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The Cortisol Awakening Response and Cognition across the Adult Lifespan

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Abstract

Although the hippocampus is thought to play a central role in the regulation of the cortisol awakening response (CAR), results from past studies examining the relationship between the CAR and hippocampally-mediated memory and cognition have been mixed. Inconsistent findings may be due to the use of cortisol samples collected on only 1 to 2 days since reduced sampling can permit unstable situational factors to bias results. We used cortisol assessments from 10 consecutive days to test the relationship of the CAR to episodic memory, working memory, and processing speed in a sample of healthy young, middle-aged, and older adults (age range: 23 – 79 years; $N = 56$). We tested if the relationship between the CAR and cognition would depend upon age and also tested if other cortisol measures, specifically waking cortisol, diurnal cortisol output (i.e., area under the curve) and diurnal cortisol slope (linear and quadratic), would be related to cognition. We found that a more positive CAR slope was related to better episodic memory and that this relationship did not depend upon age. The CAR was not significantly related to working memory. The relationship of the CAR to processing speed was not significant when using a CAR measure that corrected for non-compliant cortisol sampling. We also found that higher waking cortisol was significantly related to better working memory, but not episodic memory or processing speed. Neither diurnal cortisol output nor diurnal linear cortisol slope was significantly related to cognitive functioning. Future work should investigate the mechanisms underpinning the relationship of the cortisol awakening process to cognitive functioning.

Keywords

Cortisol awakening response; Waking cortisol; Hippocampus; Episodic Memory; Working Memory

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1. Introduction

The cortisol awakening response (CAR) is the rapid rise in cortisol that lasts 30 – 45 min immediately following morning awakening (Pruessner et al., 1997; Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007). Some correlational studies indicate that the hippocampus plays a central role in its regulation (Bruehl, Wolf, & Convit, 2009; Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004; Pruessner, Pruessner, Hellhammer, Pike, & Lupien, 2007; Wolf, Fujiwara, Luwinski, Kirschbaum, & Markowitsch, 2005). For example, the magnitude of the CAR is positively related to hippocampal volume (Bruehl et al., 2009; Pruessner et al., 2007). In people with unilateral and bilateral hippocampal damage and severe global amnesia, the CAR is not observed even though cortisol levels decrease normally across the rest of the day (Buchanan et al., 2004; Wolf et al., 2005). Adequate hippocampal function may therefore be necessary for the CAR to occur. Additionally, the amount of cortisol produced during the CAR may influence hippocampal functioning. Pharmacologic suppression of the morning rise in cortisol has been found to inhibit free recall of previously learned content in texts and pictures (Rimmele, Meier, Lange, & Born, 2010). In contrast, recognition of individual items, a cognitive process less dependent upon the hippocampus than free recall (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002), was not impaired. Since the CAR and hippocampal function appear to be closely linked, one would expect to find a relationship between the CAR and hippocampal-dependent memory, such as episodic memory, a cognitive domain known to be supported by the hippocampus (e.g., Cohen, Ryan, Hunt, Romine, Wszalek, & Nash, 1999; Davachi, Mitchell, & Wagner, 2003; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Scoville & Milner, 1957).

There have been few studies examining the relationship between CAR magnitudes and cognition. Most have focused upon middle aged and older adults (Almela, van der Meij, Hidalgo, Villada, & Salvador, 2012; Evans et al., 2011; Evans, Hucklebridge, Loveday, & Clow, 2012; Franz et al., 2011; Rickenbach, Almeida, Seeman, & Lachman, 2014) because higher cortisol, specifically higher diurnal cortisol output, has been linked to poorer cognition in this age group (Lupien et al., 2005). Long-term increases in diurnal cortisol output have been related to worse declarative memory (Li et al., 2006; Lupien et al., 1994, 1998; Seeman, McEwen, Singer, Albert, & Rowe, 1997) and executive functioning (Li et al., 2006), cognitive domains typically found to decline with age (Park et al., 2002; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Schaie & Willis, 1996). In those studies specifically investigating the relationship between the CAR and cognition, episodic memory has been assessed through word list learning, paragraph recall, and visual-spatial memory (Almela et al., 2012; Evans et al., 2012; Franz et al., 2011; Singh-Manoux et al., 2014). The dynamic of the CAR has been measured as: 1) the amount of increase in cortisol from awakening to 30 min post awakening (Franz et al., 2011; Rickenbach et al., 2014; Singh-Manoux et al., 2014), 2) the mean increase (MnInc, see Wüst, Federenko, Hellhammer, & Kirschbaum, 2000) (Evans et al., 2012), and 3) area under the curve with respect to increase (AUCi) (Almela et al., 2012). In one study, higher CAR values were related to lower visual-spatial memory (i.e., Franz et al., 2011); however, this association was not maintained when controlling for diurnal cortisol output (i.e., cortisol area under the curve). CAR magnitudes

have not been found to be associated with list learning (Evans et al., 2012; Franz et al., 2011; Singh-Manoux et al., 2014) and its association with paragraph recall has been inconsistent: one study reported a significant negative relationship (Almela et al., 2012) while another found no association (Franz et al., 2011). The CAR was found to moderate the relationship between cognitive decline and everyday memory problems (Rickenbach et al., 2014). For adults with less cognitive decline, a higher CAR was significantly related to more reports of memory problems; however, for adults with greater cognitive decline, a higher CAR was marginally related to fewer reports of memory problems.

Results from the few studies in middle-aged and older adults examining the relationship between the CAR and working memory/executive functioning have also been inconsistent. An elevated CAR was related to better working memory (Almela et al., 2012) and executive functioning (Evans et al., 2012) in two reports; however, in another study, positive associations between the CAR and working memory/executive functioning were not found (Franz et al., 2011). Because the production of the CAR is associated temporally with the reactivation of the prefrontal cortex (Balkin et al., 2002), further investigations examining the relationship between the CAR and cognitive tests of prefrontal function seem warranted.

The inconsistent findings across studies could be due to several factors including the use of different methods to assess the CAR (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010a) and participant non-adherence to the cortisol collection protocol (Clow, Hucklebridge, & Thorn, 2010b). The use of cortisol samples collected on only 1 to 2 days may also produce inconsistent results since reduced frequency of sampling allows unstable situational factors to have a stronger influence on cortisol outcomes (Hellhammer et al., 2007). To the extent that the CAR is a stable characteristic of individuals, the reliability of estimates of individual differences in CAR responses – and hence estimated correlations of the CAR with cognition -- will benefit from aggregation over multiple samples (Rushton, Brainerd, & Pressley, 1983). In the present study we used cortisol samples collected over 10 consecutive mornings to investigate the association between the CAR and both episodic memory and working memory in a sample of healthy adults ranging in age from 23 to 79 years. To our knowledge, this is the only study that has assessed the relationship between the CAR and memory aggregating CAR values over an extended sampling period.

We also tested if the CAR-cognition relationship is related to processing speed, a construct known to decline with age (Schaie, 1989; Verhaeghen & Salthouse, 1997) but which is typically not linked to hippocampal or prefrontal function. This approach allowed us to evaluate whether any association of CAR to cognition in adulthood is more specific to memory. To test for general HPA axis activity influences upon cognition, we examined the relationship of cognitive performance to both diurnal cortisol output (i.e., area under the curve) and diurnal cortisol slope. We also tested the relationship between waking cortisol and cognition because waking cortisol is thought to reflect pre-awakening mechanisms that influence the magnitude of the CAR (Clow et al., 2010a). We hypothesized a significant association between the CAR and hippocampal-dependent memory (i.e. episodic memory); however, we did not hypothesize the direction of that relationship because results from studies investigating the relationship of the CAR to episodic memory have been mixed.

2. Material and Methods

2.1 Participants

Participants were community-dwelling volunteers from the Atlanta, GA metropolitan area who were initially recruited for a study examining everyday problem solving and emotion regulation. People were excluded if they were pregnant, indicated use of recreational drugs, or reported a diagnosis of post-traumatic stress disorder, bipolar disorder, psychosis, eating disorder, dementia, or the endocrine conditions of Cushing's or Addison's disease (see Nater, Hoppmann, & Scott, 2013 for additional information). Individuals who endorsed at least 3 out of 5 questions on an alcohol abuse questionnaire (e.g., “You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health”) were determined to have a history of alcohol abuse and were excluded. Participants were also excluded if they experienced a major life event (e.g. death in the family or having surgery) or if they had a schedule that would interfere with data collection (e.g., shift work). Sixty-four out of 185 participants from the initial study agreed to participate in the present study, which occurred 8 to 38 months later. One participant who had insufficient cortisol data (i.e., 3 out of 70 assessments) was excluded. Six participants who did not have complete cognitive data were excluded and one young adult whose 3-back score was greater than 3 standard deviations lower than the sample mean was also excluded. The final sample (N = 56) ranged in age from 23 to 79 years (M = 53.04, SD = 16.94; female = 29) and contained comparable numbers of young (N = 17), middle-aged (N = 21), and older adults (N = 18). We examined if the participants in the final sample differed in age and CAR from the remaining participants in the initially recruited sample. The participants in the final sample did not significantly vary in age, $t(183) = -1.21$, $p = .23$, or CAR, $t(182) = -.29$, $p = .77$, from the remaining participants in the initially recruited sample.

2.2 Cortisol (nmol/L) measures

On 10 consecutive days, participants used Starstedt Salivettes to collect 7 saliva samples: upon waking (M = 7:00 AM, SD = 53.4 min), 30 min later (M = 7:30, SD = 54.6 min), and then approximately every three hours until 9:17 PM on average. Cortisol was analyzed from saliva using a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany) (see Nater et al., 2013 for collection details). Cortisol values for each collection time were compared to the respective 10-day within-person mean; values deviating 3 standard deviations from that mean were removed prior to calculation of cortisol measures. Following removal of outliers, a total of 508 out of a maximum of 560 (56 participants × 10 days of data) awakening and post 30 min awakening cortisol samples were available for the calculation of the CAR.

Because we had 10 consecutive days of data, we calculated within-person means for each cortisol measure. To calculate the within-person mean, we averaged cortisol across days for each person. All cortisol measures (i.e., the CAR, waking cortisol, cortisol output, and cortisol slope) represented the mean of all the within-person means in the sample. Nine days of data on average were used to calculate the CAR. Ninety-one percent of participants had 8 to 10 days of CAR data. No participant had less than 5 days of CAR data.

2.2.1 Cortisol awakening response (CAR)—The CAR was a slope measure representing the nmol/L change in morning cortisol per hour. It was calculated by taking the difference between the 30 min post awakening and awakening samples and dividing by the duration of time between the collection of the two samples: (30 min post awakening cortisol – waking cortisol)/(30 min post awakening time – waking time) (Almeida, Piazza, & Stawski, 2009). Accurate CAR values rely upon compliance with the collection protocol. In a healthy sample, negative CAR values most likely represent non-compliance with the study protocol (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Chida & Steptoe, 2009; Kupper et al., 2005) and indicate that the waking sample was most likely not collected upon awakening (Thorn, Hucklebridge, Evans, & Clow, 2006; Franz et al., 2010). Non-compliance can also be detected if the difference in collection times between the first morning and 30 min post awakening samples deviates from 30 min. To account for potential non-compliance, we calculated a corrected CAR. We first calculated a CAR by excluding samples where the time from waking to 30 min post awakening was less than 15 min or greater than 45 min and then excluded CAR values less than 0. This procedure is very similar to one employed by Franz et al. (2010). Because we had multiple days of data, calculating a corrected CAR only resulted in the exclusion of 1 young adult male, whose CAR values ranged from -3.05 to -38.61 (nmol/L)/hr.

2.2.2 Waking cortisol—Waking cortisol represented the first sample collected upon waking in the morning. Participants were instructed to collect this sample after waking-up while still lying in bed.

2.2.3 Diurnal cortisol output—Area under the curve with respect to ground (AUC) was calculated using the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) to measure diurnal cortisol output. AUC was not calculated for days when the awakening specimen and/or greater than 3 specimens were missing.

2.2.4 Diurnal cortisol slope—Linear and quadratic diurnal cortisol slopes were estimated using a linear mixed model. To prevent the CAR from obscuring the slope calculation, the 30 min post awakening cortisol sample was not included (Kumari et al., 2009). Linear and quadratic slopes were calculated using the awakening sample, sample 3 (collected on average at 9:23 AM), and the remaining 4 cortisol samples collected every three hours until 9:17 PM on average. Linear and quadratic terms for measurement occasion were group-mean centered and entered as Level 1 predictors. Slopes were estimated for each day of data. Convergence criteria were met for 7 out of the 10 days of data. More negative linear slope values represented a more rapid decline in diurnal cortisol. More positive quadratic slope values indicated a more rapid decline in cortisol across the morning and a slightly greater increase in cortisol in the evening.

2.3 Cognitive domains

Participants were assessed on the following cognitive domains: episodic memory, working memory, and processing speed.

2.3.1 Episodic memory—Episodic memory was assessed using a yes-no associative recognition task (e.g., Hines, Hertzog, & Touron, 2009). Participants were presented with sixty semantically unrelated noun-noun paired associates in random order on a computer screen and were allowed 5 s to study each pair. In the recognition test that followed immediately after study of all items was completed, half of the words in the noun-noun pairs were rearranged and the other half were left intact. Each pair was presented for 10 s and participants pressed the Y key to indicate "yes" if they remembered the pair or the N key to indicate "no" if they did not. Memory accuracy was determined by subtracting the proportion of false alarms from the proportion of hits.

2.3.2 Working memory—The 3-back and Reading Span were used to assess working memory. In the 3-back participants were presented with a series of single digit numbers and were asked on each trial to recall the number that was 3-back (Mackworth, 1959). 3-back accuracy was measured by the percentage of correct responses. In the Reading Span task, participants were asked to judge whether a series of sentences made sense while remembering a set of letters presented after each sentence (Kane et al., 2004). Sentences were presented in blocks of 3, 4, 5, 6, or 7. Participants were asked to recall the letters at the end of each block in the order that they had appeared. The Reading Span and 3-back were moderately correlated, $r(54) = .52$, $p < .001$. A composite measure of working memory capacity was computed by summing standardized scores for the 3-back and Reading Span accuracy scores (Schmiedek, Lövdén, & Lindenberger, 2014).

2.3.3 Processing speed—Letter Comparison and Pattern Comparison were used to measure processing speed. Participants viewed pairs of letters in Letter Comparison and pairs of line-segment patterns in Pattern Comparison and classified the pairs in each task as "same" or "different" as rapidly as possible (Salthouse & Babcock, 1991). One-half of the pairs were the same and the other half were different. Each test is scored as the number of correct responses in a fixed 2-minute time limit. The two measures were moderately correlated, $r(54) = .64$, $p < .001$. A composite perceptual speed score was computed by summing standardized scores for the Letter Comparison and Pattern Comparison tests.

2.4 Procedure

For 10 consecutive days, participants collected 7 saliva samples: upon awakening, 30 min later, and every 3 hours until 9:17 PM on average. A Tungsten T handheld computer (Palm, Inc.) reminded participants with a beep to collect a specimen and was used by participants to document collection times. Participants returned 8 to 38 months ($M = 28.75$; $SD = 7.32$) following cortisol collection to take cognitive tests.

2.5 Statistical approach

2.5.1 Covariates—Because of the well-recognized relationship between age and cognition, we controlled for age in all linear regression analyses. The following measures, previously shown to be related to cortisol levels or the CAR were considered as potential covariates: sex (female vs. male) (Kirschbaum et al., 1999; Wüst et al., 2009), education (years) (Cohen et al., 2006), body mass index[1] (BMI) (Stalder et al., 2013), race (White vs. not White) (Cohen et al., 2006), smoking status[1] (no cigarettes per day vs. > 0 cigarettes per

day) (Dmitrieva, Almeida, Dmitrieva, Loken, & Pieper, 2013), and waking time (Clow, Thorn, Evans, & Hucklebridge, 2004). Because of our small sample size, including all covariates would have resulted in model overfitting; thus, we selected variables as covariates if their zero-order relationship with a cognitive measure had a p value < .20. Only education, race, sex, and waking time fit this criterion. There were non-significant relationships of education and race to episodic memory; education: $r(54) = .25$, $p = .07$; race: $r_{pb}(54) = -.19$, $p = .15$. A correlation was also found between sex and working memory, $r_{pb}(54) = .23$, $p = .08$. Waking time was significantly related to processing speed, $r(54) = .32$, $p = .02$. These variables were entered into regression models predicting the particular cognitive measure to which a relationship had been detected. Thus, in addition to age, which was included in all models, education and race were included for models predicting episodic memory, sex was entered for models predicting working memory, and waking time was included for models predicting processing speed.

2.5.2 Analyses—We first computed zero-order correlations between selected covariates, cortisol, and cognition. We tested the relationship between each cortisol index and cognition using hierarchical regression. The three cognitive domains (i.e., episodic memory, working memory, and processing speed) were the dependent variables. Covariates were entered into a first step (Model 1) and cortisol was entered in the second step (Model 2). This approach allowed us to see whether the variance in cognition explained by cortisol was significantly greater than the overall variance explained by age and additional covariates. For CAR only, we tested if its relationship to cognition was dependent upon age in a third step (Model 3). CAR and age were mean-centered to reduce multicollinearity effects (Aiken & West, 1991). We also examined if the CAR explained additional variance in cognition beyond that contributed by diurnal cortisol measures (i.e., diurnal cortisol output and diurnal cortisol slope). We did this by entering covariates in Model 1, diurnal cortisol output and diurnal cortisol slope (linear and quadratic) in Model 2, and the CAR in Model 3. These analyses were designed to examine if CAR-specific mechanisms or general HPA axis function accounted for the association between the CAR and cognitive performance. A similar approach has been suggested by Clow et al. (2010b) to disentangle mechanisms responsible for an abnormal CAR. If waking cortisol was significantly related to cognition, we entered the CAR as a covariate in Model 1 and waking cortisol in Model 2 in order to isolate whether pre-awakening mechanisms underpinning the CAR remain related to cognitive performance after controlling for the CAR.

3. Results

3.1 Participant characteristics

Descriptive statistics of the study sample can be found in Table 1.

3.2 Zero-order correlations

The correlations are reported in Table 2. CAR and corrected CAR were not significantly related to age or any of the covariates (i.e., sex, race, education, and waking time). Higher

[1]Smoking status and BMI were obtained during cortisol collection.

CAR and corrected CAR slopes were significantly associated with better episodic memory, but both CAR values were not related to working memory or processing speed. The CAR and corrected CAR were significantly correlated to diurnal cortisol output and the linear diurnal cortisol slope, but neither were related to the quadratic diurnal cortisol slope or waking cortisol. Higher waking cortisol was related to better episodic memory and working memory, but waking cortisol was not significantly related to processing speed. A more negative linear diurnal slope was related to better episodic memory and working memory, but the linear slope was not significantly related to processing speed. The quadratic diurnal slope was positively related to episodic memory, but it was not significantly related to working memory or processing speed. Diurnal cortisol output was not significantly related to any cognitive measure.

3.3 Episodic memory

3.3.1 Variance explained by cortisol after accounting for covariates—Model 1, containing age, race, and education, was significantly related to episodic memory and explained 17% of its variance (see Table 3). Participants who were younger and White (vs. not White) had better memory. Of the cortisol indices assessed, only the CAR and corrected CAR were significant predictors in Model 2, increasing the overall explained variance in episodic memory by 15% and 16%, respectively (see Table 3). Participants with larger positive CAR slopes had higher memory scores (see Figure 1). The Age X CAR interaction term was not significant in Model 3 indicating that the relationship between the CAR and episodic memory was not moderated by age (see Table 3).

3.3.2 Variance explained by CAR after accounting for covariates and diurnal cortisol measures—The addition of diurnal cortisol output (i.e., AUC) and diurnal cortisol slope (linear and quadratic) in Model 2 did not significantly increase the variance explained in episodic memory by Model 1 (see Table 4). Controlling for age, covariates, and the diurnal measures, the CAR was a significant predictor in Model 3 and increased the overall explained variance in episodic memory by 14%. Participants with larger positive CAR slopes had higher memory scores. Results were the same for the corrected CAR, $B = .008$, $t(47) = 3.30$, $p = .002$, $r = .43$. When controlling for the CAR in Model 3, the quadratic slope became a significant predictor of episodic memory. More positive quadratic slope values were related to better memory.

3.4 Working memory

3.4.1 Variance explained by cortisol after accounting for covariates—Model 1, containing age and sex, was significantly related to working memory, explaining 32% of its variance (see Table 5). Participants who were younger and male had better working memory. Of the cortisol indices measured, only waking cortisol was a significant predictor in Model 2, increasing the overall explained variance in working memory by 9%. Participants with higher waking cortisol had better working memory (see Figure 2). The relationship between the CAR and working memory was not moderated by age (see Table 5). Because there was a trend for a relationship between the CAR and working memory ($p = .06$), we tested the association between waking cortisol and working memory again by adding the CAR into Model 1 and waking cortisol in Model 2. The addition of the CAR in Model 1 did not

change the variance in working memory explained by waking cortisol in Model 2, ΔR^2 = .09, F(change) (1, 51) = 8.18, p = .006.

3.4.2 Variance explained by CAR after accounting for covariates and diurnal cortisol measures—The addition of diurnal cortisol output (i.e., AUC) and diurnal cortisol slope (linear and quadratic) in Model 2 and the CAR in Model 3 did not significantly increase the variance already explained in working memory by age and sex in Model 1 (see Table 4).

3.5 Processing speed

3.5.1 Variance explained by cortisol after accounting for covariates—Model 1, containing age and waking time, was significantly related to processing speed, explaining 49% of its variance. Younger age was related to better processing speed (see Table 6). None of the cortisol measures were significant predictors of processing speed in Model 2 and the relationship between the CAR and processing speed was not moderated by age (see Table 6).

3.5.2 Variance explained by CAR after accounting for covariates and diurnal cortisol measures—Diurnal cortisol output and diurnal cortisol slope were not significant predictors of processing speed in Model 2 (see Table 4). The CAR reached the threshold for statistical significance in Model 3 when controlling for the diurnal cortisol measures. More positive CAR slopes were related to better processing speed. The corrected CAR, however, was not a significant predictor in this model, B = .05, t(48) = 1.94, p = .06, r = .27.

4. Discussion

When controlling for the covariates age, race, and education, but not diurnal cortisol measures, we found that only the CAR, out of all the cortisol measures assessed, was significantly related to episodic memory, predicting 15% of its variance. Individuals with more positive CAR slopes had better episodic memory than those with less positive slopes. The CAR was not significantly related to working memory. The CAR was positively related to processing speed when controlling for diurnal cortisol measures in addition to the covariates of age and waking time; however, this relationship was not significant when the corrected CAR, which adjusts for non-compliant sampling, was used as a predictor.

The significant relationship of the CAR to episodic memory is sensible given the linkage of hippocampal structure and function to associative memory. It is also congruent with research demonstrating elimination of the CAR in people with unilateral and bilateral hippocampal damage and severe global amnesia (Bruehl et al., 2009; Buchanan et al., 2004; Wolf et al., 2005). We found that people with larger positive CAR slopes had better episodic memory than people with smaller positive slopes, suggesting that a dynamic increase in cortisol following morning awakening is a marker of healthy hippocampal function. The production of a robust CAR may also influence hippocampal function, consequently benefiting episodic memory.

An inverted U-shaped relationship has been reported between the CAR and episodic memory (Almela et al., 2012) and spatial working memory (Moriarty et al., 2014), suggesting that intermediate CAR responses are better for memory than low or high responses, a notion consistent with findings of an inverted U-shaped relationship between corticosteroid doses and memory (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Lupien, Buss, Schramek, Maheu, & Pruessner, 2005; Schilling et al., 2013). In a supplementary analysis, we tested for but did not find a quadratic relationship between the CAR and episodic memory, $B = .02$, $p = .12$. It is possible that none of the participants in our sample had a CAR large enough to negatively influence memory.

Because we assessed the CAR using 10 consecutive morning cortisol samples and measured episodic memory 8 to 38 months following cortisol collection, the significant relationship between the CAR and episodic memory was probably due to more stable (trait-like or long-term) conditions influencing cortisol production rather than labile (state-like or situational) factors. Indeed, one of the strengths of this study is that aggregating cortisol data over an extended time period undoubtedly increased the reliability of all of the diurnal cortisol indicators for capturing stable individual differences (Doane, Chen, Sladek, Van Lenten, & Granger, 2015). Stable chronic conditions, such as chronic physical and mental health disorders, have been related to a reduced CAR (for review, see Fries, Dettenborn, & Kirschbaum, 2009) and could possibly explain the relationship between a reduced CAR and poorer episodic memory. However, since our sample on average reported to be physically and mentally healthy and we excluded people with posttraumatic stress disorder and other serious psychiatric conditions from study recruitment, we believe this explanation is unlikely for our findings. The CAR appears to be significantly influenced by genetic traits more so than cortisol measures across the rest of the day (Franz et al., 2010; Kupper et al., 2005; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000). Medium sized heritability estimates (e.g., $h^2 = .48$ for area under the cortisol awakening response curve in Wüst et al., 2000) have been reported for the CAR in contrast to statistically nonsignificant heritability estimates for cortisol collected later in the morning and throughout the day until the evening (Wüst et al., 2000). Genetic determinants of the CAR could be related to hippocampal function as manifested in episodic memory performance.

In addition to genetic factors, chronic stress has been related to both an increased (Schulz, Kirschbaum, Pruessner, & Hellhammer, 1998; Wüst et al., 2000) and decreased CAR (Buchanan et al., 2004; Juster et al., 2011; Marchand, Juster, Durand, & Lupien, 2014), with prolonged exposure to stress hypothesized to result in a hypoactive HPA axis (Fries et al., 2005) and a reduced CAR (Fries et al., 2009). Consistent with this hypothesis, a reduced CAR has been found in people who have experienced situations of chronic stress and burden, such as childhood maltreatment (Li, Chassan, Bruer, Gower, & Shelton, 2015) social strain (Friedman, Karlamangla, Almeida, & Seeman, 2012), minority status (Karlamangla, Friedman, Seeman, Stawski, & Almeida, 2013), caregiving burden (Buchanan et al., 2004), and burnout (Juster et al., 2011). The biological cost of prolonged chronic stress is allostatic load, a process which can lead to loss of neural resilience and aging of brain structure and function, especially in the prefrontal cortex, amygdala, and hippocampus (McEwen et al., 2015). Our results suggest that a reduced CAR is not beneficial to hippocampally-mediated

memory function. Future work should investigate whether allostatic load related reductions in the CAR are related to hippocampal dysfunction and episodic memory impairment.

Recently, studies have linked within-person fluctuation in cortisol and daily stress with fluctuations in cognitive function, indicating that stress-related psychological states, including anxiety and rumination, influence constructs like working memory (Sliwinski, Smyth, Hofer, & Stawski, 2006; Sliwinski, Smyth, Stawski, & Wasylyshyn, 2005). We view the present results as complementary to this line of work. Our results indicate that stable individual differences in CAR are related to individual differences in episodic memory, even when controlling on level of cortisol production. Within individuals, however, memory may covary with daily fluctuations in stress-related experiences. An interesting question for future research would be whether the type of between-person difference seen here moderates within-person variability in stress reactivity and its effects on memory performance, which might be expected given the Rickenbach et al. (2014) finding that within-person covariation of stress (including CAR) moderates the relationship of long-term cognitive decline and self-reported memory problems.

The significant relationship between the CAR and episodic memory was maintained when the corrected CAR was used as a predictor. Because the corrected CAR was calculated after removing CAR values indicative of sampling non-compliance (e.g., negative CAR values), non-compliance with the cortisol collection protocol had minimal influence upon the results. This was probably due to the use of aggregated data to calculate the CAR, which likely reduced the influence of measurement error.

Measures of global HPA axis function, specifically diurnal cortisol output (AUC) and the diurnal linear cortisol slope, and waking cortisol, a measure of pre-awakening cortisol secretion, were not related to episodic memory. The quadratic slope was significantly related to episodic memory, but only when controlling for diurnal cortisol measures and the CAR. Interpretation of this relationship is difficult considering the lack of a significant relationship with episodic memory when only age, race, and education were controlled. When accounting for the diurnal cortisol slope (linear and quadratic) and diurnal cortisol output, the CAR remained a significant predictor of episodic memory and explained 14% of its variance. Similar results were obtained with the corrected CAR. Although speculative, it is possible that post-awakening mechanisms specific to CAR regulation and independent of global HPA axis functioning, may account to some extent for the observed relationship between the CAR and episodic memory. Past studies relating the CAR to cognition have interpreted the CAR as a marker of hypothalamic pituitary adrenal (HPA) axis function (e.g., Almela et al., 2012). While the HPA axis influences the CAR, it may not be the CAR's sole regulator (Clow et al., 2010a; Fries et al., 2009). HPA-independent mechanisms involving the suprachiasmatic nucleus (SCN) and the hippocampus have also been proposed to regulate the CAR (Clow et al., 2010a). The SCN not only controls the HPA axis through direct innervations to the paraventricular nucleus of the hypothalamus but also influences adrenal sensitivity to adrenocorticotropin (ACTH) through an extra-pituitary pathway (Buijs, van Eden, Goncharuk, & Kalsbeek, 2003). As mentioned previously, an intact hippocampus has been consistently shown to be necessary for the occurrence of the CAR but not for the production of cortisol across the rest of the day. Some postulate that one way the

hippocampus assists in regulating the CAR is by modulating the extra-pituitary pathway between the SCN and adrenal cortex (Clow et al., 2010a,b). The HPA regulation of the CAR also appears to be somewhat different from HPA regulation of cortisol across the remainder of the diurnal cycle (Clow et al., 2010b; Edwards, Clow, Evans, & Hucklebridge, 2001). For example, the post-awakening peak in cortisol has been negatively related to increases in cortisol at night (Wilhelm et al., 2007). Thus, the CAR is not only a marker of general HPA axis activity but also of mechanisms specific for CAR regulation. The current results suggest that post-awakening mechanisms specific to CAR regulation may account partly for the relationship between the CAR and episodic memory.

The interaction between age and the CAR was not a significant predictor of any cognitive measure indicating that the relationship between the CAR and cognition was independent of age. Several longitudinal studies have found that higher cortisol levels predict worse cognition in older adults (e.g., Li et al., 2006; Lupien et al., 1994, 1998; Seeman et al., 1997); however, these studies measured cortisol as an average over the diurnal cycle and did not assess the CAR. Further, they did not include younger adults in their sample; thus, it is unknown if the relationship between long-term increases in cortisol and worse cognition is a sole phenomenon of older and not younger adulthood. Results from studies investigating the relationship of the CAR to cognition have not explored age as a moderator.

Neither diurnal cortisol slope (linear and quadratic) nor total cortisol output (AUC) was significantly related to working memory or processing speed. Waking cortisol, however, was significantly related to working memory, explaining 9% of its variance after controlling for age and sex. Individuals with higher waking cortisol had better working memory. Waking cortisol, however, was not related to processing speed when controlling for age and waking time. There are few studies that have examined the relationship of waking cortisol to cognition. O'Hara et al. (2007) found that higher waking cortisol was related to worse delayed recall in older adults. However, this effect was found among individuals who had at least one '*s*' allele of the serotonin transporter gene polymorphism. Working memory was not tested in that study and cortisol was collected only on two occasions. Somewhat supportive of our findings, Stawski et al. (2011) found that better cognitive function (a composite of episodic memory and executive functioning) was related to higher waking cortisol (collected over 4 days) in a sample of young, middle-aged, and older adults. Executive functioning, like working memory, is supported in part by the prefrontal cortex (Collette, Hogge, Salmon, & Van der Linden, 2006; Owen, McMillan, Laird, & Bullmore, 2005). It is difficult to explain the relationship between higher waking cortisol and better prefrontal function. One possible mechanism might be cortisol-associated increases in arousal that facilitates executive/working memory processing. In support of this, higher waking cortisol has been related to lower levels of fatigue over a three day period (Adam et al., 2006).

There are several limitations to our study. Participants did not collect cortisol at the same time and there was a delay of 8 to 38 months between the time of cortisol collection and cognitive testing. Although there was an extended time period between cortisol collection and cognitive testing, we argue that an aggregated CAR, calculated using up to 10 days of cortisol data, represents a stable trait CAR (see Hellhammer et al., 2007) that can be used to

predict cognitive functioning months following cortisol collection. Further, measuring cognition months to years following cortisol assessment is not uncommon. Cortisol has been used as a predictor of cognition measured at a time point 1 to 7 years after cortisol collection in numerous studies (Comijs et al., 2010; Csernansky et al., 2006; Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2011; Greendale, Kritz-Silverstein, Seeman, & Barrett-Connor, 2000; Kuningas et al., 2006; Li et al., 2006; Singh-Manoux et al., 2014). Greendale et al. (2000) assessed cognition an average of 4.9 years (SD = 1.1 years) after the collection of morning cortisol. Controlling for multiple variables (e.g. age, education, and BMI), they found that higher morning cortisol predicted worse category fluency. Any potential confounding variable due to the delay in time between cortisol collection and cognitive testing should serve to weaken relationships between cortisol and cognition, not strengthen them. We measured potential confounds of the relationship of cortisol to cognition (e.g., age and education) at the time of cognitive testing and controlled for these when appropriate. Age at time of testing was controlled in all of our analyses.

Though we had 10 consecutive days of cortisol data, we had only two cortisol assessments, at waking and 30 min post waking, for the calculation of the CAR slope. Additional cortisol measures throughout the awakening period may have better captured the dynamics of the CAR (Clow et al., 2004; Hellhammer et al., 2007). For example, we were unable to calculate total cortisol secretory activity during morning awakening (i.e., area under the curve relative to ground), which requires at least three cortisol measures, and differentiate whether the association to cognition was due to total cortisol output during awakening or the dynamic of the cortisol response (Clow et al., 2004).

Our study was correlational, so we cannot claim that higher CAR values improve episodic memory. We can only speculate as to the possible mechanisms that drive this association. Future studies should investigate if interindividual differences (e.g., age, chronic stress, genetic traits) explain some of the variability in the relationship between the CAR and episodic memory measured over time.

Finally, we found that the relationship of the CAR to cognition did not depend upon age. Our limited sample size may have precluded identification of small to medium sized effects due to being underpowered; having said that, the partial r squared associated with the moderated regression coefficient was essentially zero (see Table 3), indicating no evidence of age moderation in this sample.

4.1 Summary

We found that a more positive CAR slope was related to better episodic memory in an adult sample and that this relationship did not depend upon age. The CAR was not significantly related to working memory and the corrected CAR was not related to processing speed. We also found that higher waking cortisol was significantly related to better working memory, but not episodic memory or processing speed. Future work should investigate the mechanisms underpinning the relationship of the cortisol awakening process to cognitive functioning.

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- Cortisol measures were aggregated over 10 days (7 samples per day).
- More positive CAR slopes were significantly related to better episodic memory.
- Higher waking cortisol was significantly related to better working memory.
- Diurnal cortisol output and linear slope were not related to cognition.
- The relationship between the CAR and cognition did not depend upon age.

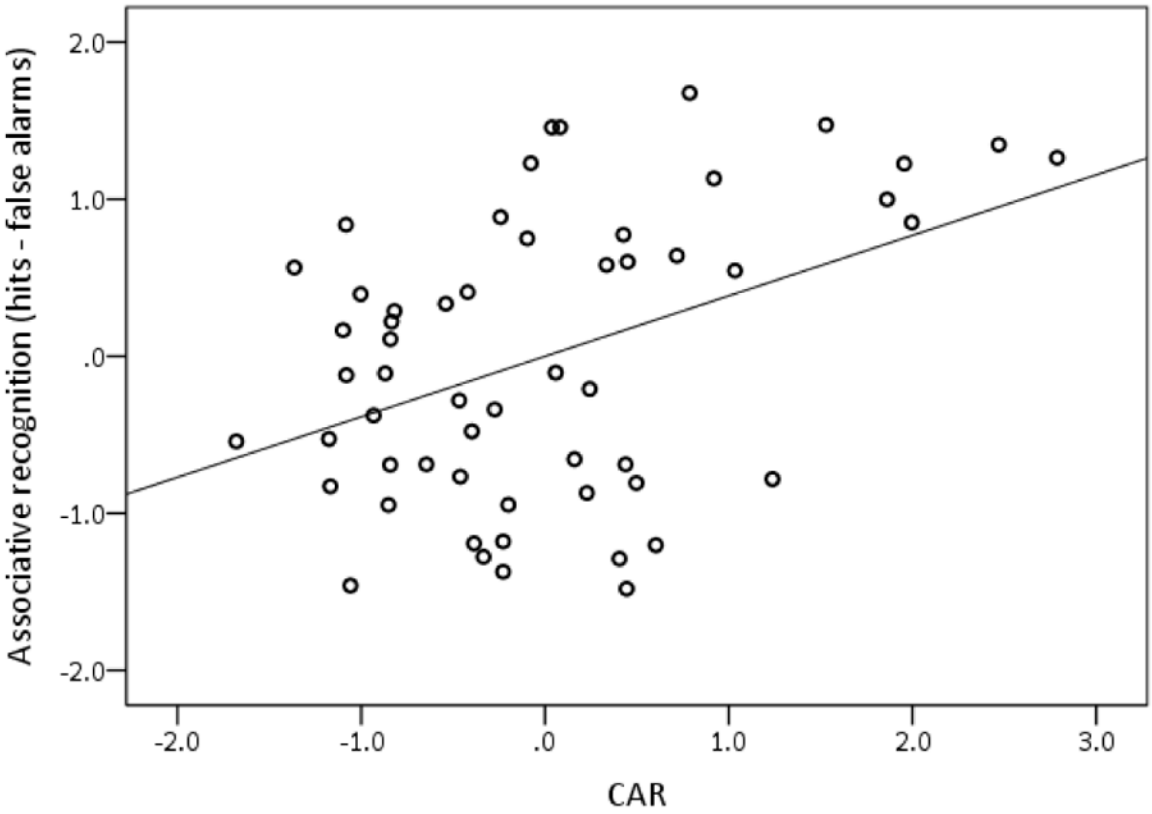

Figure 1.

Partial regression plot of the relationship between the CAR and associative recognition (i.e., episodic memory), controlling for age, race, and education. Standardized values are represented on each axis.

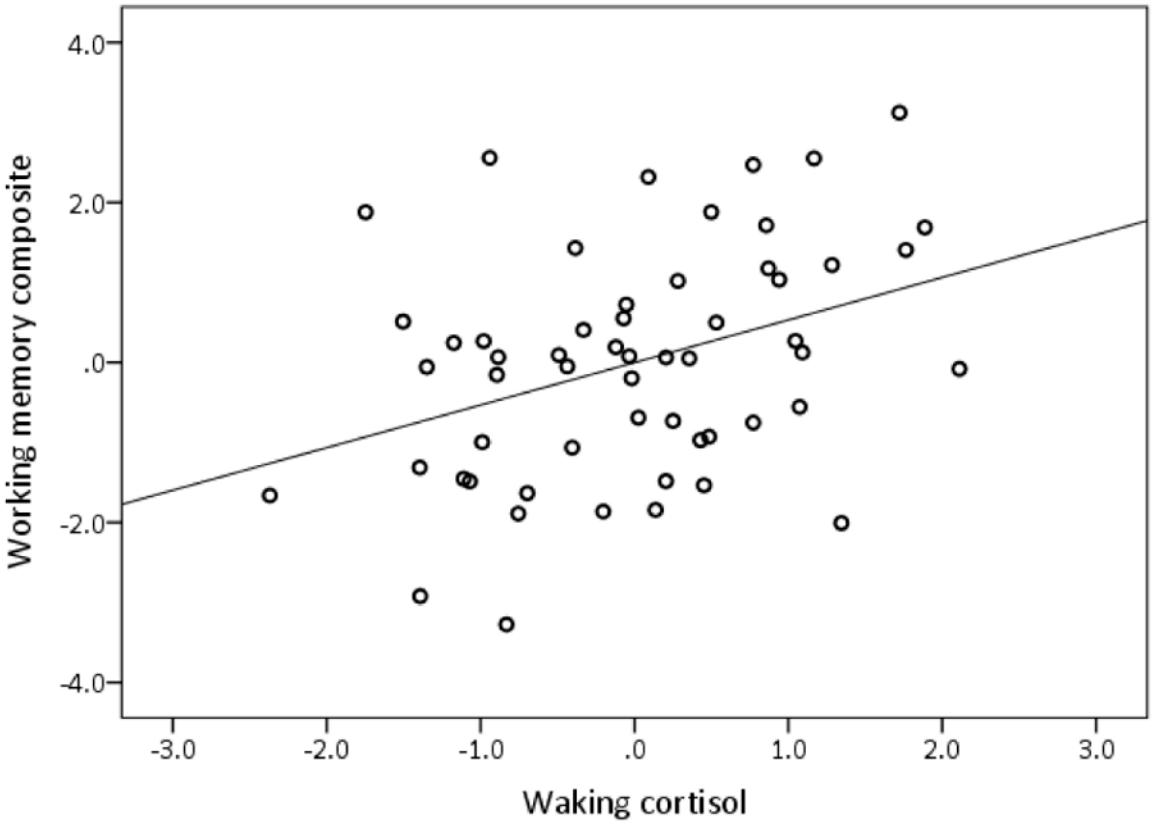

Figure 2.

Partial regression plot of relationship between waking cortisol and working memory controlling for age and sex. Standardized values are represented on each axis.

Table 1

Descriptive statistics of study variables (*N* = 56, except for BMI and corrected CAR, see below).

	N (%)	Mean (SD)	Range
Age (years)		53.04 (16.94)	23 - 79
Sex (female)	29 (51.8)		
Race (white)	44 (78.6)		
Education (years)		15.91 (1.77)	12 - 20
Smoker (yes)	6 (10.7%)		
BMI (*N* = 52)		25.57 (4.68)	14.20 – 36.74
Waking time (hours from 12 AM)		7.00 (.89)	4.62 – 8.88
CAR ([nmol/L]/hour)		11.43 (12.17)	-11.00 – 43.71
Corrected CAR ([nmol/L]/hour) (*N* = 55)		17.66 (8.60)	4.12 – 40.30
Waking cortisol (nmol/L)		15.57 (4.57)	4.92 – 25.07
30 min post waking cortisol (nmol/L)		20.61 (6.57)	7.99 – 40.07
Diurnal cortisol output (AUC)		101.43 (28.75)	37.53 – 177.23
Diurnal cortisol slope (linear)		-.91 (.24)	-1.55 - -.46
Diurnal cortisol slope (quadratic)		.06 (.03)	.00 - .12
Associative recognition (hits – false alarms)		0.74 (.14)	0.53 – 1.00
Reading span accuracy		29.30 (21.66)	0 - 75
3-Back accuracy		.76 (.13)	0.28 – 0.96
Pattern Comparison		36.61 (7.92)	20 - 59
Letter Comparison		20.38 (4.50)	12 - 34

Table 2

Zero-order correlation coefficients between age, covariates, cortisol, and cognition.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age	-													
2. Sex	.08	-												
3. Race	-.24	.11	-											
4. Education	-.09	.03	.03	-										
5. Waking time	-.23	.03	.02	-.06	-									
6. CAR	.11	-.07	-.05	-.07	.01	-								
7. Corrected CAR	.16	-.16	-.11	-.02	-.02	.72***	-							
8. Waking cortisol	.003	-.04	-.19	.29*	.10	.05	.17	-						
9. Diurnal output	.07	.07	-.08	.26*	-.24	.48***	.60***	.39**	-					
10. Linear slope	.12	.02	.16	-.28*	-.44**	-.33*	-.44**	-.69***	-.60***	-				
11. Quadratic slope	.01	-.11	-.20	.31*	.21	-.16	-.03	.70***	-.07	-.39**	-			
12. Episodic memory	-.23	-.04	-.19	.25	.06	.35**	.37**	.32*	.20	-.33*	.31*	-		
13. Working memory	-.50***	.23	-.002	.10	.10	.14	.08	.29*	.10	-.31*	.14	.34**	-	
14. Processing speed	-.68***	-.11	.06	.09	.32*	.02	-.02	.20	-.18	-.19	.21	.37**	.59***	-

Note:

* $p < .05$,

** $p < .01$,

*** $p < .001$.

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Table 3

Summary of hierarchical regression analyses for each cortisol predictor where episodic memory is the dependent variable.

Cortisol predictor →	**CAR**				**Waking cortisol**				**Diurnal cortisol output (AUC)**				**Diurnal cortisol slope**				
	B	***t***	***p***	***r***	***B***	***t***	***p***	***r***	***B***	***t***	***p***	***r***		***B***	***t***	***p***	***r***
Model 1																	
Age	-.002	-2.12	.04	-.28	-.002	-2.12	.04	-.28	-.002	-2.12	.04	-.28		-.002	-2.12	.04	-.28
Race	-.09	-2.05	.046	-.27	-.09	-2.05	.046	-.27	-.09	-2.05	.046	-.27		-.09	-2.05	.046	-.27
Education	.02	1.80	.08	.24	.02	1.80	.08	.24	.02	1.80	.08	.24		.02	1.80	.08	.24
Model 2																	
Age	-.003	-2.62	.01	-.35	-.002	-2.12	.04	-.29	-.002	-2.22	.03	-.30		-.002	-1.93	.06	-.26
Race	-.09	-2.17	.04	-.29	-.08	-1.70	.10	-.23	-.09	-1.98	.054	-.27		-.07	-1.48	.14	-.21
Education	.02	2.15	.04	.29	.01	1.25	.22	.17	.02	1.42	.16	.20		.01	.97	.34	.14
Cortisol	.005	3.30	.002	.42	.007	1.72	.09	.23	.001	1.17	.25	.16	Linear	-.10	-1.20	.24	-.17
													Quadratic	.83	1.20	.24	.17
Model 3																	
Age	-.003	-2.64	.01	-.35													
Race	-.09	-2.21	.03	-.30													
Education	.02	2.17	.04	.29													
Cortisol	.005	3.37	.001	.43													
Age X Cortisol	.000	.81	.42	.11													
Model 1																	
R^2	.17				.17				.17					.17			
$F(3,52)$	3.60				3.60				3.60					3.60			
p	.02				.02				.02					.02			
Model 2																	
ΔR^2	.15				.05				.02					.06			
$F_{(change)}$	10.91				2.96				1.38					2.04			
p	.002				.09				.25					.14			
Model 3																	

Cortisol predictor →	CAR				Waking cortisol				Diurnal cortisol output (AUC)				Diurnal cortisol slope			
	B	*t*	*p*	*r*	*B*	*t*	*p*	*r*	*B*	*t*	*p*	*r*	*B*	*t*	*p*	*r*
ΔR^2	.01															
$F_{(change)}(1,50)$	.65															
p	.42															

Note: *r* = partial correlation coefficient

Table 4

Summary of hierarchical regression analyses where the CAR and diurnal cortisol measures are predictors of cognitive outcomes.

	Episodic memory					Working memory					Processing Speed			
	B	***t***	***p***	***r***		***B***	***t***	***p***	***r***		***B***	***t***	***p***	***r***
Model 1					**Model 1**					**Model 1**				
Age	-.002	-2.12	.04	-.28	Age	-.05	-4.55	<.001	-.53	Age	-.07	-6.31	<.001	-.66
Race	-.09	-2.05	.046	-.27	Sex	.95	2.42	.02	.32	Waking time	.34	1.64	.11	.22
Education	.02	1.80	.08	.24										
Model 2					**Model 2**					**Model 2**				
Age	-.002	-2.10	.04	-.29	Age	-.05	-4.26	<.001	-.52	Age	-.07	-6.36	<.001	-.67
Race	-.07	-1.48	.15	-.21	Sex	1.00	2.58	.01	.34	Waking time	-.04	-.13	.90	-.02
Education	.008	.68	.50	.10										
AUC	.001	.97	.34	.14	AUC	-.001	-.10	.92	-.01	AUC	-.02	-1.35	.18	-.19
Linear slope	-.02	-.22	.83	-.03	Linear slope	-1.61	-1.35	.18	-.19	Linear slope	-1.70	-1.03	.31	-.14
Quadratic slope	1.18	1.51	.14	.21	Quadratic slope	5.38	.68	.50	.10	Quadratic slope	6.99	. 9 3	.36	.13
Model 3					**Model 3**					**Model 3**				
Age	-.003	-2.69	.01	-.36	Age	-.05	-4.54	<.001	-.54	Age	-.07	-6.78	<.001	-.70
Race	-.07	-1.69	.10	-.24	Sex	1.08	2.84	.007	.38	Waking time	-.11	-.34	.74	-.05
Education	.01	1.32	.20	.19										
AUC	.00007	.09	.93	.01	AUC	-.005	-.52	.60	-.07	AUC	-.02	-1.84	.07	-.25
Linear slope	.04	.41	.67	.06	Linear slope	-1.21	-1.01	.32	-.14	Linear slope	-1.52	-.94	.35	-.13
Quadratic slope	1.58	2.19	.03	.30	Quadratic slope	8.68	1.09	.28	.15	Quadratic slope	9.83	1.32	.19	.19
CAR	.005	3.35	.002	.44	CAR	.03	1.70	.10	.24	CAR	.03	2.02	.049	.28
Model 1														
R^2	.17					.32					.49			
F	3.60					12.50					25.05			
p	.02					<.001					<.001			
Model 2														
ΔR^2	.08					.07					.05			

	Episodic memory					Working memory					Processing Speed				
	B	*t*	*p*	*r*		*B*	*t*	*p*	*r*		*B*	*t*	*p*	*r*	
$F_{(change)}$		1.67					1.93					1.85			
p		.19					.14					.15			
Model 3															
ΔR^2		.14					.03					.04			
$F_{(change)}$		11.23					2.87					4.09			
p		.002					.10					.049			

Note: *r* = partial correlation coefficient

Table 5

Summary of hierarchical regression analyses for each cortisol predictor where working memory is the dependent variable.

Cortisol predictor →	**CAR**				**Waking cortisol**				**Diurnal cortisol output (AUC)**				**Diurnal cortisol slope**				
	B	***t***	***p***	***r***	***B***	***t***	***p***	***r***	***B***	***t***	***p***	***r***		***B***	***t***	***p***	***r***
Model 1																	
Age	-.05	-4.55	<.001	-.53	-.05	-4.55	<.001	-.53	-.05	-4.55	<.001	-.53		-.05	-4.55	<.001	-.53
Sex	.95	2.42	.02	.32	.95	2.42	.02	.32	.95	2.42	.02	.32		.95	2.42	.02	.32
Model 2																	
Age	-.06	-4.85	<.001	-.56	-.05	-4.87	<.001	-.56	-.05	-4.62	<.001	-.54		-.05	-4.44	<.001	-.53
Sex	1.00	2.62	.01	.34	.99	2.69	.01	.35	.93	2.36	.02	.31		.99	2.60	.01	.34
Cortisol	.03	1.91	.06	.26	.12	2.87	.006	.37	.007	1.04	.31	.14	Linear	-1.53	-1.80	.08	-.24
													Quadratic	5.72	.80	.43	.11
Model 3																	
Age	-.06	-4.81	<.001	-.56													
Sex	1.00	2.59	.01	.34													
Cortisol	.03	1.85	.07	.25													
Age X Cortisol	.000	-.18	.86	-.03													
Model 1																	
R^2	.32				.32				.32					.32			
F(2,53)	12.50				12.50				12.50					12.50			
p	<.001				<.001				<.001					<.001			
Model 2																	
ΔR^2	.05				.09				.01					.07			
$F_{(change)}$	3.66				8.25				1.07					2.95			
p	.06				.006				.31					.06			
Model 3																	
ΔR^2	.00																
$F_{(change)}$(1,51)	.03																
p	.86																

Note: r = partial correlation coefficient

Table 6

Summary of hierarchical regression analyses for each cortisol predictor where processing speed is the dependent variable.

Cortisol predictor →	**CAR**				**Waking cortisol**				**Diurnal cortisol output (AUC)**				**Diurnal cortisol slope**				
	B	***t***	***p***	***r***	***B***	***t***	***p***	***r***	***B***	***t***	***p***	***r***		***B***	***t***	***p***	***r***
Model 1																	
Age	-.07	-6.31	<.001	-.66	-.07	-6.31	<.001	-.66	-.07	-6.31	<.001	-.66		-.07	-6.31	<.001	-.66
Waking time	.34	1.64	.11	.22	.34	1.64	.11	.22	.34	1.64	.11	.22		.34	1.64	.11	.22
Model 2																	
Age	-.07	-6.36	<.001	-.66	-.07	-6.51	<.001	-.67	-.07	-6.28	<.001	-.66		-.07	-6.52	<.001	-.67
Waking time	.33	1.60	.12	.22	.30	1.47	.15	.20	.29	1.38	.17	.19		.28	1.23	.23	.17
Cortisol	.01	.91	.37	.13	.07	1.91	.06	.26	-.006	-.93	.36	-.13	Linear	.23	.27	.79	.04
													Quadratic	12.25	1.88	.07	.25
Model 3																	
Age	-.07	-6.31	<.001	-.66													
Waking time	.35	1.66	.10	.23													
Cortisol	.01	.78	.44	.11													
Age X Cortisol	-.001	-.79	.43	-.11													
Model 1																	
R^2	.49				.49				.49					.49			
$F(2,53)$	25.05				25.05				25.05					25.05			
p	<.001				<.001				<.001					<.001			
Model 2																	
ΔR^2	.008				.03				.008					.03			
$F_{(change)}$	.82				3.65				.87					1.83			
p	.37				.06				.36					.17			
Model 3																	
ΔR^2	.006																
$F_{(change)}(1,51)$	.63																
p	.43																

Note: *r* = partial correlation coefficient