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Acute stress does not impair long-term memory retrieval in older people

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ABSTRACT

Previous studies have shown that stress-induced cortisol increases impair memory retrieval in young people. This effect has not been studied in older people; however, some findings suggest that age-related changes in the brain can affect the relationships between acute stress, cortisol and memory in older people. Our aim was to investigate the effects of acute stress on long-term memory retrieval in healthy older people. To this end, 76 participants from 56 to 76 years old (38 men and 38 women) were exposed to an acute psychosocial stressor or a control task. After the stress/control task, the recall of pictures, words and stories learned the previous day was assessed. There were no differences in memory retrieval between the stress and control groups on any of the memory tasks. In addition, stress-induced cortisol response was not associated with memory retrieval. An age-related decrease in cortisol receptors and functional changes in the amygdala and hippocampus could underlie the differences observed between the results from this study and those found in studies performed with young people.

1. Introduction

Aging involves important changes in cognitive performance, especially memory. Although individual differences exist, elderly people usually perform worse on delayed recall and recognition tasks than younger people (Davis et al., 2003; Huh, Kramer, Gazzaley, & Delis, 2006). These memory deficits due to increasing age have been related to structural and functional changes in the prefrontal cortex, hippocampus and amygdala (Hedden & Gabrieli, 2004). Interestingly, these same brain regions are closely associated with important processes related to stress. In fact, a large number of studies have shown that exposure to stress can modulate memory performance through the activity of the prefrontal cortex, hippocampus and amygdala (for reviews see: Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Wolf, 2009). However, most of these studies have been performed in young people, and more research is needed to find out whether the same effects occur in older people.

Stressful situations provoke the activation of both the Hypothalamus–Pituitary–Adrenal axis (HPA-axis) and the Sympathetic Nervous System (SNS), resulting in the release of glucocorticoids (cortisol in humans) and several SNS biomarkers (e.g. catecholamines, salivary alpha-amylase) (Sapolsky, Romero, & Munck, 2001). It has been suggested that acute stress would affect memory processes through both the influence of cortisol on the hippocampus, prefrontal cortex and amygdala (Wolf, 2009) and the noradrenergic activation of the amygdala (McGaugh & Roozendaal, 2002). Additionally, studies performed mainly in young people have shown that the impact of stress on memory depends on several factors, such as the phase of the memory tested (i.e. learning, consolidation or retrieval) and the emotional valence of the material to be remembered (i.e. positive, negative or neutral) (Lupien et al., 2005).

Most studies performed in young people have revealed that stress-induced or pharmacologically-induced increases in cortisol levels usually enhance consolidation (Buchanan & Lovallo, 2001; Cahill, Gorski, & Le, 2003; Smeets, Otgaar, Candel, & Wolf, 2008), but they impair memory retrieval (e.g., Buchanan & Tranel, 2008; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005; Kuhlmann, Piel, & Wolf, 2005; Smeets, 2011; Smeets et al., 2008). This effect has been explained as a blocking effect of cortisol on retrieval processes, in favor of consolidation processes, in order to allow the brain to consolidate new important information to be used in the future (Roozendaal, 2002). Furthermore, noradrenergic activation of the amygdala and amygdala–hippocampal interactions have been shown to be necessary in order to observe cortisol effects on hippocampus-dependent memory performance (for a review see: Roozendaal, McEwen, & Chattarji, 2009).

However, it is not clear whether these effects of stress on memory processes occur in older populations as well, because only a few studies are available, and most of them investigated the effects

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of stress without distinguishing between the different memory phases (i.e. learning, consolidation and retrieval). Moreover, their results have not been consistent, as two studies observed that stress impaired learning (Almela, Hidalgo, Villada, Espín, et al., 2011; Lupien et al., 1997), while two studies found no effect (Bohnen, Houx, Nicolson, & Jolles, 1990; Domes, Heinrichs, Reichwald, & Hautzinger, 2002). To the best of our knowledge, only one study has investigated the effects of cortisol on memory retrieval in older people (Wolf et al., 2001). In this study, cortisol (0.5 mg/kg of hydrocortisone sodium succinate) was injected into young (from 19 to 30 years old) and older (from 59 to 76 years old) men 75 min after they had learned a list of neutral words. The authors found that hydrocortisone impaired memory retrieval in both age groups. However, there are major neuroendocrine differences between pharmacologically-induced glucocorticoid elevations and stress-induced glucocorticoid elevations (for more details see: Lupien & Schramek, 2006; Raison & Miller, 2003). Obviously, stress is not equal to glucocorticoid increases; many other psychological and physiological changes occur in stress that are not present with exogenous glucocorticoid administration, including mood changes or SNS activation, which also play a role in memory modulation.

In this context, it is important to study the effects of exposure to an acute psychosocial stressor on long-term memory retrieval in older men and women. Furthermore, despite the lack of studies investigating this matter, several findings suggest that the relationship between stress and memory retrieval could be affected by some age-related changes in the hippocampus and amygdala. Thus, older people may be less sensitive to the effects of cortisol on memory, due to (i) an age-related reduction in cortisol receptor density and sensitivity in the hippocampus (Bhatnagar et al., 1997; Heffelfinger & Newcomer, 2001; Mizoguchi et al., 2009; Newcomer, Selke, Kelly, Paras, & Craft, 1995; Nichols, Zieba, & Bye, 2001) and (ii) reduced functional interconnectivity between the amygdala and hippocampus in memory processes (Mather, 2006; Murty et al., 2010; St. Jacques, Dolcos, & Cabeza, 2009). Nevertheless, it is not currently known whether these age-related changes in the brain can affect the relationship between stress and memory retrieval in older people.

The main goal of the present study was to investigate the effects of stress on hippocampus-dependent memory retrieval in older people. To this end, older men and women learned a series of pictures, words and stories. Then, 1 day later, they were exposed to an acute psychosocial stressor (or a control task) before recovery of the material learned the previous day. Additionally, to investigate whether stress has different acute effects on memory retrieval for emotional or neutral material, the pictures presented on the learning day were neutral, positive and negative. According to previous studies performed with young people, we expected that stress would impair memory retrieval.

2. Methods

2.1. Participants

The sample was composed of 76 participants (38 men and 38 women) ranging in age from 56 to 76 years (Men: $M = 64.63$, $SD = 4.57$; Women: $M = 63.74$, $SD = 3.67$). Most of them had an educational level beyond high school (84.2%), and their subjective socioeconomic status was medium–high (subjective SES scale: Adler, Epel, Castellazzo, & Ickovics, 2000). Participants were randomly assigned to a stress (19 men and 18 women) or control group (19 men and 20 women). There were no significant differences between the stress and control groups in age, Body Mass Index (BMI), SES and educational level (all $p > 0.163$). Men and Women had similar ages, SES and educational levels ($p = 0.168$), but men had higher BMI (Men, $M = 27.83$, $SD = 3.34$; *Women* = 25.99, $SD = 3.67$; $p = 0.026$). All of the female participants were postmenopausal and had had their last menstrual period more than 3 years before the testing time. None of the participants scored less than 28 on the MEC (Spanish version of the Mini-Mental Status Examination; Lobo et al., 1999), indicating the absence of cognitive impairment.

Participants belonged to a study program at the University of Valencia for people over 55 years of age. Exclusion criteria were: smoking more than 10 cigarettes a day, alcohol or other drug abuse, visual or hearing problems, diabetes, presence of an HPA-axis, neurological or psychiatric disease, using any medication directly related to emotional or cognitive functioning or able to influence hormonal levels, such as glucocorticoids, psychotropic substances or sleep medications, having been under general anesthesia once or more than once in the past year, and the presence of a stressful life event during the past year. Because hypertension is a common problem in the older population (Virdis et al., 2011), we decided not to exclude participants who were taking anti-hypertensive medication (men-stress = 7; women-stress = 5; men-control = 4; women-control = 8). Nevertheless, the statistical results and conclusions of this study do not change if we exclude those participants taking anti-hypertensive medication.

2.2. Memory assessment

2.2.1. Picture recall

Participants were shown 30 color pictures (10 negative, 10 positive and 10 neutral) chosen from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005). Pictures were presented individually for 5 s on a computer screen, and then separated by a black screen that appeared for 15 s. Participants were told to look at the stimuli for the entire 5 s and, when the black screen was displayed, rate the emotional valence (from 1 = *very negative* to 9 = *very positive*) and arousal (from 1 = *low arousal* to 9 = *high arousal*) of the pictures with the Self-Assessment Manikin (SAM; Lang, 1980). Ratings of the pictures showed that negative pictures ($M = 1.21$, SEM = 0.08) were rated lower on emotional valence than neutral ($M = 4.26$, SEM = 0.22) and positive pictures ($M = 7.16$, SEM = 0.12) (for all $p < 0.001$). Neutral pictures were rated lower on valence than positive pictures (for all $p < 0.001$). There were no significant differences between groups or sex (all $p > 0.434$). Positive ($M = 4.30$, SEM = 0.18), and negative pictures ($M = 7.94$, SEM = 0.13) were rated as more arousing than neutral pictures ($M = 3.62$, SEM = 0.13; all $p < 0.004$). Women rated all the pictures as more arousing than men did (Women: $M = 5.53$, SEM = 0.20; Men: $M = 5.03$, SEM = 0.21; $p = 0.003$), and there were no differences between the control and stress groups (Control: $M = 5.27$, SEM = 0.21; Stress: $M = 5.31$, SEM = 0.21; $p = 0.738$).

The following day, participants were instructed to try to recollect as many pictures as possible from the set they had seen the previous day. They had 10 min to write a short detailed description of the pictures. Two independent judges, blind to the group to which each participant belonged, determined which picture (if any) was described by each description. Agreement between judges was 93%, and discrepancies were resolved by consensus. One man in the control group was removed from the free picture-recall analysis because his descriptions could not be matched to any pictures, as they were too vague. After that, participants performed a recognition test. The 30 originally-viewed pictures and 30 new pictures (10 negative, 10 positive and 10 neutral) were presented individually on a computer screen. Participants were asked to determine whether the picture was new or had been presented the previous day. D-prime (d') was used for the recognition analysis (MacMillan & Creelman, 1991).

2.2.2. Rey Auditory Verbal Learning Test (RAVLT)

To measure declarative memory, the Spanish version of the RAVLT (Miranda & Valencia, 1997) was used as described previously (Almela, van der Meij, Hidalgo, Villada, & Salvador, 2012). Briefly, participants had to learn a target list of 15 neutral words repeated five times (trials 1–5: Total Learning). Then, participants had to repeat an interference list presented only once, followed by the recovery of the target list. After a delay of 20 min, they had to recall the target list again (20-min delayed recall). One day later, participants performed a delayed free recall task.

2.2.3. Rivermead stories subtest

The Story Recall subtest from the Spanish version of the Rivermead Behavioral Memory Test (Wilson, Cockburn, & Baddeley, 1985) was used to obtain ecologically valid measures of verbal memory (Lezak, Howiesen, Loring, Hannah, & Fischer, 2004). Participants had to repeat two short stories immediately after their oral presentation, after a 20-min delay, and 1 day later. They had to recall as many memory units or "ideas" as possible. The sum of the correctly recalled "ideas" from the two stories was calculated for the (i) immediate, (ii) 20-min delayed recall, and (iii) 1-day delayed recall. Participants' responses were recorded and subsequently corrected by an experimenter who was blind to the sex and group of the participant. The maximum score possible in each recall trial was 42.

2.3. Procedure

Participants attended two individual sessions that took place on two consecutive days. Before each session, participants were asked to maintain their general habits, sleep as long as usual, refrain from heavy physical activity the day before the session, and not consume alcohol since the night before the first session. Additionally, they were instructed to drink only water, and not eat, smoke, take any stimulants (such as, coffee, cola, caffeine, tea or chocolate), or brush their teeth at least 1 h prior to the first session and 2 h prior to the second session. All participants provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Committee of the University of Valencia.

The first session (acquisition session) was carried out between 10:00 and 12:00 h in a laboratory at the Faculty of Psychology. In this session, participants performed the MEC, the picture-encoding task, the RAVLT, and the Rivermead Story subtest. They were not told that the next day they would be asked to recall the pictures, the RAVLT words and the Rivermead stories. Additionally, participants in both groups provided two saliva samples (pre and post memory assessment) to measure the cortisol levels during the acquisition session.

The next day, participants returned to the laboratory between 16:00 and 18:00 h to perform the second session (retrieval session) (see Fig. 1). Participants in the stress group were exposed to the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993; for a detail description of the TSST see: Almela, Hidalgo, Villada, van der Meij, et al., 2011), and participants in the control group performed a control task that consisted of 5 min of talking aloud about a recent non-emotional experience, and 5 min counting by 5 aloud. This kind of control task has been used in previous studies (Almela, Hidalgo, Villada, van der Meij, et al., 2011; Hidalgo et al., 2012), and it was designed to be similar to the stress task in mental workload and global physical activity, but without a stressful component. After the stress/control task, participants answered four questions (5-point Likert scale; not at all = 1, to extremely = 5) about their perceptions of both tasks (situational appraisal), based on the following aspects: stress, difficulty, frustration and effort (e.g. How much effort did the task require?). Fifteen min after they finished the stress/control task, they completed the free recall and the recognition test of the pictures they had seen the previous day. After that, they performed the free recall task with the RAVLT words and the Rivermead stories.

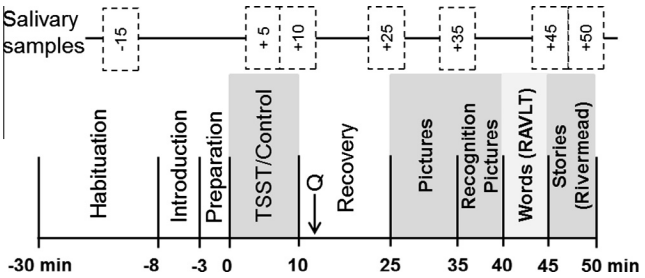

Fig. 1. Timeline of the second day for the stress and control group. Square with dotted lines depicts the time of collection of saliva samples. TSST = Trier Social Stress Test. *Q* = Situational appraisal.

During the retrieval session, participants in both groups provided six saliva samples to measure cortisol and sAA levels: 15 min before the TSST/Control task (−15 min); between the free speech/speaking aloud and arithmetic tasks (+5 min); immediately after the TSST/Control task (+10 min); before the free recall of pictures (+25 min); before the recognition of pictures (+35 min); between the RAVLT and the Rivermead recall task (+45 min); and, finally, after the Rivermead recall task (+50 min) (see Fig. 1).

2.4. Biochemical analyses

We measured the activity of the HPA-axis and the SNS by analyzing the salivary cortisol and alpha-amylase (sAA) levels, respectively. Participants provided saliva samples by using salivettes (Sarstedt, Nümbrecht, Germany). They were instructed to keep the cotton swab in their mouths for exactly 2 min, not chew the cotton, and move the swab around in a circular pattern to collect saliva from all salivary glands. The samples were centrifuged at 3000 rpm for 5 min, resulting in a clear supernatant of low viscosity that was stored at −80 °C until the analyses were performed in the Central Research Unit (Unidad Central de Investigación) of the Faculty of Medicine, University of Valencia (Spain). Both the salivary cortisol and sAA levels were measured in duplicate, and each participant's samples were analyzed in the same trial.

For the salivary cortisol levels, the samples were analyzed by a competitive solid phase radioimmunoassay (tube coated), using the commercial kit Spectria Cortisol RIA (cat. Nu 06119) from Orion Diagnostica (Espoo, Finland). Assay sensitivity was 0.8 nmol/L, and the within- and inter-assay variation coefficients were all below 8%.

The sAA concentration was measured by using an enzyme kinetic method with the commercial salivary α-amylase assay kit (cat. n° 1-1902, 1-1902-5) from Salimetrics (USA). Assay sensitivity was 0.4 U/mL. Inter- and intra-assay variation coefficients were all below 10%.

2.5. Statistical analysis and data management

Data were tested for normal distribution and homogeneity of variance using Shapiro–Wilk and Levene's tests before the statistical procedures were applied. These analyses revealed significant deviations in cortisol and sAA outcome values; therefore, they were square root transformed. We used two-way ANOVAs to investigate sex and group differences on demographic and anthropometric measures, situational appraisal, and valence and arousal of pictures. Cortisol and sAA responses in the retrieval session were assessed using ANOVAs for repeated measures with Group (stress vs. control) and Sex as between-subject factors, and Time (−15,

+5, +10, +25, +35, +45 and +50) as a within-subject factor. Two outliers in the cortisol data (one woman and one man in the control group) and one outlier in the sAA data (one man in the stress group) were removed from the cortisol and sAA analyses because their concentrations differed by more than 3 S.D. from the total sample mean.

To investigate whether there were basal differences in learning and memory performance between the control and stress groups, we performed ANOVAs with Sex and Group as between-subject factor. As dependent variables, we used the following outcomes from the (i) RAVLT: Total Learning, and 20-min Delayed recall; and (ii) Rivermead: Immediate recall and 20-min Delayed recall.

In order to investigate the effects of stress on delayed recall of pictures, data were analyzed using an ANOVA, with Sex, Group (Stress vs. Control) and Valence (Positive, Negative and Neutral pictures) as between-subject factors. Moreover, to study the effect of stress on recognition, the same analysis was performed, but with the recognition test scores (d') for Positive, Negative and Neutral pictures as the dependent variable. Additionally, to study the effects of stress on word and story memory test outcomes, we performed ANOVAs with Sex and Group as between-subject factors, and the percentage of 1-day correct delayed recall (relative to the 20-min delayed recall) of both the RAVLT and Rivermead as dependent variables.

Finally, the area under the total response curve with respect to the ground (AUCg) and with respect to the increase (AUCi) for stress-induced cortisol release was computed using all the salivary samples. The trapezoid formulas specified in Pruessner, Kirschbaum, Meinlschmid, and Hellhammer (2003) were used to calculate these two indexes. AUCi and AUCg give important information about HPA-axis activity and help to simplify the statistical analyses: (i) AUCi was employed as a measure of change in cortisol levels; and (ii) AUCg was employed as a measure of overall cortisol secretion. Correlation analyses were used to investigate the relationship between these two indexes and memory performance in the stress group.

We used Greenhouse–Geisser when the requirement of sphericity in the ANOVA for repeated measures was violated. *Post hoc* planned comparisons were performed using Bonferroni adjustments for the p values. The level of significance was fixed at <0.05. When not otherwise specified, the results shown are means ± SEM. We used SPSS 19.0 to perform the statistical analyses. To facilitate their interpretation, the values in the figures represent raw values, and not square-root-transformed values.

3. Results

3.1. Situational appraisal

The stress task was perceived as more stressful ($F(1,73) = 48.906$; $p < 0.001$), frustrating ($F(1,73) = 43.115$; $p < 0.001$), difficult ($F(1,73) = 64.004$; $p < 0.001$), and requiring more effort ($F(1,73) = 38.613$; $p < 0.001$) than the control task. Women perceived the stress task as requiring more effort than men (Group × Sex: $F(1,73) = 4.562$; $p = 0.036$; women vs. men: $p = 0.025$); however, there were no sex differences in the perception of stressfulness, frustration and difficulty of the stress task ($p > 0.108$).

3.2. Salivary cortisol and alpha-amylase response

3.2.1. Salivary cortisol

Acquisition session Fig. 2A shows the mean cortisol values for the stress and control groups during the acquisition session. ANOVAs for repeated measures with Time (pre and post acquisition) as a within-subject factor and Group (stress vs. control) and Sex as between-subject factors showed that, following the cortisol circadian rhythm, cortisol levels decreased from the beginning to the end of the acquisition session (Time: Pre vs. Post $F(1,80) = 24.794$; $p < 0.001$). The factor Group was not significant ($p > 0.6$), and the factor Sex was marginally significant ($F(1,80) = 3.300$; $p = 0.073$), showing that men had slightly higher cortisol levels than women. There were no interactions among the three factors (all $p > 0.250$).

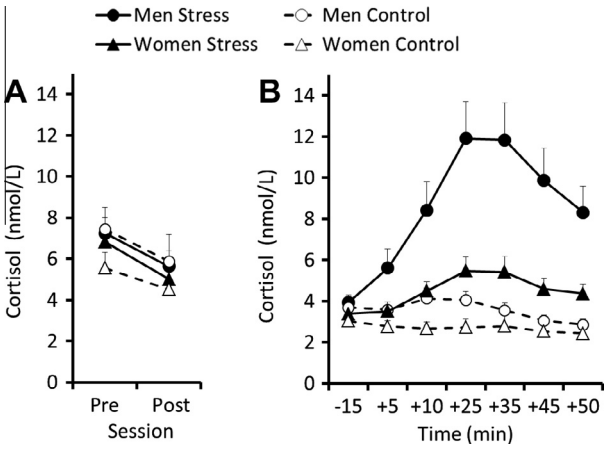

Fig. 2. (A) Salivary cortisol concentrations in the stress and control groups for the acquisition session (*Pre–Post session*). In both samples, there were no significant differences in the cortisol levels between men in stress and control groups (both $p > 0.827$) and between women in stress and control groups (both $p > 0.234$). (B) Salivary cortisol concentrations in the stress and control groups for the retrieval session (*−15*, *+5*, *+10*, *+25*, *+35*, *+45*, *+50*). Cortisol levels were higher in the stress group than in the control group from the +5 sample until the end of the study (all $p < 0.027$). Error bars represent standard error of mean (S.E.).

Retrieval session Fig. 2B shows the mean cortisol values for the stress and control groups during the retrieval session. The repeated-measures ANOVA showed the main effects of Group ($F(1,71) = 26.508$; $p < 0.001$), Time ($F(2.06,146.61) = 22.33$; $p < 0.001$), and Sex ($F(1,71) = 10.312$; $p = 0.001$), and the interaction among the three factors ($F(2.06,146.61) = 4.84$; $p = 0.039$).

In the stress and control groups, men and women showed similar baseline cortisol levels (both $p < 0.139$). In the stress group, men showed higher cortisol levels than baseline immediately after the speech (−15 vs. +5: $p = 0.007$). Then cortisol levels continued to increase until reaching peak levels 25 min after the onset of the stress task. Afterwards, cortisol levels decreased, without reaching baseline levels in the last saliva sample (−15 vs. +45: $p < 0.001$). Cortisol levels of women in the stress group were higher than baseline immediately after the arithmetic task (−15 vs. +10: $p = 0.018$), reached their peak level 25 min after the onset of the stress task, and started to decrease afterwards, reaching baseline levels before the story recall (−15 vs. +45: $p = 0.417$). In addition, in the stress group, men showed higher cortisol levels than women immediately after the speech and in the other consecutive samples (for all $p < 0.021$). In the control group, neither men nor women showed a significant increase or decrease in their cortisol levels compared to baseline (all $p > 0.99$), and men and women had similar cortisol concentrations in all samples (all $p > 0.099$). Finally, cortisol levels were higher in the stress group than in the control group, from the +5 sample in men and the +10 sample in women until the end of the study (all $p < 0.022$).

3.2.2. Salivary alpha-amylase

Fig. 3 shows the mean sAA levels for the stress and control groups in the retrieval session. The repeated-measures ANOVA with sAA as dependent variable showed that the factors Group and Sex were not significant, nor was the interaction between

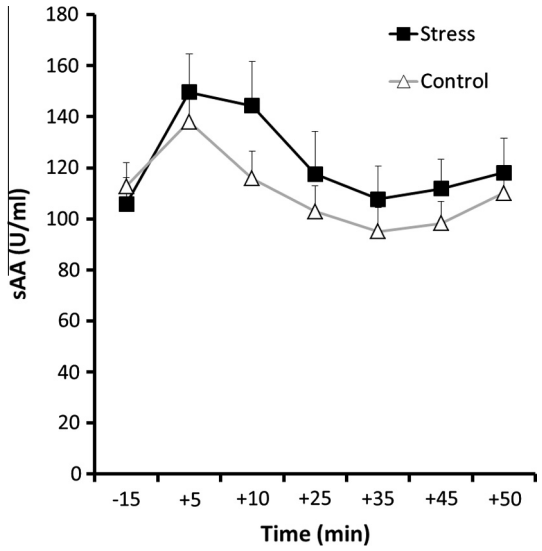

Fig. 3. Salivary alpha-amylase concentrations in the stress and control groups for the retrieval session (*−15*, *+5*, *+10*, *+25*, *+35*, *+45*, *+50*). Control and stress groups show similar sAA levels in all the samples ($p = 0.245$), but the control group recovered baseline levels 10 min after the onset of the task (−15 vs. +10: control group, $p > 0.999$; stress group, $p = 0.001$), while the stress group recovered baseline levels 25 min after the onset of the stress task (−15 vs. +25: stress and control group, both $p > 0.999$). Error bars represent standard error of mean (S.E.).

Sex and the other factors (for all $p > 0.579$). However, results showed a main effect of Time ($F(4.82,347.632) = 19.576$, $p < 0.001$) and a significant interaction between Time and Group ($F(4.82,347.632) = 2.281$, $p = 0.048$). There were no baseline differences between the stress and control groups ($p = 0.430$). In both groups, sAA levels increased above baseline 5 min after the onset of the task (−15 vs. +5: control group, $p = 0.028$; stress group, $p < 0.001$). Only in the control group, participants recovered baseline levels 10 min after the onset of the task (−15 vs. +10: control group, $p > 0.999$; stress group, $p = 0.001$); however, in the stress group, baseline levels were recovered later, 25 min after the onset of the stress task (−15 vs. +25: stress and control group, both $p > 0.999$). There were no differences between the stress and control groups in sAA concentrations in any sample (all $p > 0.245$).

3.3. Memory performance

3.3.1. Acquisition session

3.3.1.1. RAVLT. The performance of the stress and control groups was similar (all $p > 0.630$; see Table 1). There were no differences between men and women on Total Learning ($F(1,72) = 1.892$, $p = 0.173$), but women recalled more words than men in the 20-min delayed recall trial ($F(1,72) = 4.372$, $p = 0.040$). The interaction between group and sex was not significant (all $p > 0.725$).

Table 1
Memory performance in the acquisition session (Mean scores ± SEM).

		Stress	Control	$F(1,72)$	p
RVLT	Total learning[a]	49.46 (1.26)	50.39 (1.23)	0.005	0.944
	Recall 20-min after learning	10.15 (0.37)	10.42 (0.36)	0.233	0.630
Rivermead	Immediate recall[b]	16.97 (0.72)	16.49 (0.70)	0.253	0.616
	Recall 20-min after learning[b]	16.94 (0.74)	16.56 (0.72)	0.086	0.770

[a] The sum of the words recalled in the first five trials.
[b] The sum of the "ideas" recalled from the two stories.

3.3.1.2. Rivermead stories subtest. The performance was similar between the stress and control groups (all $p > 0.616$; see Table 1). The factor Sex was significant in both immediate recall ($F(1,72) = 11.867$, $p = 0.001$) and 20-min delayed recall ($F(1,72) = 7.353$, $p = 0.008$), showing that men recalled more "ideas" in these trials than women. The interaction between sex and group was not significant (all $p > 0.215$).

3.3.2. Stress effects on memory retrieval

3.3.2.1. Pictures recall. Fig. 4 shows the means of the free recall picture outcomes. There was a main effect of Valence ($F(2,213) = 50.447$, $p < 0.001$) because negative pictures were recalled more than positive ($p < 0.001$) and neutral pictures ($p < 0.001$), and positive pictures were recalled more than neutral pictures ($p < 0.001$). However, there were no differences between the performances of the stress and control groups ($F(1,213) = 0.537$, $p = 0.465$) or between men and women ($F(1,213) = 0.188$, $p = 0.665$). Furthermore, there were no interactions among Group, Sex and Valence (all $p > 0.380$).

ANOVAs with the picture recognition outcome (d') as the dependent variable revealed that there were no main effects of Group ($F(1,216) = 2.282$, $p = 0.132$), Valence ($F(2,216) = 0.208$, $p = 0.812$) or Sex ($F(1,216) = 2.640$, $p = 0.106$), nor were the interactions among these factors significant (all $p > 0.615$).

3.3.2.2. RAVLT. Fig. 5 shows the percentage of free recall of words. There were no significant differences between the stress and control groups ($F(1,72) = 0.179$, $p = 0.673$) or between men and women ($F(1,72) = 0.460$, $p = 0.500$). The interaction between these two factors was not significant ($F(1,72) = 0.116$, $p = 0.735$).

3.3.2.3. Rivermead stories subtest. Fig. 6 shows the percentage of free story recall. There were no main effects of Group ($F(1,72) = 1.262$, $p = 0.265$) or Sex ($F(1,72) = 0.002$, $p = 0.965$), and the interaction between these two factors was not significant ($F(1,72) = 1.065$, $p = 0.306$).

3.3.2.4. Stress-induced cortisol response and memory performance in the retrieval session. In the stress group, there were no significant associations between cortisol indexes (AUCi and AUCg) and free recall of positive (AUCi: $r = 0.128$, $p = 0.450$; AUCg: $r = 0.115$, $p = 0.447$), negative (AUCi: $r = 0.217$, $p = 0.196$; AUCg: $r = 0.190$, $p = 0.260$) or neutral pictures (AUCi: $r = 0.168$, $p = 0.320$; AUCg: $r = 0.151$, $p = 0.371$). The associations between cortisol response and free recall performance on the RAVLT (AUCi: $r = 0.035$ $p = 0.835$; AUCg: $r = 0.167$, $p = 0.323$) and Rivermead Stories (AUCi:

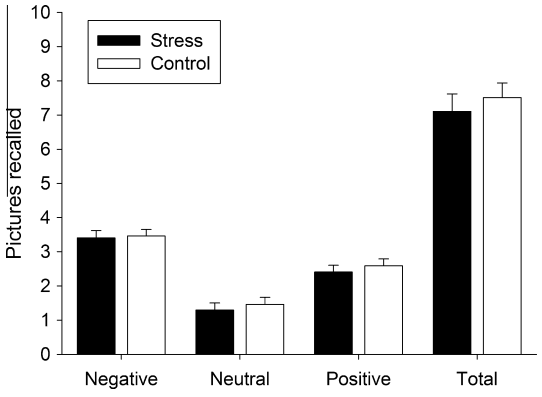

Fig. 4. Number of negative, neutral, positive and total pictures recalled for the stress and control groups. Stress had no effect on memory retrieval of negative, positive or neutral pictures.

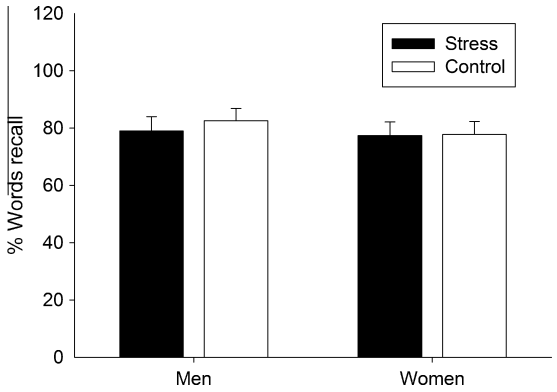

Fig. 5. Percentage of words recalled for the stress and control groups during the retrieval session with respect to the recall 20 min after learning in the acquisition session. Stress had no effect on memory retrieval of words.

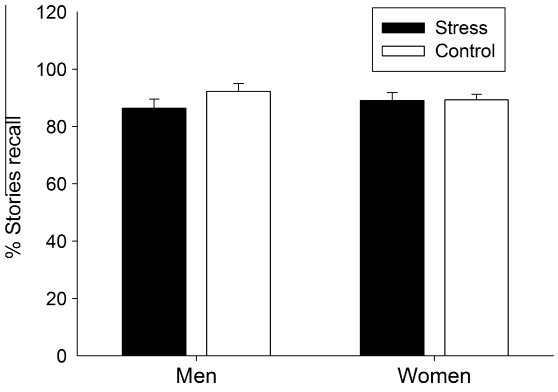

Fig. 6. Percentage of "ideas" recalled from the stories for the stress and control groups during the retrieval session with respect to the recall 20 min after learning in the acquisition session. Stress had no effect on memory retrieval of stories.

$r = 0.056$, $p = 0.741$; AUCg: $r = 0.026$, $p = 0.878$) were not significant either.

4. Discussion

This is the first study to investigate the effects of acute stress on long-term memory retrieval in older people. To this end, we tested 1-day delayed memory retrieval for different kinds of material (pictures, words and stories) after stress induction or a control situation. No significant effect of stress on memory retrieval was observed for pictures, words or stories. Additionally, no association was observed between stress-induced cortisol response and memory retrieval.

The stress task was more stressful, frustrating and difficult, and required more effort, than the control task. In addition, the TSST provoked a greater cortisol and sAA release than the control task. However, although the TSST was effective in triggering a stress response, it did not significantly affect recall in the stress group, for pictures (positive, negative or neutral), words or stories. Therefore, our results show that a stress-induced cortisol increase does not produce any effect on memory retrieval in older people. It is important to note that our findings cannot be explained by basal differences in cortisol levels or memory performance between the stress and control groups.

Our findings do not agree with those observed by Wolf et al. (2001), who found impairment in memory retrieval of words in young and older men after an injection of hydrocortisone. However, in the same study, Wolf et al. found that cortisol affected working memory in young men, but not in older men. Wolf et al. (2001) explained this age-related difference as a reduced sensitivity in older people to cortisol effects in the prefrontal cortex, but not in the hippocampus. Based on the results of our study, the lack of stress-induced cortisol effects on recall of pictures, words and stories suggests that older people may also be less sensitive to cortisol effects on hippocampus-dependent memory retrieval. There are at least two possible explanations for the discrepancy with Wolf et al. First, the cortisol increase in Wolf et al. was four times higher than in our study. Therefore, it is possible that memory retrieval in older people is only affected by large cortisol increases. Second, Wolf et al. injected hydrocortisone approximately 75 min after the participants had learned the word list, and then they measured cortisol effects on memory retrieval 30 min later. Therefore, as the authors discuss, it is likely that they observed an effect of cortisol on memory consolidation and not on memory retrieval (McGauch, 2000; Wang & Morris, 2010). In contrast, we found no effects of stress on long-term memory retrieval in older people.

The current findings are supported by previous animal studies suggesting that older individuals may be less sensitive than younger individuals to cortisol-induced memory effects (Heffelfinger & Newcomer, 2001; Newcomer et al., 1995; Nichols et al., 2001). Along these lines, the current results show that, contrary to what has been observed in young people, stress does not impair long-term memory retrieval in older men and women (Buchanan & Tranel, 2008; de Quervain et al., 2000; Kuhlmann, Kirschbaum, et al., 2005; Kuhlmann, Piel, et al., 2005; Smeets et al., 2008). Basically, this age-difference in stress (or cortisol) effects cannot be explained by differences in cortisol concentrations, as in our study the increase in cortisol in response to the TSST was similar to that observed in studies performed with young participants (e.g. Buchanan, Tranel, & Adolphs, 2006; Kuhlmann, Kirschbaum, et al., 2005; Smeets, 2011). Moreover, this discrepancy cannot be explained by the type of memory tested or by the emotional valence of the material, as no effects were found for the recall of pictures, words and stories, and no effects were found for emotional and neutral material.

At least two different age-related changes in the central nervous system could underlie this decrease in stress-induced cortisol effects on memory retrieval in older people: (i) a reduction in hippocampal Type II cortisol receptor density and sensitivity (Bhatnagar et al., 1997; Mizoguchi et al., 2009) (ii) and a reduction in hippocampal activity and in the interconnectivity between the amygdala and hippocampus (Mather, 2006; Murty et al., 2010; St. Jacques, Dolcos, & Cabeza, 2009). With age, (i) there is a reduction in Type II cortisol receptor density and sensitivity, especially in the hippocampus (Bhatnagar et al., 1997; Mizoguchi et al., 2009). Both kinds of cortisol receptors, the mineralocorticoid receptors (MRs or Type I) and the glucocorticoid receptors (GRs or Type II), are located throughout the forebrain, especially in important areas for memory performance, such as the hippocampus, amygdala and prefrontal cortex (de Kloet, Oitzl, & Joëls, 1999). In these areas, stress effects on memory performance have been associated with a greater occupation of Type II cortisol receptors (Cahill & McGaugh, 1998; de Kloet et al., 1999; Oitzl, van Haarst, & de Kloet, 1997). In fact, Rimmele, Besedovsky, Lange, and Born (2013) have shown that Type II cortisol receptors are necessary to observe the detrimental effect of high cortisol levels on memory retrieval, since high cortisol levels do not impair long-term memory retrieval after administration of mifepristone (a blocker of Type II cortisol receptors). Therefore, an age-related reduction in Type II cortisol receptor density and sensitivity would reduce the stress-induced cortisol effects on memory performance in older people (Heffelfinger & Newcomer, 2001; Newcomer et al., 1995; Nichols et al., 2001). This explanation is supported by studies performed in patients with major depression disorder, which seems to be charac-

terized by a reduction in Type II cortisol receptor sensitivity (Holsboer, 2000; Webster, Knable, O'Grady, Orthmann, & Weickert, 2002). Thus, several studies have observed that an acute cortisol increase does not impair memory performance in patients with major depression, due to the altered glucocorticoid receptor (Type II) functioning (Bremner et al., 2004; Schlosser et al., 2010; Terfehr et al., 2011a, 2011b).

Moreover, (ii) a reduced activity of the hippocampus and in the interconnectivity between the amygdala and the hippocampus could explain the lack of effects of stress on memory retrieval in older people. Previous studies have found that noradrenergic activation of the amygdala and its interactions with the hippocampus is necessary in order to observe cortisol effects on memory retrieval (Roozendaal et al., 2009). Thus, it has been observed that an administration of a β-adrenoceptor blocks the cortisol-induced effect on memory retrieval (de Quervain, Aerni, & Roozendaal, 2007; Schwabe et al., 2009). Interestingly, fMRI studies have shown that healthy aging is associated with reduced functional interconnectivity between amygdala and hippocampus in memory processes (Mather, 2006; Murty et al., 2010; St. Jacques et al., 2009), which may reduce the stress-induced cortisol effects on memory retrieval in older people. Certainly, further studies are needed to test these possible explanations.

Similar to previous studies in young and older people, in the stress group, women showed a lower cortisol response than men (Almela, Hidalgo, Villada, Espín, et al., 2011; Hidalgo et al., 2012; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004). Thus, it is possible that the lack of stress effect on memory retrieval observed in women may be due to this low cortisol reactivity. Nevertheless, it has been suggested that, contrary to what has been observed in learning or fear conditioning, cortisol affects memory retrieval in young men and women similarly (Smeets et al., 2008; Wolf, 2008). Therefore, in our opinion, it is likely that women in the stress group would have shown also no effect of stress on memory retrieval even if they had shown a similar cortisol response than men. Future research may help to clarify this matter by showing if in older people there is a lack of effect of stress on memory retrieval when women have a similar cortisol response than men.

It is worth noting that some participants were taking antihypertensive medication, which has been observed to affect noradrenaline levels (Wenzel et al., 2000). Thus, this medication might affect the noradrenergic activation of the amygdala and, thus, the relationship between stress and memory (de Quervain et al., 2007; Schwabe et al., 2009). However, no stress effect on memory retrieval was observed, even when we excluded from the analyses those participants taking anti-hypertensive medication (total sample: 52 subjects; men-stress = 12; women-stress = 13; men-control = 15; women-control = 12). Therefore, the current absence of memory impairment seems to be due to age-related changes in the central nervous system and not to a possible effect of this medication.

With regard to the design of the current study, memory retrieval was tested in the afternoon, when, following its circadian rhythmicity, baseline cortisol levels are low (Rosmond, Dallman, & Björntorp, 1998), which could affect the relationship between cortisol and memory performance, since it has been proposed that this relationship has an inverted-U shaped and depends on the time of day when memory is tested (Lupien & McEwen, 1997; Lupien et al., 2002). Thus, as stress was applied when cortisol levels were low, it could also promote performance. However, although our data were able to show memory enhancement for pictures or words (but not for story recall, given that our participants showed a high performance on this task, and we observed a possible ceiling effect), this positive effect on performance was not observed in the current data. Along these lines, it is possible that we did not observe memory enhancement since, as has been proposed in previous research, cortisol-related retrieval impairment would not be due to absolute cortisol concentrations, but instead to cortisol reactivity (Smeets, 2011). In fact, a meta-analysis performed by Het, Ramlow, and Wolf (2005) suggests that, while time of day is an important modulator of acute cortisol effects on learning, the impairing effect of high cortisol levels on retrieval seems to be independent of time of day. Accordingly, several studies performed in young people have demonstrated that an acute cortisol increase impairs memory retrieval in the afternoon (Buchanan & Tranel, 2008; Buchanan et al., 2006; Kuhlmann, Kirschbaum, et al., 2005; Smeets, 2011; Smeets et al., 2008), as well as in the morning (Kuhlmann, Piel, et al., 2005; Smeets, 2011; Wolf et al., 2001).

Related to this methodological issue, our results might be affected (at least partially) by the time when learning and retrieval took place, as acquisition took place in the morning (when basal cortisol levels were high), whereas retrieval occurred in the afternoon (when basal cortisol levels were low). Thus, differences in cortisol levels at the moment of the acquisition and retrieval might affect our results. However, previous studies in young people have observed detrimental stress/cortisol effects on retrieval, even when learning took place in the morning and retrieval in the afternoon (e.g. Kuhlmann & Wolf, 2005; Kuhlmann, Kirschbaum, et al., 2005; Smeets, 2011). Taken together, these studies suggest that the lack of a stress effect on retrieval in the current study would also be observed if the retrieval session took place in the morning. However, further studies are needed to investigate whether the time of day might affect the relationship between stress and retrieval, specifically in older people.

A limitation of the present study is that it cannot be concluded that stress-induced cortisol levels did not have any effect on story recall in women, because they had recovered baseline levels before story recall was assessed. However, their cortisol levels were higher than those of the women in the control group, and still no differences were found in their memory performance on this memory test. Furthermore, although cortisol levels in men in the stress group remained high when they performed the story recall, we did not find any effects compared to the control group (men and women), or to women in the stress group. Therefore, we would expect women in the stress group to not show cortisol effects on memory retrieval of stories, as observed for picture and word recall. Another limitation is that we did not counterbalance the order of the three memory tasks. Thus, differences in cortisol levels across the three memory tests might affect the relationship between stress and retrieval. Further studies should counterbalance the order of the memory tests to control for this possible effect.

In sum, results of our study show for the first time that acute social stress does not affect long-term memory retrieval in older people. Moreover, this lack of stress-induced cortisol effects was observed consistently for pictures, words and stories, and for neutral and emotional material. Therefore, our findings provide empirical evidence showing that, as suggested previously, older people are less sensitive to cortisol effects on memory retrieval (Heffelfinger & Newcomer, 2001; Newcomer et al., 1995; Nichols et al., 2001). An age-related decrease in cortisol receptors and functional changes in the amygdala and hippocampus could underlie the differences observed with studies performed with young people.

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