampus are crucial to finding cortisol effects on hippocampus-dependent memory performance.

The majority of studies about the relationship between the exposure to an acute stressor and memory have been performed on declarative memory in young people, reporting mixed results. When subjects have to learn neutral material after stress induction, worsening effects (Jelicic et al., 2004; Kirschbaum et al., 1996; Payne et al., 2006, 2007; Smeets et al., 2006), enhancing effects (Espin et al., 2013; Schwabe et al., 2008), and even a lack of effects (Hidalgo et al., 2012; Wolf et al., 2001b) have been described in mixed-sex samples. When studying only one sex, enhancing effects were found in young men (Nater et al., 2007), but non-effects were detected in women when they were grouped without taking age into account (32–68 years) (Domes et al., 2002). Bohnen et al. (1990) compared two groups of women (41–49 vs. 61–69 years) exposed to a 4-hour mental task, finding no significant differences.

To our knowledge, only Wolf et al. (2001a) have investigated the pre-learning cortisol effects on short-term memory considering the role of age by directly comparing young and older people, specifically

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men. These authors reported that cortisol did not influence the recall of a list of neutral words learned after they injected a cortisol agonist (hydrocortisone). However, there are important differences between the glucocorticoid increases induced by pharmacological administration and those produced by exposure to stress. As mentioned above, in addition to the cortisol increase that occurs with drug administration, stress provokes other physiological (i.e. SNS activation) changes (Lupien and Schramek, 2006). Hence, the use of stress paradigms in the laboratory allows a more complete study of stress effects on memory performance. In recent years, SNS activation has been measured by means of the salivary alpha-amylase (sAA), an oral enzyme secreted by the salivary glands (mainly parotid glands) due to parasympathetic and sympathetic nerve stimulations innervating the salivary glands. sAA is involved in converting starch into glucose and maltose in the oral cavity (Baum, 1993), eliminating bacteria from the mouth, and preventing bacterial attachment to oral surfaces (Scannapieco et al., 1993). A growing body of literature considers sAA to be a sensitive biomarker for stress-related changes in the body reflecting sympathetic nervous system activation (Granger et al., 2007; Nater and Rohleder, 2009; Rohleder and Nater, 2009). Moreover, as it is readily accessible and easily obtained, sAA is a good surrogate for catecholamines in psychoneuroendocrinological research.

Reactivity to stress changes throughout the lifespan; while the role of age in the cortisol response has been investigated more extensively, with most studies reporting that older people have a higher cortisol response than young people (for a review see: Kudielka et al., 2009), for the sAA response, results are fewer and mixed (Almela et al., 2011b; Strahler et al., 2010). Thus, the HPA-axis and the SNS activity could influence memory performance differently as a function of age. Furthermore, since both the HPA-axis and the SNS work in alliance to generate the stress response, in addition to the action of each system separately, it seems logical to study the two systems concurrently. According to Bauer et al. (2002), to obtain an optimal adaptation to stress, a coordinated response of the two stress systems is necessary. Thus, an uncoordinated response could mean a maladaptive response related to health or behavior problems. Studies examining this relationship in children and adolescents have suggested its value in predicting individual differences in behavioral adjustments to stress (Allwood et al., 2011; El-Sheikh et al., 2008; Gordis et al., 2006, 2008; Vigil et al., 2010). Recently, a few studies have focused on the effects of stress on cognitive functioning and even academic achievement (Berry et al., 2012; Keller et al., 2012); however, as mentioned above, these interactions, and specifically their potential effects on cognitive performance, have not been studied in young and older people.

With all this in mind, the purpose of the present study is to investigate age-related differences in memory performance in response to acute psychosocial stress, taking into account the sex and the relationship between the two stress systems, the HPA-axis and the SNS. No previous studies have been published on the influence of an acute laboratory social stressor on declarative memory in young and older people of both sexes. Previously, we reported stress effects on declarative memory in older people, especially in post-menopausal women (Almela et al., 2011a), but not in young people (Hidalgo et al., 2012). Based on these results, in the present study we have directly compared two different age samples employing the same protocol, a statistically different approach, and both stress markers (cortisol and sAA), in order to examine the different effects of stress on declarative memory depending on age or sex. The present study compares sixty-seven healthy participants divided into two age groups, 35 young adults and 32 older adults, with a similar number of men and women in each group. All the older women were postmenopausal, and all the young women were in the early follicular phase of their menstrual cycle, that is, the period with lower sex hormone levels. In a crossover design, the participants were exposed to both psychosocial stress (Trier Social Stress Test, TSST; Kirschbaum et al., 1993) and a control condition. In each condition, declarative memory performance was measured after the task. Previous studies employing a limited age range (41–49 vs. 61–69 years) and a 4-hour mental stressor in women (Bohnen et al., 1990) or cortisol administration in men (Wolf et al., 2001a) did not find age-related differences in stress/cortisol effects on declarative memory. However, we think that with a broader age range and a psychosocial stress task as the stressor, age differences would appear in the stress effects on declarative memory. To test this, we directly compared two age groups (18–35 years vs. 54–78 years) containing men and women, and we employed the TSST, which provokes both HPA-axis and SNS activation. In addition, we investigated stress reactivity by combining the two main stress physiological systems, considering that the imbalance between the two systems (an uncoordinated response) could prejudice memory performance. Finally, since sex differences have been reported in the effects of stress on memory in older people, greater negative stress effects were expected in older women.

## Method

### *Participants*

This study is part of extensive research on the moderating role of age and sex in the effects of acute stress on memory. Partial results from the older (Almela et al., 2011a) and young (Espin et al., 2013; Hidalgo et al., 2012) participants have been previously published. Here, we employed a subsample to directly compare the stress effects on declarative memory, taking into account the age and sex factors.

The final sample employed was composed of sixty-seven participants divided into two age groups (older adults: N = 32; 16 men and 16 women; young adults N = 35; 18 men and 17 women). There were no differences between the two age groups with regard to sex, in subjective socioeconomic status (SES) or educational level, but there were differences in body mass index (BMI), with young men showing a higher BMI than young women ($p = 0.047$) (Table 1). SES was measured using the MacArthur Scale of Subjective Social Status (Adler et al., 2000). Subjects were asked to rate themselves according to their subjective socioeconomic status and compared to other people in Spain, 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).

The older participants belonged to a study program at the University of Valencia for people over 50 years of age (NAU GRAN). We chose this University Program to increase the homogeneity of the sample and the likelihood of getting healthy volunteers to compare with young people.

**Table 1**
Descriptive statistics (mean ± SEM of young ($N = 35$) and older groups ($N = 32$).*SES: Subjective Socio-Economic Status Scale, ranging from 1 (lowest SES) to 10 (highest SES) (Adler et al., 2000). **Range: 0 = no studies, 1 = primary school, 2 = secondary education, 3 = university and higher education, 4 = postgraduate (Master, PhD).

| | Young group | | | Older group | | |
|---|---|---|---|---|---|---|
| | Total | Men | Women | Total | Men | Women |
| Age (years) | 21.1 (0.7) | 22.1 (1.2) | 20.0 (0.7) | 62.1 (0.8) | 60.5 (1.2) | 63.7 (1.1) |
| BMI (kg/m$^2$) | 23.0 (0.5) | 23.9 (0.7) | 21.9 (0.7) | 26.5 (0.5) | 27.0 (0.5) | 26.0 (1.0) |
| SES* | 6.3 (0.1) | 6.4 (0.2) | 6.1 (0.2) | 6.0 (0.2) | 6.1 (0.3) | 5.9 (0.3) |
| Education level** | 2.3 (0.1) | 2.5 (0.2) | 2.2 (0.1) | 2.8 (0.2) | 2.7 (0.3) | 2.9 (0.2) |