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The cortisol awakening response and memory performance in older men and women

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Sex differences

Summary The activity and regulation of the hypothalamus-pituitary-adrenal axis has been related to cognitive decline during aging. This study investigated whether the cortisol awakening response (CAR) is related to memory performance among older adults. The sample was composed of 88 participants (44 men and 44 women) from 55 to 77 years old. The memory assessment consisted of two tests measuring declarative memory (a paragraph recall test and a word list learning test) and two tests measuring working memory (a spatial span test and a spatial working memory test). Among those participants who showed the CAR on two consecutive days, we found that a greater CAR was related to poorer declarative memory performance in both men and women, and to better working memory performance only in men. The results of our study suggest that the relationship between CAR and memory performance is negative in men and women when memory performance is largely dependent on hippocampal functioning (i.e. declarative memory), and positive, but only in men, when memory performance is largely dependent on prefrontal cortex functioning (i.e. working memory).

1. Introduction

There are large individual differences in the patterns and magnitudes of cognitive decline during the aging process. This is illustrated by the fact that in older people there is a larger variability in declarative memory and working memory performance than in young adults (Rabbitt, 1993; Christensen et al., 1999). This variability is important since it may mean the difference between maintaining independence or becoming dependent on others for daily activities. Being able to predict the magnitude of the age-related cognitive decline is essential for those affected, their families, health care specialists, and society as a whole. To do so, it is necessary to understand the main mechanisms involved in these individual differences, especially when considering the advantages of the treatments and interventions that could be derived from this knowledge. The aim of the current study was to investigate whether the cortisol awakening response (CAR), which is a fast increase in the hypothalamus-pituitary-adrenal axis (HPA-axis) activity that occurs immediately after awakening, is related to individual differences in the memory performance of people from middle to older ages.

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The HPA-axis controls the organism's stress response through the release of glucocorticoids, with cortisol being the most noteworthy in humans (Sapolsky et al., 2000). Age-related cognitive decline has been linked to HPA-axis activity, mainly because of the role that the hippocampus and the prefrontal cortex play in the regulation of the HPA-axis. These two brain structures are crucial for declarative memory (Scoville and Milner, 1957) and working memory (Galloway et al., 2008). Moreover, they are exposed to the action of glucocorticoids, since they have a high density of mineralocorticoid and glucocorticoid receptors (Lupien and Lepage, 2001), and they are involved in HPA-axis negative feedback (Diorio et al., 1993; Crane et al., 2003; Herman et al., 2005). In support of this, it has been shown that, in older people, the risk of memory impairment increases after years of cumulative increases in basal cortisol levels (Lupien et al., 1994; Seeman et al., 1997; Karlamangla et al., 2005; Li et al., 2006). Furthermore, high morning cortisol levels are associated with poorer performance on declarative memory tests (Logical Memory test of the Weschler Memory Scale and Rey Auditory Verbal Learning Test) and processing speed tests (Digit-Symbol Substitution Test and a Coding Task) (MacLullich et al., 2005; Comijs et al., 2010).

However, the relationship between CAR and memory performance has hardly been investigated in older adults. The CAR is a period of increased cortisol secretory activity initiated by morning awakening that typically peaks between 30 and 45 min post-awakening. It is a crucial point of reference within the cortisol circadian rhythm that is not completely understood, as it seems to be independent from the cortisol release during the rest of the day (Pruessner et al., 1997; Wilhelm et al., 2007; for reviews see: Fries et al., 2009; Clow et al., 2010). Several studies have pointed to the hippocampus as a key brain structure in the integrity of the CAR, since hippocampal volume and the magnitude of the CAR are positively related (Pruessner et al., 2007; Bruehl et al., 2009) and the CAR is attenuated in patients with structural damage in their hippocampus (Buchanan et al., 2004; Wolf et al., 2005).

Studies investigating the impact of aging on the CAR are sparse, and their results are contradictory. Thus, two studies did not find any age effect on the CAR (Pruessner et al., 1997; Wust et al., 2000), and one study found that older age was associated with a lower CAR (Kudielka and Kirschbaum, 2003). Furthermore, a more recent study performed with a larger sample (n = 2802) distinguished between two patterns of CAR in older people: a group with a normal CAR (prevalence of 73%) and a group who showed a larger CAR together with a greater diurnal cortisol output and a flatter pattern of cortisol release during the day (prevalence of 27%) (Kumari et al., 2010).

To our knowledge, only two studies have investigated whether the CAR is related to the memory performance of older people, and their results are contradictory. Thus, Franz et al. (2011) reported that, in men between 51 and 60 years of age, a greater CAR was related to poorer visual spatial memory, poorer working memory and poorer short term memory. However, after controlling for several confounds and the overall cortisol outcome throughout the day, these relationships were non-significant. Therefore, Franz et al. concluded that the CAR did not appear to contribute meaningfully to the association between cortisol and memory performance. Conversely, Evans et al. (2011), in an older sample (60—91 years old) of men and women, found that a larger CAR was associated with better performance on memory tests mainly dependent on prefrontal cortex functioning (Trail making-B and Verbal fluency). However, these relationships disappeared after controlling for age. In our opinion, the main reason for these weak and mixed results could be related to methodological issues when measuring the CAR.

The aim of our study was to investigate whether, among older adults, individual differences in the CAR are related to individual differences in memory performance. To obtain a reliable CAR measure, it is crucial for participants to provide the first saliva sample directly after waking. The saliva collection is usually done at home, which introduces ecological validity but also the possibility of error due to delays in the saliva sampling times. In fact, following the exact sampling times can be difficult because the post-awakening period is characterized by deficits in alertness, psychomotor performance and cognitive performance, referred to as 'sleep inertia effects' (Lubin et al., 1976; Balkin et al., 2002). To control for this, in our study we followed the method proposed by Thorn et al. (2006) that maximizes the ratio of proper measured CARs to CARs that could be influenced by uncontrolled sources of variability and, therefore, should be treated with caution. Thorn et al. proposed that those participants with a flat or negative CAR should be identified as suspected non-adherents to the protocol, since EEG and mobility data have shown that a flat or negative CAR in healthy people is most likely an artifact caused by saliva sampling after the actual awakening response has occurred (Kupper et al., 2005). Nevertheless, other causes of a flat or negative CAR are also possible, such as an undiagnosed pathology or other still undetermined reasons. Additionally, our sample was composed of an equal number of men and women, as it has been shown that sex can be a crucial factor in the relationship between HPA-axis activity and cognitive performance among older people (Seeman et al., 1997; Almela et al., 2011). In sum, we investigated whether the magnitude of the CAR is related to declarative memory and working memory performance, and whether sex moderated these relationships.

2. Methods

2.1. Participants

The sample was composed of 88 participants (44 men and 44 women) from 55 to 77 years old (Men: M = 63.41, SD = 4.91; Women: M = 63.73, SD = 3.90). Most of them (86%) had an educational level beyond high school, and were retired (91%). Men reported a slightly higher subjective socioeconomic status (Adler et al., 2000) than women (SES scale, from 1 — lowest SES — to 10 points — highest SES —: Men: M = 6.52, SD = 1.19; Women: M = 5.98, SD = 1, p = 0.022), and men had a higher body mass index than women (Men: M = 27.71, SD = 3.49; Women: M = 25.62, SD = 3.34, p = 0.005). There were no sex differences in age or educational level (for both $p > 0.7$). All female participants were postmenopausal and had had their last menstrual period more than one year before the testing time. None of these women were receiving estrogen replacement therapy.

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Participants belonged to a study program at the University of Valencia for people older than 50 years of age. One hundred sixty-six persons volunteered to participate. These volunteers were interviewed and completed an extensive questionnaire to check whether they met the study prerequisites. In order to avoid a large number of potentially confounding factors that could interfere with the CAR or with cognitive functioning, we selected a homogeneous healthy sample using very restrictive criteria. The criteria for exclusion were: smoking more than 5 cigarettes a day, alcohol or other drug abuse, visual or hearing problems, presence of a cardiovascular, endocrine, neurological or psychiatric disease, having been un general anesthesia once or more than once in the past year, and the presence of a stressful life event during the last year. Volunteers were excluded from participation when they met the criteria for dementia as defined by the DSM-IV and the NINCDS-ADRDA criteria for Alzheimers disease, and when they were using any medication directly related to emotional or cognitive function, or medication that was able to influence hormonal levels, such as glucocorticoids, anti-diabetic medication, antidepressants, benzodiazepines, and psychotropic substances. Vitamins and sporadic use of painkillers were allowed.

2.2. Procedure

Participants meeting the criteria were contacted by telephone and asked to attend a neuropsychological assessment which took place in a laboratory at the Faculty of Psychology. The study was conducted in accordance with the Declaration of Helsinki, and the protocol and conduct were approved by the Ethics Research Committee of the University of Valencia. All the participants received verbal and written information about the study and signed an informed consent form.

The neuropsychological assessments were all performed individually by the first author. Half of the sample began the session at 10 h (21 men and 23 women) and the other half at 12 h (23 men and 21 women). The distribution of men and women between the two turns was not different ($p > 0.6$). The neuropsychological assessment was composed of tests that have proven to be valid and reliable (Sahakian and Owen, 1992; Lezak et al., 2004). The neuropsychological assessment consisted of two tests of declarative memory (Logical Memory and Auditory Verbal Learning Test), and two tests of working memory (Spatial Span and Spatial Working Memory). Each participant's answers on the declarative memory tests were audio recorded and corrected by an expert, following each test manual.

Logical Memory The Spanish version of this subtest from the Wechsler Memory Scale III was administered (Pereña et al., 2004). The administration of this test was performed according to the manual. The experimenter read aloud two brief narratives, and afterward participants had to recall as many memory units or ''ideas'' as possible. After a delay of 25 min, the participants were asked again to recall as many ''ideas'' from the two narratives as possible. The final part of the test consisted of a recognition trial composed of several questions related to the two narratives. From this test, four outcomes were used in the subsequent analyses: (i) Immediate Recall: total ''ideas'' recalled from the two narratives immediately after having heard them, (ii) Delayed Recall: total ''ideas'' recalled from the two narratives after the 25-min delay, (iii) Percentage of Delayed Retention: percentage of ''ideas'' recalled after the 25-min delay from the ''ideas'' of the two narratives that were recalled immediately after having heard them, (iv) Recognition: total number of correct answers on the recognition trial.

Auditory Verbal Learning Test The Spanish version of the WHO-UCLA Auditory Verbal Learning Test was used (AVLT, Maj et al., 1994). This test consists of a five-trial presentation of a 15-word list (learning trials), followed by a single presentation of an interference list. After that, there are two recall trials, the first one is done right after the recall of the interference list (immediate recall after interference), and the second one after a delay of 30 min (delayed recall). The test finishes with a recognition trial of the target words presented together with new words. Four outcomes were used in subsequent analyses: (i) Learning Slope: total number of words recalled on the first five trials, (ii) Recall after Interference: total number of words recalled after the interference trial, (iii) Delayed Recall: total number of words recalled after the 30-min delay, and (iv) Recognition: the difference between the standardized proportion of correct hits and the standardized proportion of false alarms (d-Prime).

Spatial Span This test from the Cambridge Neuropsychological Test Automated Battery was applied (CANTAB®, Cambridge Cognition, Cambridge, UK). This test measures short term memory capacity and is based on the Corsi Block Tapping Task (Milner, 1971). Participants were presented with a set of nine white squares on a tactile computer screen. In each trial, a number of squares changed their color, starting with 2 squares in the first trial which increased to all 9 squares in the last trial. At the end of each trial, a tone indicated that the participant had to touch the squares that had changed their color, either in the same order (forward) or in the reverse order (backward) as they were presented. Two outcome measures were obtained: (i) Span Length Forward: the last number of squares that the participants were able to touch correctly in the same order as they were presented, (ii) Spatial Length Backward: the last number of squares that the participants were able to touch correctly in the reverse order of their presentation.

Spatial Working Memory We also measured working memory with the Spatial Working Memory test of the CANTAB (Owen et al., 1995). In this test, several boxes were presented on a tactile computer screen. Participants were instructed to find a token that was hidden beneath one of these boxes. By touching a box they could reveal if there was a token under it, after which the box returned to its original state. Once the first token was located, the participants had to locate another token in the same set of boxes. However, they were instructed that in every trial the token would never be under a box where a token had been found previously. As an outcome measure, we used the total errors committed, which includes returning to a box in which a token was already found and returning to a box that was already found to be empty.

2.2.1. Preliminary analyses: factor analysis with memory tests outcomes

To reduce the number of memory variables, we performed an exploratory factor analysis with varimax rotation. The Kaiser criterion (dropping all components with eigenvalues < 1.0)

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Table 1 Factor loadings of the memory tests outcomes.

	Paragraph recall	Word list learning	Working memory
Logical Memory WMS-III			
Immediate recall	**0.801**	0.297	0.231
Delayed recall	**0.923**	0.278	0.124
% Delayed retention	**0.742**	0.081	−0.104
Recognition	**0.859**	0.030	−0.073
AVLT			
Learning slope	0.151	**0.804**	0.295
Recall after interference	0.199	**0.886**	0.010
Delayed recall	0.107	**0.909**	0.096
Recognition	0.117	**0.612**	−0.224
CANTAB			
Spatial span forward	−0.063	0.099	**0.805**
Spatial span backward	0.182	−0.007	**0.736**
TE spatial working memory	0.060	0.007	**−0.817**

Numbers in bold are factor loadings higher than 0.5. WMS-III: Wechsler Memory Scale III; AVLT: Auditory Verbal Learning Test; CANTAB: CANTAB Eclipse Battery; TE: Total Errors.

and screen plot inspection were used to determine the number of factors. Three factors were identified: (i) Paragraph Recall, which explained 36.28% of the total variance, (ii) word list learning, which explained 18.61%, and (iii) Working Memory, which explained 16.15% (total variance explained: 71.04%). Table 1 shows the factor loadings of the variables on the three factors. The Kaiser–Meyer–Olking (KMO) indicated a satisfactory relationship between sample size and the number of variables (0.668), and Bartlett's test indicated that the correlations between variables were sufficient to warrant a factor analysis, $C^2(66) = 637.148$, $p < 0.001$. The participant's performance on each factor was not different between those who began the neuropsychological assessment at 10 h or 12 h (Paragraph Recall: $p > 0.8$, word list learning: $p > 0.09$, Working Memory: $p > 0.8$). The sample's overall performance on the paragraph recall test was as follows: 2% had a performance below the 25th percentile, 50% had a performance between the 25th and 75th percentiles, and 48% performed higher than the 75th percentile. On the word list learning test, 68% had a performance between the 25th and 75th percentiles, and 32% performed higher than the 75th percentile. Finally, on the working memory tests 58% of the sample had a performance between the 25th and 75th percentiles, and 42% performed higher than the 75th percentile.

2.3. Saliva sampling

To control for cortisol concentrations at the moment of memory testing, participants provided two saliva samples using salivettes (Sarstedt, Nümbrecht, Germany) before and after the neuropsychological assessment.

To measure the CAR, participants provided in their own homes 4 saliva samples per morning for 2 consecutive mornings using salivettes. There was a mean of 12 days (±2.3) between the neuropsychological assessment and the measurement of the CAR. No samples were provided during the weekend. Participants provided the samples immediately after awakening, and 30, 45, and 60 min post-awakening. Additionally, they recorded in a log their awakening time and the time of each saliva collection. After providing the saliva samples, participants stored their samples in their home fridge and brought the samples to the university within three days after completion.

Participants were instructed thoroughly about how to provide the saliva samples. A demonstration was made by the experimenter, and participants were given written instructions. The instructions were as follows: (i) place the tubes, the written instructions, and the log near your bed so you do not have to stand up to provide the first saliva sample; (ii) to provide the saliva sample take the cotton roll out of the tube and place it in your mouth for 2 min and move it around while chewing it slightly; (iii) after you have provided the first saliva sample you can stand up and move around; (iv) you cannot drink (except water), eat, brush your teeth, take any medication or do any physical exercise until you have finished the fourth saliva sample. Two women did not return the saliva samples.

Once in the lab, the salivettes were centrifuged at 3000 rpm for 5 min (4000 rpm for 15 min), resulting in a clear supernatant of low viscosity that was stored at −80 °C until assay. Free salivary cortisol levels were measured in duplicate by a competitive solid phase radioimmunoassay (tube coated) using a commercial kit Coat-ACount Cortisol (DPC, Siemens Medical Solutions Diagnostics). Assay sensitivity was 0.5 ng/ml. Each subject's samples were analyzed in the same trial. The within and inter assay variation coefficients were all below 8%. Three participants (1 man and 2 women) were excluded from the analyses as their AUCs differed more than 3 *SD* from the rest of the sample.

2.3.1. Cortisol awakening response profiles

Self-reported adherence cannot be relied upon (Kudielka et al., 2003; Broderick et al., 2004); therefore, to control for non-adherence to the protocol and other causes of uncontrolled variability, we decided to replicate the analyses performed in the total sample in a sub-sample of participants who showed the CAR on both days of the study. This method was proposed by Thorn et al. (2006), and has been used in other studies, because, although a positive CAR is no guarantee of adherence, this method maximizes the ratio of properly measured CARs to CARs that could be influenced

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by uncontrolled variables such as non-adherence, undiagnosed diseases or other unknown reasons for not showing a cortisol increase after awakening (Kupper et al., 2005; O'Connor et al., 2009; Walker et al., 2011).

The method proposed by Thorn et al. (2006) estimates that if there was a delay in providing the first saliva sample upon awakening, its cortisol concentrations would be too high (nearer to the peak than they should be) and too low at the 45 min sample (more post-peak than they should be). Therefore, participants were divided into two groups: the 2 Day-CAR group, which was composed of those who showed a positive CAR on both days, and the 1 or 0 Day-CAR group, which was composed of those who showed a negative CAR on one or both days. The 2 Day-CAR group was composed of 53 participants (26 men and 27 women) who represented 62% of the total sample. The 1 or 0 Day-CAR group was composed of 22 participants (9 men and 13 women) who did not show CAR on one of the days (25% of the total sample) and 11 participants (9 men and 2 women) who did not show CAR on either of the two days (13% of the total sample).

2.4. Statistics

Cortisol values were square root transformed because they did not have a normal distribution. The two saliva samples taken before and after the neuropsychological assessments were averaged. The cortisol values measuring CAR were averaged across days according to their sampling time, because their values did not differ across days ($p > 0.7$) and were correlated (r between 0.3 and 0.5, for all $p \leq 0.005$). The following two variables were used in the subsequent analyses: the CAR (cortisol AUCi) and the cortisol AUCg. The CAR, as a dynamic change in cortisol levels post-awakening, was operationalized as the cortisol AUCi. The cortisol AUCg was employed as a measure of overall cortisol secretion post-awakening. See Pruessner et al. (2003) for the specific formulas.

Student's t-tests were used to investigate sex differences in the demographic variables. To analyze the CAR profile and the adherence to the saliva sampling protocol we performed ANOVAS for repeated measures. We used the Greenhouse–Geisser procedure when the requirement of sphericity in the ANOVA for repeated measures was violated. Post hoc planned comparisons were performed using the Bonferroni adjustments for the p-values. We performed regression analyses to investigate whether there was a relationship between the CAR and memory outcomes, and, according to Aiken and West (1991), we performed a moderator regression analysis to investigate whether sex was a moderator.

All p-values reported are two-tailed, and the level of significance was marked at <0.05. Scatterplots were inspected to investigate whether the relationships were linear or quadratic. When not otherwise specified, values are mean $\pm$ standard error of mean (SEM). We used SPSS 17.0 to perform the statistical analyses.

3. Results

3.1. Cortisol awakening response profiles

A repeated-measures ANOVA was used to analyze the cortisol profile of the 2 Day-CAR and the 1 or 0 Day-CAR groups. Time (Awakening, +30, +45, +60) was included as a within-subject factor, and CAR groups (2 Day-CAR vs. 1 or 0 Day-CAR) and Sex were included as between-subject factors. SES and BMI were included as covariates.

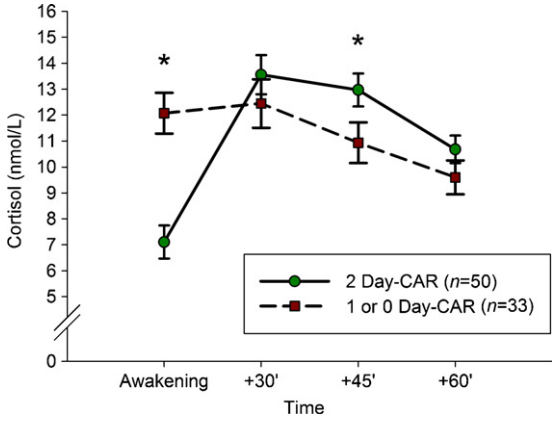

Figure 1 CAR of 2 Day-CAR and 1 or 0 Day-CAR groups. The CAR was different between the two groups, $p < 0.001$. The 2 Day-CAR group increased their cortisol from Awakening to +30 min after ($p < 0.001$), and started to decrease afterward without reaching awakening levels in the last sample ($p < 0.001$). In the 1 or 0 Day-CAR group, awakening levels were already high, and not different from the +30 min and +45 min samples (both $p > 0.999$). The 1 or 0 Day-CAR group had higher cortisol levels in the awakening sample ($p < 0.001$), but lower in the +45 sample ($p = 0.024$), than the 2 Day-CAR group. *$p < 0.05$.

As expected, the cortisol release profile was different in the two groups, see Fig. 1 (Time $\times$ CAR groups: $F(1.73, 133.59) = 41.512$, $p < 0.001$). In the 2 Day-CAR group, cortisol levels increased from awakening to 30 min later ($p < 0.001$), and started to decrease afterward, without reaching awakening levels in the last saliva sample (Awakening vs. +60 min, $p < 0.001$). In the 1 or 0 Day-CAR group, cortisol concentrations were already high at the awakening sample, and they were not different from samples +30 min and +45 min, for both samples, $p > 0.999$. Cortisol levels in the +60 min sample were lower than in the awakening sample, $p = 0.036$. The 1 or 0 Day-CAR group had higher cortisol concentrations than the 2 Day-CAR group at the awakening sample ($p < 0.001$), but lower concentrations 45 min after awakening, $p = 0.024$.

The factor Sex was not significant, and there were no interactions with the other factors, $p > 0.3$.

3.2. Relationship between CAR and total cortisol output and memory performance

We performed regression analyses to identify how much factor variance was explained by the CAR indices, and whether this relationship was moderated by sex. As covariates we included age, BMI, SES, and cortisol levels during the memory testing, because these variables have been related to performance on neuropsychological assessments. In Step 1, we included the covariates, one of the cortisol indices (CAR or AUCg) and Sex (0 = Women, 1 = Men). In Step 2, we included the interaction between sex and one of the cortisol indices. Regression analyses were performed for the complete sample and for the 2 Day-CAR group.

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Table 2 Regression analyses with paragraph recall as a dependent variable.

	CAR (AUCi)				AUCg			
	Total sample		2 Day-CAR		Total sample		2 Day-CAR	
Step 1	Adj $R^2 = 0.06$ $F_{6,76} = 1.85^{\#}$		Adj $R^2 = 0.14$ $F_{6,43} = 2.34^{*}$		Adj $R^2 = 0.13$ $F_{6,76} = 3.10^{**}$		Adj $R^2 = 0.15$ $F_{6,43} = 2.48^{*}$	
	β	p	β	p	β	p	β	p
Age	−0.079	*ns*	−0.049	*ns*	−0.103	*ns*	−0.094	*ns*
BMI	−0.057	*ns*	−0.031	*ns*	−0.104	*ns*	−0.072	*ns*
SES	0.235	0.041	0.314	0.036	0.274	0.014	0.349	0.021
Cortisol[a]	0.142	*ns*	0.101	*ns*	0.187	0.082	0.157	*ns*
Sex	−0.066	*ns*	−0.044	*ns*	−0.104	*ns*	−0.099	*ns*
AUC	−0.101	*ns*	−0.349	0.018	−0.287	0.008	−0.377	0.013
Step 2	*ns*		*ns*		*ns*		*ns*	

[a] Mean of cortisol levels during the neuropsychological assessment. BMI: body mass index; SES: subjective socio-economic status; AUC: area under the curve (AUCi, left panel; AUCg, right panel).
* $p \leq 0.05$.
$^{\#}$ $p \leq 0.10$.
** $p \leq 0.01$.

3.2.1. Paragraph recall

Results from the regression analyses (Table 2) showed that, only in the 2 Day-CAR group, a greater CAR was related to worse paragraph recall performance. In the total sample, there was no linear relationship between CAR and paragraph recall, but there was a quadratic relationship (inverted U-shaped form, $F(2,80) = 3.520$, $p = 0.034$), showing that in the total sample, a larger cortisol decrease and increase were related to worse paragraph recall performance (see Fig. 2).

In addition, a higher total cortisol output (AUCg) was related to worse paragraph recall performance (total sample and 2 Day-CAR). Sex did not moderate the relationship between CAR or AUCg and paragraph recall performance in either of the two groups. As a complementary result, we also found that a higher subjective socioeconomic status (SES) was related to better paragraph recall.

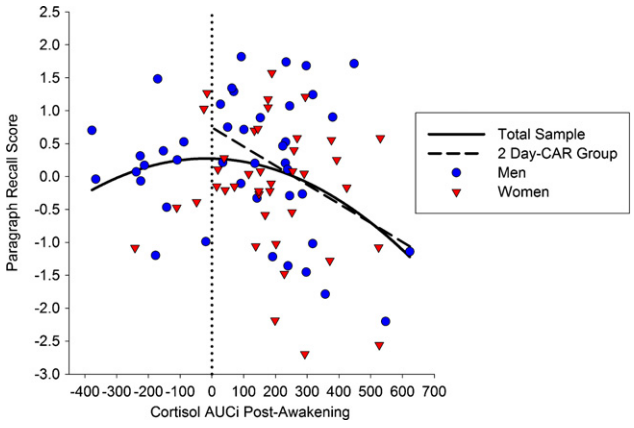

Figure 2 Relationship between cortisol AUCi post-awakening and paragraph recall performance. Among the total sample (line), a larger cortisol decrease or increase was related to worse paragraph recall performance, $p = 0.034$. Among the 2 Day-CAR (dotted line), a larger cortisol increase post-awakening was related to worse paragraph recall performance, $p = 0.018$.

3.2.2. Word list learning

Results from the regression analyses (Table 3) showed that the relationship between CAR and word list learning performance was moderated by the sex of the participants, but only in the total sample. Among men, a larger CAR was related to worse word list learning performance, while among women a larger CAR was related to better word list learning performance. However, post hoc tests of the slopes for men and women were non-significant. For the 2 Day-CAR group, there was no moderation of sex in the relationship between CAR and word list learning performance.

Regarding the global cortisol output (AUCg), sex moderated the relationship between word list learning and the cortisol increase post-awakening in both the total sample and the 2 Day-CAR group. Although there was a significant interaction, post hoc test of the slopes were non-significant. Nevertheless, in men, higher AUCg was related to better word list learning performance, and in women, higher AUCg was related to worse word list learning performance, see Fig. 3.

3.2.3. Working memory

Results from regression analyses (Table 4) show that the CAR was related to working memory performance and moderated by the sex of the participants only among the 2 Day-CAR group. Among men, a greater cortisol increase was related to better working memory performance. Among women, the relationship was negative but non-significant, see Fig. 4.

The global cortisol output (AUCg) was not related to working memory performance, nor was the relationship moderated by the sex of the participants.

3.2.4. Correlational analyses

To analyze the relationship between CAR and each specific test outcome, and improve the comparison of this study with other studies, we correlated, only for the 2 Day-CAR group, the raw data from the memory tests with the cortisol indices. For the word list learning test and working memory tests, the correlations were performed for men and women separately because the regressions showed that the relationship

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Table 3 Regression analyses with word list learning as a dependent variable.

	CAR (AUCi)			AUCg			
	Total sample		2 Day-CAR	Total sample		2 Day-CAR	
Step 1	*ns*		*ns*	*ns*		*ns*	
Step 2	Adj $R^2 = 0.05$, $\Delta R^2 = 0.05$ $F_{1,75} = 4.44^*$		*ns*	Adj $R^2 = 0.06$, $\Delta R^2 = 0.06$ $F_{1,75} = 5.54^*$		Adj $R^2 = 0.11$, $\Delta R^2 = 0.08$ $F_{1,42} = 4.46^*$	
	β	p		β	p	β	p
AUC × Sex	2.887	0.038		−1.388	0.021	−1.824	0.041
Post hoc	β	p		β	p	β	p
Men	−0.212	*ns*		0.322	0.067	0.363	*ns*
Women	0.320	*ns*		−0.196	*ns*	−0.261	*ns*

AUC: area under the curve (AUCi left panel, AUCg right panel).
* $p \leq 0.05$.

between cortisol indices and performance was moderated by the sex of the participants. Results from correlational analyses are shown in Table 5.

4. Discussion

This study investigated the relationship between the cortisol awakening response (CAR) and memory performance among men and women between 55 and 77 years of age. The relationship between CAR and memory performance was analyzed in the total sample and in a subsample of participants who showed the CAR on two different days. The main results of this study show that, in both men and women, a greater CAR is related to poorer declarative memory performance, and, only in men, it is related to better working memory performance.

To measure declarative memory performance we employed a paragraph recall test. We found that a greater cortisol output (AUCg) was related to poorer performance on this test. Additionally, a larger CAR (AUCi) was related to poorer performance on this test only in the participants who showed the CAR on both days. Interestingly, for the total sample this latter relationship was quadratic (inverted U-shaped form), showing that those participants who had a larger cortisol decrease also performed worse on this test. In our opinion, the discrepancy in the results between the total sample and the 2 Day-CAR group could be explained by the possibility that some people in the total sample did not provide their first sample exactly when they awakened, but some time later. Therefore, the measurement of their CAR shifted, and instead of showing the typical cortisol increase post-awakening, their samples showed the recovery after this increase had already happened. Moreover, it seems likely that those who showed a relative large cortisol decrease had a relative large CAR (thus making a large decrease possible). This reasoning can explain the left side of the inverted U relationship (see Fig. 2), as those participants with a large cortisol decrease had a poorer performance just as those participants on the right side of the inverted U curve (large CAR also poorer performance). In fact, in healthy people the main reason for not showing the typical cortisol increase post-awakening has been found to be a delay in providing the first saliva sample (Kupper et al., 2005). However, based on our data, we cannot discard the

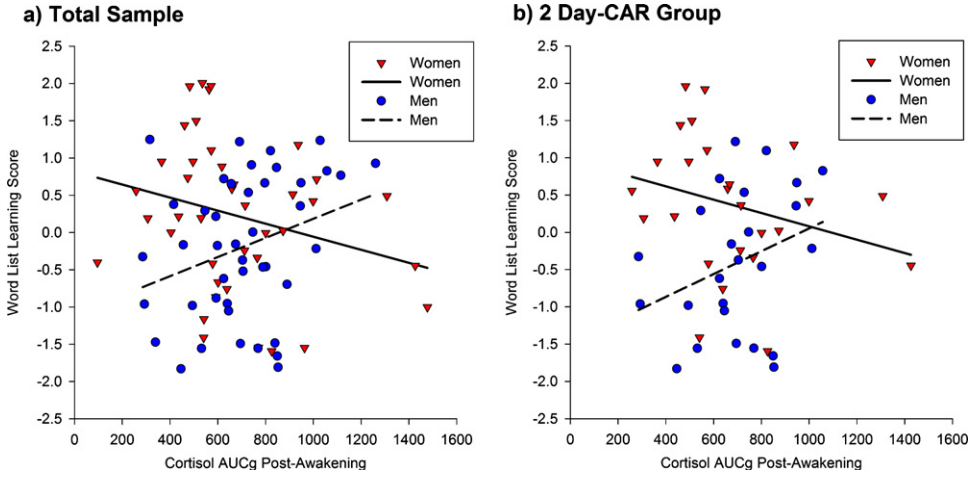

Figure 3 Relationship between cortisol AUCg post-awakening and word list performance. The relationship was moderated by the sex of the participants (Left: Total Sample: $p = 0.021$, Right: 2 Day-CAR: $p = 0.041$). Although non-significant, among men the relationship was positive, and among women it was negative.

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Table 4 Regression analyses with working memory as a dependent variable.

	CAR(AUCi)				AUCg			
	Total sample		2 Day-CAR		Total sample		2 Day-CAR	
Step 1	Adj $R^2 = 0.20$ $F_{6,76} = 4.48^{**}$		*ns*		Adj $R^2 = 0.20$ $F_{6,76} = 4.33^{**}$		*ns*	
	β	p			β	p		
Age	−0.440	<0.001			−0.423	<0.001		
BMI	0.114	*ns*			0.098	*ns*		
SES	−0.170	*ns*			−0.161	*ns*		
Cortisol[a]	0.050	*ns*			0.071	*ns*		
Sex	−0.075	*ns*			−0.094	*ns*		
AUC	−0.089	*ns*			−0.008	*ns*		
Step 2	*ns*		Adj $R^2 = 0.17$, $\Delta R^2 = 0.10$ $F_{1,42} = 5.87^{*}$		*ns*		*ns*	
			β	p				
AUC × Sex			−6.725	0.020				
Post hoc			β	p				
Men			0.459	0.022				
Women			−0.261	*ns*				

[a] Mean of cortisol levels during the neuropsychological assessment. BMI: body mass index; SES: subjective socio-economic status; AUC: area under the curve (AUCi left panel, AUCg right panel).
* $p \leq 0.05$.
** $p \leq 0.01$.

possibility that a larger cortisol decrease after awakening was due to another cause (e.g. undiagnosed pathology, larger cortisol secretion during sleep). Clearly, more research is needed in order to uncover the reasons of not showing a CAR and its relationship with declarative memory performance.

A second measure of declarative memory performance, a word list learning test, was applied. All the outcomes of this test loaded in a second factor. In the total sample and the 2 Day-CAR group, the performance on this test was also related to the amount of cortisol secreted after awakening (AUCg), but in this case the relationship was moderated by the sex of the participants. Although post hoc tests were non-significant, results showed that among men this relationship was positive, and among women it was negative (see Fig. 3). It is worth noting that previous studies support the existence of sex differences in the performance on this test (Gale et al., 2007), and most interestingly, in the relationship between HPA-axis activity and performance on this kind of memory test. Thus, we found in another study that, among middle-aged people, and only in women but not in men, greater cortisol reactivity to acute stress was related to poorer performance on a word list learning test when it was applied on a day without stress (Almela et al., 2011).

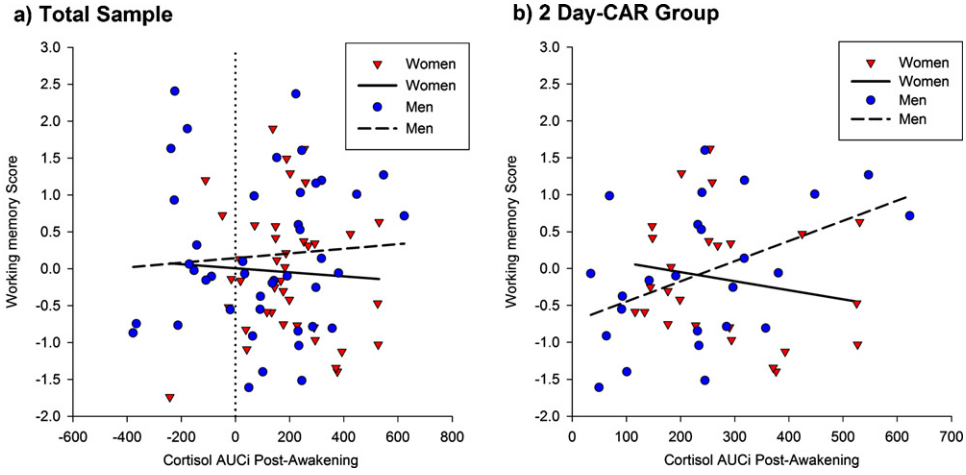

Figure 4 Relationship between cortisol AUCi post-awakening and working memory performance. The relationship was moderated by the sex of the participants in the 2 Day-CAR group ($p = 0.020$). Only among men, a larger cortisol increase was related to better working memory performance ($p = 0.022$). Among women the relationship was negative but non-significant ($p > 0.2$).

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Table 5 Correlation analyses between the memory tests outcomes and cortisol indices.

	Total sample	
	CAR	AUCg
Paragraph recall		
Immediate recall		
Delayed recall	−0.29*	−0.27*
Percentage of delayed retention	−0.36**	−0.27*
Recognition	−0.37**	−0.24#

	Men		Women	
	CAR	AUCg	CAR	AUCg
Word list learning				
Learning slope ($\sum$ Trial 1−5)		0.35#		−0.48*
Trial 1	0.42*	0.45*		−0.40*
Trial 2	0.35#			−0.48*
Trial 3	0.40*	0.35#		
Trial 4				−0.47*
Trial 5				−0.41*
Trial 6 recall after interference				
Trial 7 delayed recall				
Recognition				
Working memory				
Spatial working memory				
Spatial span forward	0.34#			
Spatial span backward	0.47*	0.38#		

* $p \leq 0.05$.
** $p \leq 0.01$.
\# $p \leq 0.10$.

Unexpectedly, the relationship between CAR and memory performance was not the same when using the word list learning test as when using the paragraph recall test. In our opinion, a main reason for this discrepancy is that the two tests were not measuring exactly the same. Supporting this notion, the factorial analyses revealed that the performance on each test explained unique variance, and previous research has shown that there is only a modest relationship between the outcomes on these two memory tests (Macartney-Filgate and Vriezen, 1988; Helmstaedter et al., 2009). Furthermore, it has been proposed that a paragraph recall test is the ''purest'' measure of episodic memory, while a word list learning test could be considered a measure of general cognitive functioning, due to its overlapping with other measures, including measures of working memory, which suggests a higher involvement of prefrontal cortex functioning in its performance (Vanderploeg et al., 1994; Woodard et al., 1999; Lezak et al., 2004). In fact, the relationship between CAR and the performance on the word list learning test was closer to the relationship found with the performance on the working memory tests than with the performance on the paragraph recall test.

To measure working memory, two different neuropsychological tests were employed, and the factorial analyses revealed that both were measuring the same construct. We found that a larger CAR (AUCi) was related to better working memory performance, but only among men from the 2 Day-CAR group. Moreover, the correlational analyses confirmed that those men, who increased their post-awakening cortisol concentrations more, had a better performance on the first trials of the word list learning test and on the spatial span backward, all of which have an important involvement of working memory and, therefore, the prefrontal cortex functioning. The relationship found between a greater CAR and better working memory is in line with Evans et al. (2011) who found that a larger cortisol increase post-awakening was related to better performance on the Trail-making test (form B) and on a test of verbal fluency, both of which are strongly linked to executive function (Lezak et al., 2004; Kemper and McDowd, 2008). Unfortunately, they did not investigate whether there were sex differences in these relationships.

Taken together, our results suggest an opposite relationship between CAR and memory processes that are either highly dependent on the hippocampus (declarative memory) or the prefrontal cortex (working memory). However, the function and regulation of the CAR are not clearly understood. The final mechanism through which the hippocampus and the prefrontal cortex play a role in the regulation of the CAR is unknown (for a reviews see: Fries et al., 2009; Clow et al., 2010). It has been suggested that the hippocampus, despite its general inhibitory effect on the HPA-axis activity throughout the day, could exert a permissive effect on the sharp cortisol release that occurs post-awakening. This permissive effect should happen during the pre-awakening period, because awakening has been associated with the switching off of hippocampal activation (Braun et al., 1997; Balkin et al., 2002). Studies have shown that patients with structural damage in their hippocampus do not show the

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CAR (Buchanan et al., 2004; Wolf et al., 2005). Interestingly, our study suggests that in healthy older people the relationship between hippocampal functioning and the CAR is reversed, since we found that in healthy older people a larger CAR was related to poorer declarative memory performance. In support of this reasoning, a recent study showed that in a large population of older people a larger CAR was associated with (i) a larger diurnal cortisol output and (ii) a flatter pattern of cortisol release (Kumari et al., 2010), whereas other studies have demonstrated that these two indices are consistently associated with worse declarative memory performance (e.g. Lupien et al., 1994; Li et al., 2006; Evans et al., 2011). Less is known, however, about the function of the prefrontal cortex on the CAR, not even whether its role is inhibitory or permissive. However, it is suspected that it plays a part because the CAR dynamic closely parallels that of prefrontal cortex reactivation and the attainment of full alertness (Clow et al., 2010). To disentangle the ultimate mechanisms in these relationships, more research is clearly warranted.

As in the current study, other studies have suggested that sex can moderate the relationship between HPA-axis activity and cognitive processes, which are dependent on prefrontal cortex functioning. For example, we found in another study that a stress-induced cortisol increase impaired working memory performance only in middle-aged women and not in middle-aged men (Almela et al., 2011). An explanation for this sex difference is that after menopause women experience a reduction in estrogen production, whereas men do not experience such a drastic change in hormonal levels. It has been hypothesized that estrogens could work to contain the HPA-axis and counteract some of the potentially damaging actions of glucocorticoids on nerve cells (McEwen, 2002). Furthermore, the prefrontal cortex and its neural circuitry are prime mediators of estrogen's role in cognition, and menopausal cognitive decline could be secondary to executive dysfunction (Keenan et al., 2001). An alternative explanation for the sex differences is that men and women use different strategies to resolve memory tests, i.e. men and women may use different neural paths to reach the same behavioral end point (Andreano and Cahill, 2009). Therefore, the sex differences found in the current study can also be explained by a different involvement of the hippocampus and prefrontal cortex to resolve the same task.

This study has several limitations that need to be addressed in order to properly interpret its results. We did not include any objective measures to assess adherence to the saliva sampling protocol. However, to address this issue we have presented our results for the total sample and for a subgroup consisting of participants who showed a CAR on both days. The percentage of participants who did not show the CAR on both days of the study was relatively high. Results showed that not selecting the 1 or 0 Day-CAR group did not change the relationships between memory performance and cortisol AUCg. However, when investigating the relationships between cortisol AUCi and the three memory factors, the results changed substantially when we eliminated the participants who did not have a CAR on both days. This result shows that it is of extreme importance to take participants' cortisol profiles into account, and it can explain the mixed and weak results found in the literature.

Moreover, the results of this study are specific to people from middle- to older ages, as no group of young people was included in the study. It would be interesting in future research to replicate these findings including younger samples to investigate whether the effects we found are applicable to the aging process or are present also in earlier stages of the human life span. Finally, we want to mention that the overall performance of the participants on memory tests was high, since around 40% of the total sample had a performance higher than the 75th percentile. This result could have been due to the selection criteria for participation. Only very healthy people were allowed to participate, which could have introduced a sample bias toward people who also have well-maintained cognitive abilities. Therefore, a recommendation for future studies would be to replicate these findings in different kinds of samples with age-related diseases.

The present study extends previous findings showing that HPA-axis activity and regulation are related to memory performance in older adults, and that sex is an important moderator of this relationship. Our results draw a complex picture of associations between the CAR and memory performance, and they suggest that, among people from 55 to 77 years of age, a greater CAR is related to poorer performance on hippocampus-dependent memory tasks. However, only among men, a larger CAR is related to better performance on tasks that are dependent on prefrontal cortex functioning. More research is needed to further disentangle the mechanisms in these relationships.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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