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Cortisol awakening response and cognitive performance in hypertensive and normotensive older people

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ABSTRACT

Healthy older people with a cortisol awakening response (CAR) of decreased magnitude show worse frontal cortex-related cognitive performance. Systemic hypertension has been related to a CAR of decreased magnitude. Additionally, worse executive function and processing speed have been observed in older people with systemic hypertension. This is the first study to examine the relationship between the CAR (measured with six saliva samples at home on two consecutive weekdays) and cognitive performance, in both hypertensive ($n = 26$) and normotensive ($n = 28$) older people (from 56 to 78 years old). Hypertensive participants showed lower morning cortisol secretion, and they also woke up earlier. No differences in CAR were observed. A CAR of decreased magnitude was related to worse executive function in both hypertensive and normotensive participants, but to slower processing speed only in normotensive participants. Being treated with antihypertensive for a longer period of time was related to a CAR of increased magnitude and better performance on executive function. Our findings suggest that earlier awakening time in hypertensive older people might underlie the lower overall morning cortisol secretion observed in previous studies. Additionally, this study confirms that a dysregulation of the CAR is related to worse executive function, and it extends this association to hypertensive older people. Finally, it is worth noting that hypertension may moderate the relationship between CAR and processing speed.
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1. Introduction

Cardiovascular risk factors and cognitive functioning problems have a strong tendency to increase with age. However, it is still not fully understood whether (and how) they might be interlinked. Hypertension, the most common risk factor for cardiovascular diseases, has been related to cognitive decline in older people, especially to worse frontal cortex functioning (see Tzourio et al., 2014). Studies have indicated that high blood pressure (BP) may affect cognitive performance through vascular brain injury (Verhaaren et al., 2013); however, the activity of the hypothalamic-pituitary-adrenal axis (HPA-axis) might also play a role in the relationship between hypertension and changes in cognitive performance in older people. The HPA-axis affects cognitive function and BP through the effects of cortisol, the main hormone secreted by the HPA-axis in humans, on receptors that are especially located in the frontal cortex and the limbic system, as well as in cardiovascular tissues (Ku, 2006; Lupien et al., 2007). In this regard, previous studies have shown that worse HPA-axis regulation is related to worse cognitive performance (Lupien et al., 2007) and systemic hypertension in older people (Gold et al., 2005). In spite of this evidence, research investigating whether the HPA-axis may be associated with cognitive performance in hypertensive and normotensive older people is sparse, and more studies are needed.

The circadian rhythm of the HPA-axis involves three discrete components: (i) the cortisol awakening response (CAR), a rapid increase in cortisol levels that peaks between 30 and 45 min following morning awakening; (ii) a decrease in the secretion of cortisol during the rest of the day; and (iii) an increase in cortisol levels from the second half of the night until waking (Fries et al., 2009). While previous studies have shown a relationship between higher overall diurnal cortisol secretion (without distinguishing between the CAR and the rest of the diurnal cortisol secretion) and worse cognitive performance in older people (e.g., Franz et al., 2011; Lee et al., 2007; MacLullich et al., 2005; Pulopulos et al., 2014; but see Singh-Manoux et al., 2014), few studies have examined the specific relationship between CAR and cognition in healthy older people. Additionally, this relationship has not been studied in older people with hypertension.

The CAR has characteristics that are unrelated to the cortisol secretion during the rest of the day, and the frontal cortex and hippocampus have been found to be especially involved in its regulation (Clow et al., 2010; Fries et al., 2009). Along these lines, an increasing number of studies have highlighted the importance of investigating the CAR's contribution to cognitive performance in older people. We

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showed that a lower increase in cortisol levels after awakening (i.e., higher CAR) was related to better performance on a hippocampus-dependent memory task and, especially in older men, to worse performance on a frontal cortex-dependent spatial working memory task (Almela et al., 2012). Similarly, Evans et al. (2012) observed that a CAR of decreased magnitude was associated with worse performance on executive functioning (i.e., a frontal cortex-related ability) in healthy older people. Recently, Law et al. (2015) showed that daily variations in CAR predict daily variations in executive function performance in a young adult researcher-participant case study (with a CAR of decreased magnitude being related to worse executive function performance), and Tortosa-Martinez et al. (2015) showed that a 3-month aerobic exercise training program increases executive function performance and, in a marginally significant way, the magnitude of the CAR. Additionally, a CAR of decreased magnitude has been observed in young children with worse performance on prospective memory (i.e., a frontal and hippocampal-related memory task) (Bäumler et al., 2014) and in young adults with frontal and hippocampal-related amnesia (Buchanan et al., 2004; Wolf et al., 2005). In spite of all this evidence, some studies did not observe any relationship between CAR and cognitive performance in middle-aged and older people (Franz et al., 2011; Singh-Manoux et al., 2014); however, these studies only measured cortisol at awakening and 30 min later. Given that the CAR shows the cortisol peak between 30 and 45 min after awakening, it is possible that with only two samples, the CAR of some participants was underestimated in these studies. Together, these results suggest that the magnitude of the CAR might be related to cognitive performance, but more research is needed to understand its relationship with different cognitive domains.

Systemic hypertension and other cardiovascular risk factors have also been associated with a dysregulation of cortisol secretion immediately after awakening (DeSantis et al., 2011; Kuehl et al., 2015; Rosmond and Björntorp, 2000; Wirtz et al., 2007). Wirtz et al. (2007) showed an attenuated CAR and HPA-axis feedback sensitivity in hypertensive middle-aged people who were not taking antihypertensive medication. Similarly, Kuehl et al. (2015) observed a negative relationship between BP and overall cortisol secretion post-awakening (i.e., a measure that included both the CAR and the total cortisol exposure the first hour after awakening). However, differences in the magnitude of the CAR have not always been observed. In a study performed to investigate differences in diurnal patterns of cortisol and alpha-amylase between controls and competitive ballroom dancers, Strahler et al. (2010) found no differences in CAR between 46 older subjects not taking medication for hypertension and 18 older subjects taking antihypertensive medication. This study might suggest that differences in CAR between hypertensive and normotensive subjects disappear when antihypertensive medication is used. However, some other factors could also contribute to this result, such as differences in sample size between groups or some other characteristics of the participants (e.g., half of the participants were competitive ballroom dancers).

Previous studies suggest that hypertensive individuals may show worse performance and a more rapid decline in executive function and processing speed (for a review see Tzourio et al., 2014). Executive function is a frontal cortex-related cognitive ability (Lezak et al., 2004). Similarly, processing speed is also related to the activity of the frontal cortex, but the connections between the frontal, parietal and temporal cortex seem to also play an important role in its performance (Turken et al., 2008). Together, it is possible that changes in CAR observed in hypertensive subjects might contribute to changes in frontal cortex-related cognitive performance observed in hypertension. Along these lines, Gold et al. (2005) showed that reduced HPA-axis feedback sensitivity was associated with frontal lobe atrophy in hypertension. The authors also showed worse performance on executive function in hypertensive participants, but no association was observed between overall night cortisol secretion and cognitive performance. In their study, the CAR was not measured, and the question of whether morning cortisol response may be related to frontal cortex-related functioning in hypertension has not yet been studied.

With this in mind, the first aim of this study was to investigate differences in CAR and overall morning cortisol secretion in hypertensive and normotensive older people. The second aim was to study whether the CAR was associated with their cognitive performance. To do so, participants provided ambulatory saliva samples to measure morning cortisol levels, and they performed a neuropsychological session focused especially on frontal cortex-related tasks (working memory, word-list learning, attention, switch tasks, processing speed and inhibition). Based on previous studies (DeSantis et al., 2011; Kuehl et al., 2015; Rosmond and Björntorp, 2000; Wirtz et al., 2007), we expected to find an attenuated CAR and lower overall morning cortisol exposure in hypertensive participants. Furthermore, a positive relationship was expected between the CAR and performance on frontal cortex-dependent tasks in normotensive and hypertensive individuals.

2. Method

2.1. Participants

Fifty-eight participants from 56 to 78 years old were recruited from classes in a study program at the University of Valencia for people over 55 years old. In order to avoid potentially confounding factors, we recruited participants who, except for the diagnosis of hypertension, reported being in good mental and physical condition. The exclusion criteria were: alcohol or other drug abuse, current smoking, presence of an endocrine, neurological or psychiatric disease, and using any medication directly related to emotional or cognitive function or medication that was able to influence hormonal levels (e.g., glucocorticoids, anti-diabetic medication, antidepressants, and psychotropic substances). Having been under general anesthesia once or more in the past year, the presence of a stressful life event in the past year, and a diagnosis of secondary hypertension were also reasons for exclusion. All female participants were postmenopausal, and they had had their last menstrual period >2 years before the testing time. None of them were taking estrogen replacement therapy. Results on the Spanish version of the Mini-Mental Status Examination (Lobo et al., 2001) indicated the absence of cognitive impairment (all the participants scored 28 or more on this test). None of the participants met the criteria for dementia, as defined by the NINCDS-ADRDA criteria for Alzheimer's disease, or the criteria for Mild Cognitive Impairment, as defined by the European Consortium on Alzheimer's Disease (Portet et al., 2006).

The hypertensive group was composed of 29 participants (16 men and 13 women). Following the WHO/ISH definition, participants were included in the hypertensive group if they showed a systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic blood pressure (DBP) of 90 mm Hg or higher, and/or if they were undergoing treatment for a previous diagnosis of essential hypertension (Kjeldsen et al., 2002). All the participants in this group had been taking antihypertensive medication for more than one year ($M = 8.17$ years, ± 1.37; range from 1.33 to 30.5 years). Twenty-two participants were taking angiotensin II receptor antagonists, five participants were taking calcium antagonists, four participants were taking angiotensin-converting-enzyme inhibitors, three participants were taking beta blockers, and one participant was taking renin inhibitors. Four participants were undergoing treatment with more than one antihypertensive drug. The control group was composed of 29 participants (13 men and 16 women) with similar ages and educational levels. Participants in the control group did not have a previous diagnosis of hypertension, and they were considered normotensive after SBP and DBP measurements (<140/90 mm Hg) at the beginning of the neuropsychological session.

2.2. Procedure and neuropsychological assessment

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics Committee of the University of Valencia. All participants provided written informed consent to participate in the study.

Before the neuropsychological assessment, participants were asked to refrain from heavy physical activity the day before the session, sleep as long as usual, and not consume alcohol since the night before the session. Additionally, they were instructed to drink only water, and not eat, smoke, take any stimulants (e.g., coffee, cola, tea, chocolate), or brush their teeth at least 1 h prior to the session. The neuropsychological assessments started between 1000 h and 1200 h. Upon arrival to the laboratory and after a 15 min rest, three seated BP measurements were obtained using an automated sphygmomanometry device (Omron M6 HEM-7223-E, Omron Healthcare Europe B.V. Hoofddorp, The Netherlands). The average of the three BP measurements was calculated. Next, the participants performed the MMSE and completed the Beck Depression Inventory (BDI; Beck et al., 1996).

To measure cognitive performance, the following cognitive tests were used in the neuropsychological session:

Stroop Color-Word Interference Test: Golden's version of the Stroop Color-Word Interference Test was used (Golden, 1978). This version of the STROOP contains three different pages with 100 color words printed in black ink (words page), 100 "Xs" printed in color (red, green, and blue) (colors page), and 100 words from the first page printed in colors from the second page (the color and the word do not match) (Interference page), respectively. Participants were asked to read the words on the first page and name the ink color on the second and third pages as fast and precisely as possible for 45 s. Two outcomes from this test were used: (i) Word-Color naming: Given that both the word page and the color page measure processing speed, and that their performance is highly correlated ($r = 0.567$; $p < 0.001$), the scores on the word and color pages were z-transformed and averaged, and this outcome was used as a measure of processing speed; (ii) Interference Stroop: The interference index (calculated as indicated in Chafetz and Matthews, 2004) was used as a measure of the ability to inhibit automatic responses (i.e., higher scores indicate better performance).

Trail Making Test A and B (Reitan, 1992): The Trail Making Test form A (TMT-A) was used to assess general psychomotor speed and attention, and the Trail Making Test form B (TMT-B) assesses the efficiency of attention-switching performance. The outcome of each form was the time (seconds) needed to perform the test (i.e., lower time means better performance). To specifically pinpoint the executive function measured by the TMT-B (i.e., set-shifting ability), we included the TMT-A as a covariate in all the analyses performed with the TMT-B.

Digit Span: The digit span forward Subtest (DS-Forward) of the Wechsler Memory Scale III (Wechsler, 1997) was used as a measure of the attention and memory span component of working memory, and the digit span backward subtest (DS-Backward) was used as a measure of the executive component of working memory (Conklin et al., 2000). To specifically pinpoint the executive function measured by the DS-Backward (i.e., executive component of working memory), we included the DS-Forward as a covariate in all the analyses performed with the DS-Backward.

Rey Auditory Verbal Learning Test: The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) was used to measure learning and verbal memory. Three indexes were used in subsequent analyses: (i) Total learning: total number of words recalled on the first five trials (trial I to V); (ii) Immediate recall: total number of words recalled after the interference trial (trial VI); (iii) Delayed recall: percentage of the total number of words recalled after 20 min (trial VII), compared to the number of words recalled on the immediate recall trial.

2.3. Cortisol measurements

All the saliva samples were collected using salivettes (Sarstedt, Nümbrecht, Germany). Salivary samples to measure the CAR were collected at home on two consecutive weekdays. The saliva samples were provided immediately after waking (cortisol awakening) and 30 min (+30 min) and 45 min (+45 min) post-awakening. Additionally, to control whether possible differences between groups could be explained by differences in cortisol levels the previous night, participants provided one saliva sample immediately before they went to sleep on the nights prior to the two CAR measurements (cortisol night). Participants were thoroughly instructed about how to provide saliva samples, and they were given written instructions. They were instructed to drink only water and not eat or brush their teeth at least 1 h prior to each saliva sample. To objectively verify participant adherence to the saliva sampling time at home, salivettes were stored in MEMS TrackCap containers (MEMS 6 TrackCap Monitor, Aardex Ltd., Switzerland). Additionally, participants recorded on a log the time of each saliva collection, the time they went to bed, their sleep duration the nights before the CAR measurements, and their awakening time. There was a mean of 11 days (±2.15) between the neuropsychological assessment and the measurement of the cortisol levels at home. To control for the possible effect of acute cortisol levels at the moment of neuropsychological testing, participants provided a saliva sample at the beginning and at the end of the neuropsychological session.

Salivary samples were analyzed to measure cortisol levels in duplicate through 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 intra- and inter-assay variation coefficients were all below 8%.

2.4. Statistical analysis and data management

Cortisol values did not show normal distributions; therefore, they were log transformed. Two indexes were calculated using cortisol levels on awakening, +30 min and +45 min: (i) the area under the curve with respect to the increase, used as a measure of the CAR (i.e., the dynamic of the cortisol increase after awakening); and (ii) the area under the curve with respect to the ground (AUCg), used as a measure of the overall morning cortisol secretion (see Pruessner et al., 2003 for the formula).

To compute differences in subjects' characteristics, cortisol outputs (cortisol night, cortisol awakening, CAR, and AUCg) and cognitive performance, student's *t*-test was used for interval data, X^2 for categorical data, and ANCOVAs for the TMT-B and DS-Backward (controlled by TMT-A and DS-Forward, respectively). Based on the results obtained, partial correlations were used to explore possible relationships among cortisol outputs (cortisol night, cortisol awakening, CAR, and AUCg), sleep parameters (time they went to bed, time of awakening, mean sleep time) and time being treated for hypertension. Age was included as a covariate to control for its possible effect on these associations.

Regression analyses were used to investigate relationships between the CAR and cognitive performance, controlled by possible confounders, and find out whether these relationships were different for the hypertensive and normotensive groups. First, we explored whether CAR and/or cognition were related to possible confounders observed in previous studies (i.e., age, BMI, SES, Sex, physical activity, the mean cortisol levels during the neuropsychological assessment, the cortisol change

during the neuropsychological assessment, time of awakening and mean sleep time) (e.g., Clow et al., 2010; Cournot et al., 2006; Sindi et al., 2013; Wright and Steptoe, 2005). In order to avoid overfitting the regression analyses, only those variables showing a correlation $p < 0.10$ were included as covariates The results of the correlation analyses for CAR, cognitive outcomes, and selected covariates are provided in the Supplementary material. The Variance Inflation Factor indicates that there is no multicollinearity problem between the variables included as covariates. In step 1, we included the covariates, and in step 2, we added CAR. In step 3, we included the interaction between the CAR and hypertension.

Four participants were removed from the analyses because their cortisol concentration at home differed by >3 S.D. from the total sample mean (one hypertensive man and one normotensive woman), due to lack of information about sleep parameters and the time of saliva collection (on the log and MEMOTRACK) (one hypertensive man), and due to sleep problems the days of cortisol measurement at home (one hypertensive man). Additionally, one participant (one hypertensive man) did not perform the Stroop test and the TMT due to problems in differentiating the ink colors and letters because he was not wearing his glasses. Therefore, the final sample was composed of 26 hypertensive subjects and 28 normotensive subjects (25 hypertensive and 28 normotensive subjects for the Stroop test and TMT data analyses). *Post hoc* analyses were performed using Bonferroni adjustments for *p* values. When not otherwise specified, the results shown are means ± S.D. Eta squared and Cohen's d are reported as measures of effect sizes for ANOVAs and pair-wise comparisons, respectively.

3. Results

3.1. Preliminary analyses

Previous studies have shown that a delay in the first saliva sample results in higher cortisol awakening values and affects the reliability of the CAR measurement (Griefahn and Robens, 2011; Smyth et al., 2013). Thus, it has been proposed that a flat or negative CAR in most individuals may be caused by a delay in performing the first saliva sample (Thorn et al., 2006). To control for this possible effect, and as done in previous research (Almela et al., 2012; Thorn et al., 2006), we identified those participants who showed a positive CAR on both days (i.e., cortisol AUCi >0) and those who showed a negative CAR on one or both days. Thirty-nine participants (hypertensive = 17; normotensive = 22) showed a positive CAR on both days (2 Day-CAR subgroup), and 15 participants (hypertensive = 9; normotensive = 6) showed a positive CAR on only one day (1 Day-CAR subgroup). There were no significant differences in the number of hypertensive and normotensive participants who showed a positive CAR on two days or only one day ($p = 0.280$). The 2 Day-CAR and the 1 Day-CAR subgroups did not differ on age, educational level, subjective Socio-Economic Status (SES, measured using the MacArthur Scale of Subjective Social Status; see Adler et al., 2000), Body Mass Index (BMI), level of physical activity performed every week (0 = None; 1 = Low; 2 = Moderate; 3 = High), BDI scores, time they went to bed, mean sleep time, time of awakening or time taking antihypertensive medication (all $p > 0.104$).

For 2 Day-CAR participants, given that there were no differences between the cortisol levels at home across days ($p > 0.475$), the data for the two days of the study were averaged to compute the cortisol outcomes and sleep parameters. For 1 Day-CAR participants, higher cortisol on awakening on the day with negative CAR were observed ($p < 0.001$), indicating that there could be a delay in performing the first salivary sample. Therefore, for these participants, only the data for the day that showed a positive CAR were used in the analyses (see Supplementary material for a detailed description of the cortisol patterns for each day of salivary sampling).

All the analyses were performed with the complete sample (2 Day-CAR participants and 1 Day-CAR participants together, $n = 54$). Afterwards, and following Thorn et al. (2006), the analyses were repeated with the 2 Day-CAR participants alone ($n = 39$) to find out whether the same results are observed when only participants showing a positive CAR on the two days of salivary sampling are included in the analyses (results provided in Supplementary material).

3.2. Subjects' characteristics and differences in cortisol levels and cognitive performance

Table 1 shows the characteristics of the sample and differences in sleep parameters and cognitive performance for the complete sample (2 Day-CAR and 1 Day-CAR). Hypertensive participants showed a higher BMI, SBP and DBP, and they woke up earlier ($p < 0.024$). No significant differences were observed in cognitive performance ($p > 0.184$). The hypertensive group showed lower cortisol awakening ($t(52) = -3.12$, $p = 0.003$, $d = 0.85$) and AUCg (hypertensive ($n = 26$): 462.40 ± 187.68, normotensive ($n = 28$): 608.79 ± 221.92; $t(52) = -2.77$, $p = 0.008$, $d = 0.75$). No significant differences in cortisol night ($t(52) = 0.05$, $p = 0.996$, $d = 0.85$) and CAR were observed (hypertensive ($n = 26$): 202.71 ± 125.87, normotensive ($n = 28$): 250.53 ± 136.98; $t(52) = 0.80$, $p = 0.426$, $d = 0.22$) (Fig. 1).

3.3. Relationships among cortisol levels, time of awakening, mean sleep time and time receiving treatment for hypertension

Given the observed differences between groups in AUCg and cortisol awakening, but not in CAR, we examined the relationships among cortisol outcomes, sleep parameters, and treatment for hypertension in order to better understand these differences. Table 2 shows the partial correlations, controlling for age, in the analyses for the hypertensive and normotensive older people. In the hypertensive group, higher cortisol at night was related to less mean sleep time and an earlier waking time. The participants who went to bed later slept fewer hours. Higher cortisol at awakening was related to higher AUCg. The participants taking antihypertensive medication for a longer time showed a higher CAR (Fig. 2). In the normotensive group, the participants who went to bed later slept fewer hours and woke up later. Higher cortisol awakening was related to higher AUCg and a later waking time (all $p < 0.040$).

3.4. Relationship between CAR and cognitive performance

We first investigate the association between the CAR and cognitive outcomes, controlling the age of the participants. Results showed that after controlling for age, a CAR of increased magnitude was related to better performance on the TMT-B ($\beta = -0.23$, $p = 0.041$) and Word-Color naming ($\beta = 0.31$, $p = 0.019$), and worse performance on the TMT-A ($\beta = 0.31$, $p = 0.018$). None of the other associations were significant for the complete sample (all $p > 0.408$).

We then repeated these analyses, controlling for covariates related to the CAR and/or each cognitive outcome (see Supplementary material for the specific covariates included in the regression analyses for each cognitive outcome). Table 3 shows the results of the regression analyses with CAR as predictor and cognitive test outcomes as dependent variables. A CAR of increased magnitude was related to better performance on the TMT-B ($\beta = -0.28$, $p = 0.022$) and Word-Color naming ($\beta = 0.39$, $p = 0.006$). The interaction between CAR and hypertension was significant for Word-Color naming ($p = 0.031$), indicating that, although the relationship between CAR and Word-Color naming was positive for both groups, it was significant only for the normotensive group (Normotensive group: $\beta = 0.72$, $p = 0.001$; Hypertensive group: $\beta = 0.16$, $p = 0.349$). None of the other relationships were statistically significant (all $p > 0.118$).

Table 1
Participants' characteristics, sleep parameters, and cognitive performance.

	Hypertensive	N	Normotensive	N	t,X^2,F	gl	p	Effect size
Age	66.04 ± 4.71	26	65.18 ± 3.80	28	0.74	52	0.462	$d = 0.20$
Educ. Level	2.38 ± 1.07	26	2.32 ± 1.10	28	3.37	4	0.497	$d = 0.03$
SES	5.23 ± 1.63	26	5.57 ± 1.26	28	−0.86	52	0.393	$d = 0.23$
BMI	29.34 ± 4.46	26	26.92 ± 2.82	28	2.39	52	0.020	$d = 0.65$
Physical activity	1.50 ± 0.13	26	1.75 ± 0.09	28	7.53	3	0.057	$d = 0.74$
BDI	4.92 ± 3.94	26	4.46 ± 3.76	28	0.43	52	0.663	$d = 0.12$
Systolic BP	136.48 ± 14.41	26	122.43 ± 11.36	28	3.99	52	<0.001	$d = 1.09$
Dystolic BP	85.71 ± 8.19	26	78.61 ± 5.32	28	3.80	52	0.001	$d = 1.03$
Bedtime	00:13 ± 00:33	26	00:27 ± 00:50	28	−1.25	52	0.217	$d = 0.34$
Sleep hours	06:28 ± 00:54	26	06:49 ± 00:47	28	−1.54	52	0.130	$d = 0.42$
Wake time	06:40 ± 00:53	26	07:17 ± 00:50	28	−2.54	52	0.014	$d = 0.69$
MMSE	29.54 ± 0.58	26	29.50 ± 0.74	28	0.21	52	0.834	$d = 0.06$
W-C naming	0.02 ± 1.04	25	0.00 ± 1.00	28	0.07	51	0.939	$d = 0.02$
Stroop Interf.	6.32 ± 8.42	25	5.07 ± 7.23	28	0.58	51	0.562	$d = 0.16$
TMT A	38.84 ± 12.53	25	35.36 ± 9.48	28	1.14	51	0.256	$d = 0.31$
TMT B	94.80 ± 36.40	25	84.14 ± 25.17	28	1.22	1,50	0.227	$\eta^2 = 0.01$
DS-Forward	9.46 ± 2.34	26	8.86 ± 1.88	28	1.05	52	0.298	$d = 0.29$
DS-Backward	6.08 ± 2.15	26	6.14 ± 1.69	28	−0.12	1,50	0.901	$\eta^2 < 0.01$
RAVLT Learn	50.92 ± 9.86	26	51.28 ± 6.28	28	−0.16	52	0.872	$d = 0.43$
RAVLT Immed.	9.92 ± 3.05	26	10.86 ± 1.84	28	−1.35	52	0.184	$d = 0.37$
RAVLT Delayed	105.04 ± 17.18	26	100.20 ± 11.55	28	1.22	52	0.227	$d = 0.33$

Legend. Educ Level: Educational level (range: 0 = no. studies, 1 = primary school, 2 = secondary education, 3 = university and higher education, 4 = postgraduate); SES: Subjective socioeconomic status; BMI: Body Mass Index; BDI: Beck Depression Inventory; BP: Blood Pressure; Awak: Awakening; MMSE: Mini-Mental Status Examination; W-C naming: Word and Color task of the Stroop test; TMT: Trail Making Test; DS: Digit Span; RAVLT: Rey Auditory Verbal Learning Test. Educational level: 0 = no. studies, 1 = primary school, 2 = secondary education, 3 = university and higher education, 4 = postgraduate. Physical activity: 0 = None; 1 = Low; 2 = Moderate; 3 = High.

3.5. Relationship between time taking antihypertensive medication and cognitive performance

Given that the CAR was related to time taking antihypertensive medication and performance on executive function and processing speed (see Sections 3.3. and 3.4), we explored whether time taking antihypertensive medication was related to these two cognitive outcomes. Controlling for age, partial correlations showed that a longer time taking antihypertensive medication was related to better performance on the TMT-B ($r = -0.487$, $p = 0.018$), but not to processing speed ($r = 0.029$, $p = 0.893$).

4. Discussion

The first aim of this study was to investigate differences in CAR and morning cortisol secretion in normotensive and hypertensive older people. We observed that hypertensive and normotensive older people did not show differences in CAR, (i.e., the dynamic of the cortisol increase after awakening), but lower cortisol at awakening and AUCg (a measure of the overall cortisol exposure) were observed in participants with systemic hypertension. Additionally, we observed a relationship between longer time taking antihypertensive medication and a CAR of increased magnitude. The second aim of this study was to investigate the relationship between CAR and cognitive performance in both groups. After controlling for possible confounders, we observed that a CAR of increased magnitude was related to better performance on an attention-switching task (TMT-B) and processing speed (Color reading and Word naming on the Stroop test) in both groups together. However, the interaction between CAR and Hypertension showed that the relationship between CAR and processing speed was significant in the normotensive group, but not in the hypertensive group. Finally, we observed that a longer time taking antihypertensive medication was related to better performance on the TMT-B. All these results were also observed when we excluded from the analyses the participants with a possible delay in performing the first salivary sample on one day of CAR measurement (see Supplementary material).

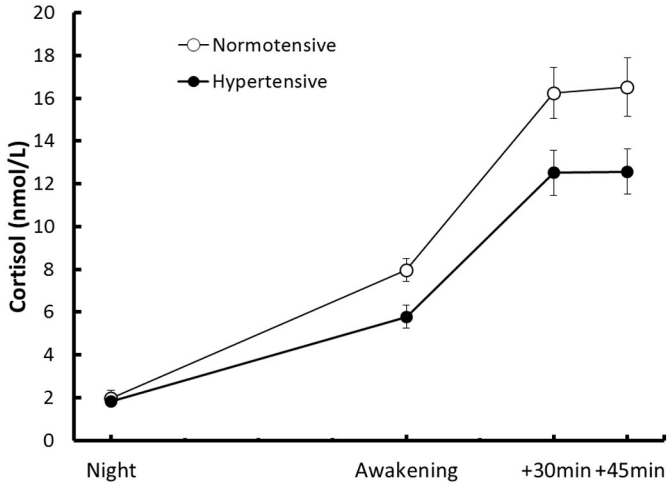

Fig. 1. Mean cortisol levels (±SEM) for hypertensive ($n = 26$) and normotensive ($n = 28$) participants. No differences were observed in cortisol levels at night and CAR ($p > 0.426$), but hypertensive participants showed lower cortisol levels at awakening, +30 min, +45 min and AUCg ($p < 0.026$).

Our results for AUCg and cortisol awakening agree with previous studies showing a relationship between lower overall morning cortisol exposure and higher BP (Kuehl et al., 2015) and cardiovascular risk factors, including high BP (DeSantis et al., 2011; Rosmond and Björntorp, 2000). In contrast to these previous studies, in the present study we measured the self-reported time of awakening, showing that hypertensive participants woke up earlier in the morning. Although we did not observe a statistically significant difference in mean sleep time, previous studies have shown that older people with hypertension sleep fewer hours and wake up earlier in the morning than normotensive older people (Gottlieb et al., 2006; Vgontzas et al., 2009). Thus, the differences in AUCg and cortisol awakening observed in our study and in previous research could be explained by the fact that the hypertensive participants woke up earlier in the morning, when cortisol levels were lower (Elder et al., 2014). Along these lines, higher cortisol levels the preceding night were related to less sleep time and an earlier waking time in hypertensive participants, suggesting that an HPA-axis dysregulation during the night might contribute to an earlier awakening time in this group. This idea agrees with previous studies showing that dysregulated HPA-axis functioning during the night is related to sleep problems (Elder et al.,

Table 2
Correlation analyses for cortisol data, sleep parameters, and time taking antihypertensive for hypertensive (top of the table) and normotensive (bottom of the table) participants.

	Bed time	Mean sleep time	Wake-up time	Cortisol night	Cortisol awakening	CAR	AUCg
	Hypertensive group ($n = 26$) (top right of the table)						
Time medication	$r = -0.02$	$r = 0.05$	$r = -0.04$	$r = 0.16$	$r = 0.15$	$r = 0.45$	$r = 0.39$
	$p = 0.897$	$p = 0.188$	$p = 0.839$	$p = 0.441$	$p = 0.450$	$p = 0.023$	$p = 0.054$
Bedtime		$r = -0.41$	$r = 0.21$	$r = 0.07$	$r = -0.98$	$r = -0.20$	$r = -0.20$
		$p = 0.040$	$p = 0.308$	$p = 0.718$	$p = 0.643$	$p = 0.332$	$p = 0.338$
Mean sleep time	$r = -0.47$		$r = 0.80$	$r = -0.55$	$r = 0.23$	$r = 0.18$	$r = 0.32$
	$p = 0.017$		$p < 0.001$	$p = 0.004$	$p = 0.259$	$p = 0.374$	$p = 0.114$
Wake-up time	$r = 0.56$	$r = 0.47$		$r = -0.54$	$r = 0.18$	$r = 0.06$	$r = 0.21$
	$p = 0.002$	$p = 0.013$		$p = 0.005$	$p = 0.369$	$p = 0.751$	$p = 0.299$
Cort. night	$r = 0.20$	$r = 0.02$	$r = 0.22$		$r = -0.99$	$r = -0.10$	$r = -0.10$
	$p = 0.304$	$p = 0.903$	$p = 0.257$		$p = 0.636$	$p = 0.964$	$p = 0.630$
Cort. awakening	$r = 0.23$	$r = 0.17$	$r = 0.40$	$r = 0.21$		$r = -0.20$	$r = -0.86$
	$p = 0.233$	$p = 0.372$	$p = 0.038$	$p = 0.288$		$p = 0.319$	$p < 0.001$
CAR	$r = -0.11$	$r = -0.25$	$r = -0.34$	$r = 0.12$	$r = -0.22$		$r = 0.32$
	$p = 0.585$	$p = 0.208$	$p = 0.082$	$p = 0.552$	$p = 0.255$		$p = 0.119$
AUCg	$r = 0.18$	$r = 0.06$	$r = 0.24$	$r = 0.26$	$r = 0.89$	$r = 0.22$	
	$p = 0.348$	$p = 0.743$	$p = 0.213$	$p = 0.179$	$p < 0.001$	$p = 0.264$	
	Normotensive group ($n = 28$) (botton left of the table).						

Partial correlation analyses, controlling for age, for the hypertensive (top right of the table) and normotensive (botton left of the table) groups.

2014; Van Cauter et al., 2000). Further research is needed to investigate whether hypertensive and normotensive people differ in their nighttime cortisol rhythms, and if this difference is related to waking time and cortisol levels on awakening.

With regard to the dynamic of the cortisol increase after awakening (i.e., the CAR), we found no statistical differences between hypertensive and normotensive participants. This finding coincides with Strahler et al. (2010), who showed no effects of hypertension on the CAR of older people. However, it does not agree with Wirtz et al. (2007), who reported an attenuated CAR in middle-aged people with systemic hypertension. One important difference in these studies could explain these contradictory results and deserve attention in further research; in our study and in Strahler et al. (2010), but not in Wirtz et al. (2007), all the hypertensive participants were undergoing treatment with antihypertensive medication. Therefore, it is possible that no differences were observed in morning cortisol increases because antihypertensive medication might contribute to a regularization of the CAR. This idea is supported by the positive relationship observed between the length of time taking antihypertensive and the magnitude of the CAR in our study. This latter relationship might be explained by several factors, such as the effect of antihypertensive medication on cerebral blood flow (improving brain functioning) or the effects of antihypertensive drugs related to angiotensin II on HPA-axis activity (Saavedra et al., 2011; 2005; Saavedra and Benicky, 2007; Lipsitz et al., 2005; Triambake et al., 2013). However, it is important to note the cross-sectional and exploratory nature of this analysis. Therefore, more research is clearly needed to investigate a potential effect of antihypertensive medication on CAR.

We observed that a CAR of increased magnitude was related to better performance on an attention-switching task (TMT-B), a measure of cognitive flexibility, and on processing speed (Word-Color naming on the Stroop test). Our results are consistent with previous studies showing a positive association between CAR and cognitive flexibility (Evans et al., 2012; Law et al., 2015). Indeed, Evans et al. (2012) observed the same relationship between CAR and the TMT-B in a sample of healthy older people. By contrast, no significant relationships were observed for word-list memory, verbal working memory or Stroop

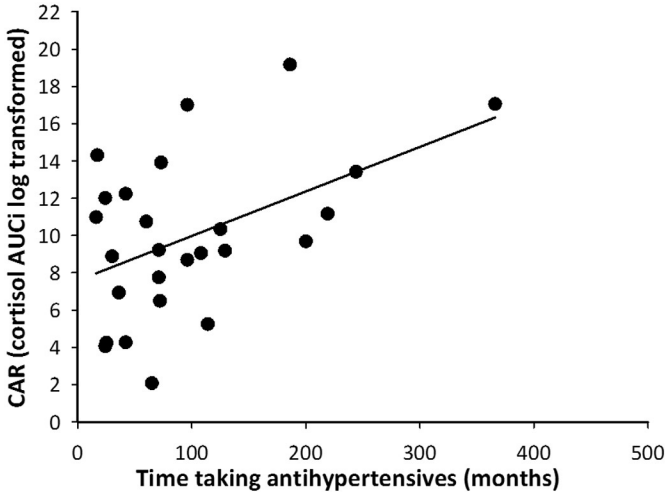

Fig. 2. Scatter plot for the relationship between time taking antihypertensive medication and CAR ($n = 54$, $r = 0.44$, $p = 0.024$). This relationship is also significant if age is included as a covariate ($r = 0.45$, $p = 0.023$). For the time taking antihypertensive medication raw data there is one outlier participant. If this participant is excluded from the analyses, the relationship is still high, but it becomes marginally significant ($r = 0.348$, $p = 0.095$). Using Fisher's Z analyses, we observed that the relationship between CAR and time taking antihypertensive was not statistically different when including or not this participant ($z = 0.41$, $p = 0.682$). Additionally, if this variable is sqrt transformed, this participant is no longer an outlier and the relationship remind statistically significant ($r = 0.408$, $p = 0.043$). The exclusion of this participant does not change any other result of the study.

Table 3
Step 2 and *Step 3* of the regression analyses with CAR as a predictor and cognitive performance as dependent variable.

	N	CAR			CAR*group	
		Adj. R^2	β	*p*	*p*	*Post hoc*
W-C naming	53	0.21	0.39	0.006	0.031	Hypertensive group: β = 0.156, $p = 0.349$ Normotensive group: β = 0.72, $p = 0.001$
Stroop interf.	53	0.02	−0.03	0.821	0.138	
TMT-A	53	0.24	0.21	0.118	0.150	
TMT-B	53	0.44	−0.28	0.022	0.274	
DS-forward	54	0.38	0.15	0.212	0.998	
DS-backward	54	0.23	−0.05	0.710	0.216	
RAVLT learn.	54	0.16	0.18	0.189	0.546	
RAVLT imme.	54	−0.01	0.07	0.647	0.657	
RAVLT del.	54	0.25	0.04	0.751	0.763	

Legend. Adj: Adjusted; W-C naming: Word and Color task of the Stroop test; TMT: Trail Making Test; DS: Digit Span; RAVLT: Rey Auditory Verbal Learning Test; Learn: Learning; Imme: Immediate; Del: Delayed.
Step 1 (*covariates*) = In the first step of the regression analyses we included as covariates: age, BMI, SES, mean cortisol levels during the session, change in cortisol levels during the session, Sex (0 = Women; 1 = Men), Group (0 = Hypertensive; 1 = Normotensive), time of waking and mean sleep time, TMT-A scores (for analyses with TMT-B) and Digit Span Forward (for analyses with Digit Span backward). See Supplementary material for the specific covariates included in the regression analyses for each cognitive outcome.

interference. Similar results were shown for word-list memory in Almela et al. (2012) and Evans et al. (2012), and for verbal working memory and Stroop interference in Franz et al. (2011). This latter study also showed no CAR relationship with TMT-B and processing speed; however, only two samples were used to measure the CAR, an issue that could affect CAR measurements. An explanation for the specific relationship between CAR and executive function has been proposed by Law et al. (2015). Previous authors have proposed that the CAR plays a role in a psychological and/or physiological boost that occurs on awakening, and that the CAR would contribute to preparing individuals to tackle the demands of the day ahead (Clow et al., 2010; Law et al., 2015; Fries et al., 2009). Along these lines, Law et al. (2015) proposed that the CAR would show a stronger relationship with executive function due to the relevance of this cognitive ability in activities in daily life (Bell-McGinty et al., 2002; Cahn-Weiner et al., 2007; Vaughan and Giovanello, 2010).

Our study extends previous findings and indicates that the relationship between CAR and executive function may also be observed in older people with hypertension. Thus, it is possible that changes in the CAR, as observed in older people with systemic hypertension who are not taking antihypertensive medication (Wirtz et al., 2007), might contribute to worse executive function. This idea would be supported by our result showing that a longer time taking antihypertensive medication is related to both a CAR of increased magnitude and better performance on the TMT-B. In the future, it is important to use longitudinal studies to investigate a possible effect of antihypertensive medication on CAR and cognitive performance.

As proposed for cognitive flexibility, it is possible that the relationship between a CAR of increased magnitude and slower processing speed is explained by the fact that processing speed also plays an important role in everyday activities (Aartsen et al., 2002; Edwards et al., 2005). However, it is worth noting that we observed a significant relationship between CAR and processing speed for both groups together, but the interaction between CAR and hypertension showed that the relationship was statistically significant only for the normotensive group. For processing speed performance, white matter integrity in the frontal, parietal and temporal cortex and the connections between the frontal cortex and other brain areas seem to play an important role. It is well known that hypertension increases white matter lesions in older people (Tzourio et al., 2014). Thus, it is possible that the relationship between CAR and processing speed is weaker in hypertensive older people because of the larger white matter lesions in frontal, parietal and temporal areas that would also contribute to variability in processing speed.

In contrast to our result for TMT B and W-C naming, a CAR of increased magnitude was related to worse performance on the TMT-A when regression analyses were performed controlling only the age of the participants. Importantly, this association was not observed after controlling for several confounders, and it was not significant in any of the analyses performed with the 2 Day-CAR subgroup alone. Thus, the association between CAR and TMT-A could be due to the effect of confounding factors in the analyses.

A limitation of this study is that we did not use any electronic devices to objectively assess time of awakening. To control for this possible confounder, we identified the participants with a possible delay in performing the first salivary sample, which can affect the reliability of the CAR measurements. Most of the study's statistical conclusions do not change if we eliminate these participants from the analyses. Thorn et al. (2006) indicates that this methodology should be used with caution in people with cardiovascular disease because it might exclude adherent participants with aberrant CAR. However, all the participants in this study showed a positive CAR on at least one day, and there was no difference in the number of hypertensive and normotensive participants who showed a positive CAR on only one day of sampling. This suggests that a negative CAR was not a characteristic of a specific number of participants, and that a delay in the first salivary sample is a possible explanation. To control for possible unknown effects, we collected a cognitively and physically healthy sample. Therefore, these results can only be generalized to older people who, except for the diagnosis of hypertension, have a good health status. Another limitation is related to the possibility of type I and II error in our study. We performed a set of exploratory analyses that could have increased the possibility of type I error, and so it is especially important to interpret the results of the correlation analyses with caution, due to their exploratory nature. Additionally, a larger sample size would be optimal to test interactions between CAR and hypertension. Thus, it is possible that type II error contributes to the fact that a significant interaction was observed only for processing speed. Taking this into account, it is worth noting that our study achieved a power higher than 0.80 to investigate medium to high differences in cortisol levels and the relationship between CAR and cognitive outcomes (controlling for the effect of four covariates), and that these results coincide with previous research (Almela et al., 2012; Evans et al., 2012; Kuehl et al., 2015; Law et al., 2015; Strahler et al., 2010). Thus, this study provides important findings about differences in cortisol between hypertensive and normotensive older people, and about the relationship between the CAR and cognitive performance.

In conclusion, this study indicates that an earlier time of awakening in hypertensive older people might underlie the lower cortisol levels on awakening and lower overall morning cortisol secretion observed here and in previous studies. Moreover, we observed that hypertensive (receiving antihypertensive treatment) and normotensive participants did not differ in the magnitude of the CAR. Finally, our study replicates previous research showing positive relationships between CAR and executive function, extending this result to older people with systemic hypertension. Additionally, we observed that a CAR of increased magnitude is related to better processing speed performance in normotensive, but not in hypertensive, older people.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yhbeh.2016.05.014.

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