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Salivary cortisol and memory function in human aging

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Abstract

Objective: To examine the association of salivary cortisol with cognitive changes in a 3 year longitudinal study. Previous studies have suggested that elevated glucocorticoid concentrations alter hippocampal neuronal morphology, inhibit neurogenesis, and impair cognition.
Methods: Salivary cortisol samples were collected at home by 79 cognitively intact older persons (mean age 78 ± 7 years) at 08:00, 15:00 and 23:00 h, and collections were repeated annually for 3 years. Cognitive function was also assessed annually.
Results: The mean cortisol level of samples taken at three times of day and the cortisol concentration at 23:00 h were significantly associated with poorer performance on tasks of declarative memory and executive function. Of 46 subjects who completed the entire 3 year study, higher initial cortisol concentration at 23:00 h predicted a decline in performance of delayed paragraph recall.
Conclusion: These results partially confirm previous findings that high cortisol is associated with impaired declarative memory function in non-demented older persons. In addition, our data show that high salivary cortisol concentrations predict a decline in memory function over the next 3 years.

Keywords: Cortisol; Hypothalamic–pituitary–adrenal; Memory; Cognitive function; Longitudinal study; Aging

1. Introduction

Increased brain exposure to glucocorticoids in aging rodents is associated with cognitive deficits that appear attributable to dendritic atrophy, disruption of calcium homeostasis, and/or reduced neurogenesis in the hippocampus [27,30,58,79]. In tree shrews (a species intermediate between insectivores and primates), stress-induced glucocorticoid elevations are associated with hippocampal neurodegenerative changes [20]. In human aging, peripheral and cerebrospinal fluid (CSF) cortisol concentrations are increased [3,46,50,52,63], and cortisol feedback inhibition of the hypothalamic–pituitary–adrenocortical (HPA) axis is reduced [4,76,77]. These neuroendocrine findings suggest the possibility that brain exposure to higher cortisol concentrations with human aging contribute to the pathophysiology of hippocampus-dependent memory deficits that occur in some older persons [35,36,38,39] and are a central feature of Alzheimer's disease (AD) [2].

Several studies have explored relationships between changes in cortisol and hippocampally-mediated memory function over time in normal older persons [25,35,62]. In a longitudinal study of older persons, Lupien et al. found a significant inverse correlation between increased cortisol over time (positive cortisol slope) and declarative memory at the end of the study [35] as well as smaller hippocampal volume in those subjects with both positive slope and high cortisol concentration at the end of the study [38]. In another longitudinal study, Seeman et al. addressed changes in urinary cortisol concentration and cognitive function over time in a sample of 194 older "above average" persons aged 70–79

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years participating in the MacArthur Studies of Successful Aging [62]. Cognitive function and 12 h overnight urinary cortisol were determined initially and again at follow-up 2.5 years later. Among women (but not men), small but significant inverse relationships between changes in nighttime urinary cortisol (20:00–08:00 h) and delayed recall performance over time were consistent with adverse effects of increasing cortisol on memory. Although, both studies provide support for the possible pathophysiologic involvement of increased endogenous cortisol levels in later life memory deficits, neither determined if initial high cortisol concentrations predicted subsequent cognitive decline over time. Kalmijn et al. [25] in a prospective study, measured serum cortisol and dehydroepiandrosterone sulfate (DHEAS) in 189 subjects between 55 and 80 years of age and correlated initial morning (08:00–09:00 h) hormone levels with changes between initial Mini-Mental State Exam (MMSE) scores and follow-up scores 1.9 years later. The ratio of free cortisol to DHEAS was significantly correlated with initial cognitive impairment, and estimated free cortisol exhibited a positive but non-significant correlation. Neither free cortisol nor the cortisol/DHEAS ratio was found to be significantly correlated with cognitive decline over time.

Here we addressed the relationship between salivary cortisol and cognitive function in a sample of cognitively normal, medically stable older persons in an initial evaluation and subsequent annual evaluations for 3 years. Cortisol concentrations were determined in saliva samples collected at home to eliminate the possible nonspecific stress associated with obtaining blood samples by venipuncture in a laboratory setting and the inconvenience of urine collections. It has been shown that determination of cortisol in saliva provides a reliable measure of the free unbound fraction of cortisol [66], and salivary cortisol relationships with cognitive function in older persons were equivalent to those between plasma cortisol and cognitive function in the study of Lupien et al. [37]. We hypothesized that initial high salivary cortisol concentrations would predict declining performance over time on tests of declarative memory that reflect hippocampal integrity [29]. If high cortisol exposure indeed lowers the threshold for disruption of hippocampal neuronal function [42,59], we reasoned that higher initial cortisol concentrations should be a physiologically meaningful predictor of subsequent decline of hippocampally-mediated cognitive functions. We also hypothesized that we would replicate previous findings [35,62] demonstrating inverse correlations between the slope of cortisol change over time and declarative memory, and inverse correlations between cortisol concentration and declarative memory at the end of the study.

2. Methods

2.1. Subjects

Seventy-nine cognitively normal subjects aged 63 years and above (mean of 77.9 ± standard deviation (S.D.) of 7.1) entered the 3 year longitudinal study. They were recruited from the "normal control" cohort of the Clinical Core of the University of Washington (UW) Alzheimer's Disease Research Center (ADRC). There were 42 women and 37 men. Mean education was 15.0 (±2.8) years. All subjects had MMSE [19] scores of ≥24 and neither subjects nor informants reported changes in social/occupational functioning suggesting a decline in cognitive function. Exclusion criteria were current depression (all Hamilton Depression Rating Scale [HDRS] [22] scores were below six); history of chronic major psychiatric disorder, alcoholism or drug abuse; unstable medical conditions, such as congestive heart failure or unstable cardiac arrhythmia, marked hypertension (>160 mmHg systolic or >95 mmHg diastolic), insulin dependent diabetes, chronic pulmonary disease, hepatic disease or endocrine disease; or treatment with glucocorticoids or any medication known to alter hypothalamic–pituitary–adrenal (HPA) axis function.

Forty-six (22 men and 24 women) of 79 subjects completed the entire 3 year study. The non-completers were slightly but statistically significantly older (79.9 ± 7.4 versus 76.5 ± 6.6) and had slightly but statistically significantly lower baseline MMSE scores (27.3 ± 2.2 versus 28.5 ± 1.5) than those who completed the 3 year study. Initial salivary cortisol levels did not significantly differ between the completers and the non-completers.

2.2. Cognitive testing

At the initial and each of the three subsequent annual evaluations, subjects were administered a neuropsychological test battery and saliva was obtained for measurements of salivary cortisol. Tests in the neuropsychological battery had equivalent alternate versions (except for the MMSE), for which the order was randomly assigned and counterbalanced. The battery consisted of the following.

2.2.1. Global cognitive measure

Mini-mental state examination (*MMSE*) [19]: The MMSE measures attention, orientation, memory, visuoconstructional abilities and naming abilities. It has been shown to be sensitive in discriminating between healthy controls and individuals with AD [24,48,70], and between modest effects of a cholinesterase inhibitor compared to placebo in mild to moderate AD [78].

2.2.2. Verbal memory

Proactive interference (*PI*): Participants listened to a list of 10 words from the same semantic category (e.g. articles of clothing), and then recalled as many of these words as possible. The task was adapted from a previous task [45]. The procedure was repeated for a total of four trials, each containing different words drawn from the same semantic category. On the fifth trial, 10 words from a new semantic category (e.g. types of furniture) were read, and participants were asked to recall these words. The total number of words

recalled correctly on each trial was recorded. The decrease in the number of correct items recalled between trial one and trial four is a measure of proactive interference. Performance on trial five is a measure of release from proactive interference. In this study, rather than focus on the pattern of interference effects, the total number of words recalled correctly from first four trials was used in the analysis. The reliability of the test is generally good, including validity studies conducted with brain-damaged patients and controls [33].

Paragraph recall: The paragraph recall task was modeled on the Wechsler memory scale-revised and measured memory for aurally presented contextual material. Participants listened to two brief narratives, each containing 44 informational bits, and were asked to recall as much as possible immediately after hearing each story and following a 20 min delay [11,73]. The total number of words recalled from both stories was summed to provide measures of immediate and delayed recall for a total possible score of 88 [11]. Reliability and validity of WMS-R and WMS-III logical memory and this modified version are very good [8–11,73,74]. The delayed paragraph recall score was used as the primary outcome in this analysis.

2.2.3. Visual memory

Delayed object recall: This task is based on the 7/24 test [53]. Participants were presented with a large (3 feet × 5 feet) grid with 12 objects (e.g. doll) and were asked how much each item costs. After a half-hour delay, participants were asked to place the objects in the proper place on the grid. The task measures visual-spatial incidental memory.

2.2.4. Attention measures

Stroop color word interference task: This task was based on the original version and utilized three trials for which total reading time and errors were recorded [65]. The first condition (word reading) required participants to read 100 color words (red, green, blue), presented in rows on a sheet of paper as quickly as possible. The second condition (color naming) required participants to name the color of 100 colored blocks presented in rows on a sheet of paper. In the third condition (color word interference), stimuli consisted of color names that were printed in discordant colors (e.g. the word 'blue' printed in green letters). Participants were asked to name the ink color of the printed words, and were thus required to inhibit the reading of the words themselves. Because only the interference trial is a measure of divided attention, the total time in seconds for trial three was used as the dependent measure. The test has demonstrated good reliability and validity when examined in closed head injured individuals compared to controls [33].

Trail making test (*TMT*): This test has two parts, A and B. Part A required participants to rapidly connect numbered dots on a page in order. Part B required that participants draw a line between alternating numbers and letters in order [55]. Time to completion and errors were recorded for both A and B. Time to completion for part B was used in this analysis. The task has been shown to be sensitive to frontal lobe damage and executive function deficits associated with dementia [47,54].

2.2.5. Language

Boston naming test (15-item shortened version by the Consortium to Establish a Registry for Alzheimer Disease [44]): Participants were shown line drawings of 15 objects and asked to name them. If they had difficulty, either a perceptual or phonemic cue or both were given. One point was given for each spontaneously correct item. This test is sensitive to language changes associated with Alzheimer's disease [40].

2.3. Assays and genotyping

2.3.1. Salivary cortisol measurement:

Saliva was collected at home, 2–3 days prior to administration of neuropsychological tests at the study site. Saliva samples were collected at 8:00, 15:00, and 23:00 h. Each subject was given a sour gelatin candy (Sour Patch Kids®) to chew to stimulate saliva flow. The subject then inserted a dental cotton roll between the cheek and gum until it was saturated with saliva, then placed the cotton roll in a screw-top vial and screwed the top on tightly (Salivettes, Sarstedt, Newton, NC). The samples were mailed back to the laboratory for analysis [6]. Salivary cortisol was measured using a ^{125}I cortisol kit from Pantex (Santa Monica, CA), modified for use with saliva samples [63]. Salivettes were centrifuged at 4 °C at approximately 1800 × *g* for 30 min; 100 μl samples of the supernatant were assayed in duplicate. The sensitivity of the assay for saliva samples was 0.2 ng/ml. The intra-assay coefficient of variation was 6.0% and the inter-assay coefficient of variation was 6.9%.

Although salivary cortisol samples were collected at three times of day, we focused our analysis on the late evening (23:00 h) sampling time for several reasons. Late evening is the period during which aging-related elevations of cortisol levels are most frequently observed as well as the time during which spontaneous fluctuations in cortisol secretion are minimal. Changes in circulating glucocorticoids characteristic of aging include a gradual increase in basal concentrations, often revealed only in studies with a relatively large number of subjects [3,46,50,52,63], a phase advance in the cortisol circadian rhythm, and a flattening of the rhythm resulting from failure of cortisol levels to fall to normal trough values at the circadian nadir [14,16–18,26,41,68,69,71]. Circadian rhythms are decreased in amplitude and daily secretion of cortisol is increased due to an elevation of minimum values in the late evening [52]. Because of this pattern, late evening samples are most likely to show changes during the course of a longitudinal study.

Early morning and mid-afternoon samples are subject to rapid fluctuations due to secretory spikes at awakening and following the midday meal, respectively. The timing of the

morning peak of cortisol is linked to the time of awakening. Cortisol responses to awakening consist of a pronounced (50–160%) and rapid increase during the first 30 min after awakening [7,61] followed by a steep decline during the succeeding morning hours. Because of the rapid rate at which cortisol concentrations rise and subsequently fall after awakening, a small deviation in sampling time relative to awakening will result in greater variability within subjects, and the variation among subjects is also high at this time [5]. Sampling at a specific hour in the morning, as we chose to do, is also problematic because the specific timing of the peak is related to the time of awakening.

The occurrence of a pronounced postprandial spike in cortisol secretion after midday meals has been well documented, as well as a period of feedback inhibition following this spike [67,68]. Depending on subjects' meal times, these fluctuations may alter the reliability and consistency of the 15:00 h sample.

In contrast, the 23:00 h sample occurs during what has been characterized as the "quiescent period" of cortisol secretion when secretory bursts are least probable and when transient stress due to everyday activities is likely to be minimal [64,68,69]. The average concentration of the three samples and the area-under-the-curve both tend to be unduly weighted by morning cortisol levels, because of the substantially higher values at that time. We believe that the cortisol concentration at 23:00 h is most likely to reflect impairments in HPA axis and excessive exposure to cortisol at night. The relative intraperson stability of the evening cortisol measurement is confirmed by the significant Spearman's rank correlation between samples taken at the beginning of the study and those taken 3 years later ($\rho = 0.39$; $p = 0.01$).

2.3.2. Genotyping:

Apolipoprotein E (APOE) genotypes were determined using previously described PCR conditions and the HhaI restriction digest method [23].

2.4. Statistical analysis

Salivary cortisol levels were logarithmically transformed for statistical analysis to reduce skew. *T*-tests were used to examine the significance of differences in mean cortisol levels between groups according to gender and APOE genotype. After analysis, all transformed variables were retransformed into natural units for presentation. Simple correlations between cortisol levels and neuropsychological test scores at the beginning and end of the 3 year study were calculated by the non-parametric Spearman formula which is unaffected by skewed distribution of salivary cortisol.

We then examined effects of cortisol on trends of memory changes over time. Our primary hypothesis was that initially high cortisol levels would predict more rapid memory/cognitive decline; i.e. the slope of delayed paragraph recall changes over time in the high cortisol group would be more negative compared to the slopes of those with moderate or low initial levels of cortisol. The initial salivary cortisol levels at 23:00 h and the average level at 23:00 h over 3 years were categorized into three groups based on quartiles: the high level group had values in the top quartile, the moderate level group had values in the middle two quartiles, and the low level group had values in the bottom quartile.

We assumed a linear relationship between memory (delayed paragraph recall) and time. To account for clustering of within-subject responses over time, a modification of the analysis of covariance model using the Statistical Analysis System (SAS) MIXED procedure was used to compare the slopes of delayed paragraph recall change over time among groups [60]. Specifically, the delayed paragraph recall score was modeled as a dependent variable, and follow-up time, groups based on initial cortisol levels, and the interaction of the two were fitted as independent covariates. The coefficient of the interaction term reflects a group-specific slope of the delayed paragraph recall changes.

3. Results

3.1. Salivary cortisol: effects of time, age, and gender

The diurnal rhythm of salivary cortisol in the subjects who completed the 3 year study was consistent with the repeatedly described diurnal rhythm of plasma cortisol: high levels in the morning at 08:00 h, decreased levels at 15:00 h and lowest levels at 23:00 h (Fig. 1) [14,36]. Salivary cortisol levels at 23:00 h tended to be lower at the end of the 3 year study than at the beginning. However, the regression analysis of salivary cortisol over time revealed that the trend was not statistically significant (regression coefficient = −0.031, $p = 0.40$). There was no significant correlation between age and cortisol level at 23:00 h at either the beginning or the end of the study. Salivary cortisol at 23:00 h did not differ significantly by gender initially (men = 2.7 ± 3.5 ng/ml, women = 1.90 ± 1.7 ng/ml,

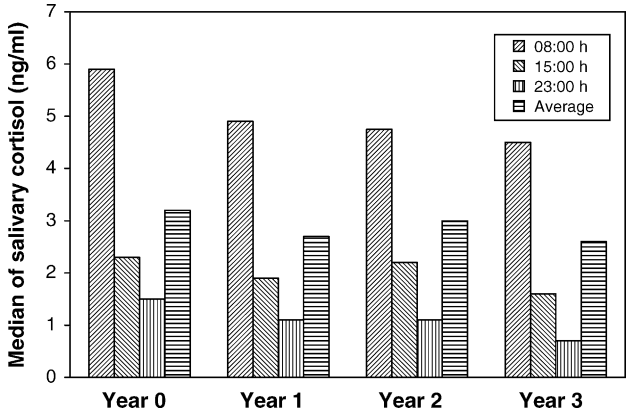

Fig. 1. Median salivary cortisol concentrations at three times of day at the beginning of the study (Year 0) and at yearly intervals during a 3 year follow-up period. At each yearly interval, the mean cortisol value of the three daily samples was calculated for each subject. ▨ denotes the median of these average values for the 46 study completers.

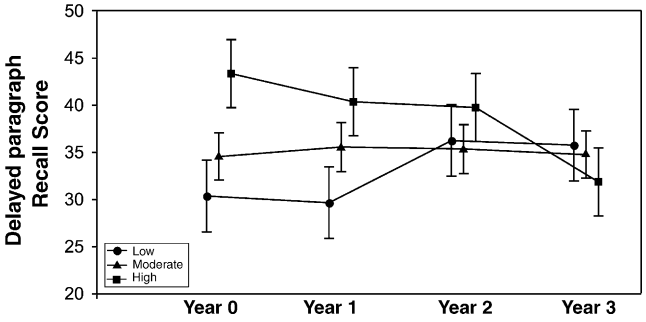

Fig. 2. Delayed paragraph recall scores of groups of subjects based on quartiles of salivary cortisol concentration at 23:00 h at the beginning of the study (Year 0). (●) Bottom quartile ($n = 11$), (▲) middle two quartiles ($n = 23$), (■) top quartile ($n = 12$). Symbols indicate mean concentration ± standard error of the mean (S.E.M.).

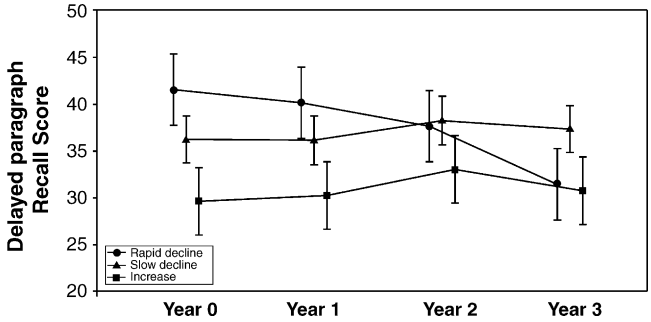

Fig. 3. Delayed paragraph recall scores of groups of subjects based on the slope of the change in 23:00 h salivary cortisol concentration during the course of the study. (●) Bottom quartile ($n = 11$), (▲) middle two quartiles ($n = 23$), (■) top quartile ($n = 12$). Symbols indicate mean concentration ± S.E.M.

$p = 0.56$) or at the end of the study (men = 1.0 ± 0.7 ng/ml, women = 0.9 ± 0.9 ng/ml, $p = 0.42$). Neither initial nor final salivary cortisol concentration at 23:00 h differed significantly between subjects with one or two APOE-ε4 alleles ($n = 11$) and those with no ε4 allele ($n = 35$).

3.2. Salivary cortisol and longitudinal changes in memory

We divided subjects into three groups on the basis of the initial salivary cortisol concentration at 23:00 h: bottom quartile (<0.8 ng/ml), middle two quartiles (0.8–2.6 ng/ml), and top quartile (≥2.7 ng/ml). There was no significant overall change in delayed paragraph recall score over the 3 year period of time (fixed effect of time, $F[1, 43] = 0.39$, $p = 0.53$) (Fig. 2). Consistent with the primary hypothesis, delayed paragraph recall scores in the high cortisol group *declined* steeply over time; those with an initial low level of cortisol had a slight improvement in the delayed paragraph recall test over time (the interaction of time with initial cortisol levels, $F[2, 85] = 4.89$, $p < 0.01$). These differences in longitudinal changes in delayed paragraph recall in the different cortisol groups remained the same when adjusted for initial age, gender and presence of APOE-ε4 allele. Unexpectedly, subjects in the high cortisol group had higher initial delayed paragraph recall scores than those in the moderate ($t = 1.93$, $p = 0.06$) and low ($t = 2.48$, $p = 0.01$) cortisol groups.

We examined whether the slope of cortisol changes over time predicted changes in delayed paragraph recall scores. We used the same statistical model as above and again divided subjects into three groups, this time by slope: bottom quartile (<−0.33), middle two quartiles (−0.33 to 0.01) and top quartile (≥0.01). Positive cortisol slope changes were associated with lower delayed paragraph recall scores (fixed effect of group, $F[2, 85] = 4.81$, $p = 0.01$). The slope of the change in cortisol was also associated with longitudinal changes in delayed paragraph recall (interaction term of time × group, $F[2, 85] = 3.04$, $p = 0.05$), primarily due to a decline in those subjects with the most negative slope of cortisol (Fig. 3).

We used the same statistical model and group division strategy (bottom quartile, middle two quartiles, and top quartile) to examine whether the mean of 23:00 h cortisol levels over the 3 year period predicted changes in delayed paragraph recall scores. No significant differences in the longitudinal change in recall scores were found among groups (data not shown).

Finally, we divided subjects into four groups based on both initial 23:00 h cortisol concentrations and the slope of the 23:00 h cortisol level: *low cortisol/rapid decline group* (initial cortisol concentration ≤ median of 0.15 and slope ≤ median of −0.22, $n = 6$), *low cortisol/slow or no decline* (initial cortisol concentration ≤ median and slope > median, $n = 17$), *high cortisol/rapid decline* (initial cortisol concentration > median, slope ≤ median, $n = 17$) and *high cortisol/slow or no decline* (initial cortisol concentration > median and slope > median, $n = 6$). Fig. 4 shows group means of delayed paragraph recall scores over time for each group. There was an overall difference in the mean delayed paragraph recall

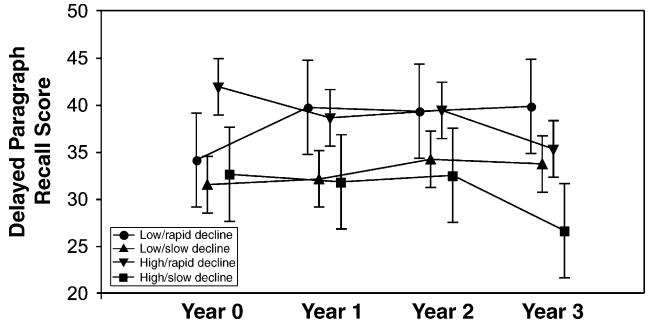

Fig. 4. Delayed paragraph recall scores of groups of subjects based on based on a combination of initial 23:00 h cortisol concentration and the slope of the 23:00 h cortisol concentration over the course of the study. (●) *Low cortisol/rapid decline group* (initial cortisol concentration ≤ median of 0.15 and slope ≤ median of −0.22, $n = 6$), (▲) *low cortisol/slow or no decline* (initial cortisol concentration ≤ median and slope > median, $n = 17$), (▼) *high cortisol/rapid decline* (initial cortisol concentration > median and slope ≤ median, $n = 17$), and (■) *high cortisol/slow or no decline* (initial cortisol concentration > median and slope > median, $n = 6$). Symbols indicate mean concentration ± S.E.M.

Table 1
Correlations between salivary cortisol parameters and neuropsychological test scores

Cognitive tests at end of study	Salivary cortisol							
	3 Year study completers ($n=46$)						All subjects ($n=79$)	
	Cortisol slope (log)		Average over 3 years		At end of 3 years		At end of study	
	Mean[a]	23:00 h	Mean[a]	23:00 h	Mean[a]	23:00 h	Mean[a]	23:00 h
Memory								
Paragraph recall								
Immediate	−0.11	−0.11	−0.13	−0.13	−0.21	−0.34*	−0.18	−0.32*
Delayed	−0.10	−0.06	−0.19	−0.22	−0.25	−0.35*	−0.19	−0.28*
Proactive interference	−0.07	−0.15	−0.31*	−0.26	−0.40**	−0.42**	−0.28*	−0.30*
Object recall	−0.03	−0.02	−0.14	−0.03	−0.10	0.12	−0.16	−0.07
Executive function								
Trails B (time)	0.33*	0.34*	0.08	0.08	0.43*	0.21	0.34**	0.23*
Stroop (interference time)	0.32*	0.35*	−0.01	−0.07	0.28	0.04	0.35**	0.35**
Language								
Boston naming	0.05	0.06	0.09	0.07	0.17	−0.04	0.03	−0.10
Global cognition								
MMSE	−0.12	0.01	−0.12	−0.10	−0.25	−0.15	−0.29*	−0.32**

[a] Mean cortisol level of samples taken at three times (at 08:00, 15:00 and 23:00 h) of day.
* $0.01 < p < 0.05$.
** $p < 0.01$.

scores among groups (fixed effect of cortisol groups, $F[3, 85] = 2.80$, $p = 0.04$), but no statistical difference in longitudinal change by group (interaction of time × group, $F[3, 85] = 1.65$, $p = 0.18$). Consistent with the data in Figs. 2 and 3, those with initially low cortisol concentrations tended to do better over time. Those with initially high cortisol levels appear to have downward trends in the delayed paragraph recall scores. A positive (or less negative) slope of cortisol change appears to be related to overall poor memory function, but not to the rate of decline in memory function over time.

Using the same statistical model and group division strategy (bottom quartile, middle two quartiles, and top quartile), we examined the effect of the mean of the three daily salivary cortisol measures on longitudinal changes in delayed paragraph recall scores. In contrast to salivary cortisol concentrations at 23:00 h, neither the initial mean of the concentrations from the three time points nor the slope of the mean daily cortisol changes over time was significantly associated with changes in delayed paragraph recall score (data not shown).

3.3. Cross-sectional correlation between salivary cortisol and neuropsychological tests

Cross-sectional correlational analysis in the 46 study completers revealed the predicted inverse associations between final cortisol concentrations and measures of memory. Several significant correlations emerged, particularly between cortisol slope and final cognitive measures (Table 1). Consistent with our hypotheses, higher final 23:00 h cortisol concentrations were significantly associated with poorer performance on both immediate and delayed paragraph recall and proactive interference in Year 3. In contrast, cortisol concentration averaged across the three times of day at the end of the study was not associated with performance on immediate or delayed paragraph recall, but was significantly negatively correlated with performance on the proactive interference test. High mean cortisol levels were also associated with increased time (poorer performance) on the Trail Making Part B. There were no statistically significant associations between average level of 23:00 h salivary cortisol over the 3 year period and any neuropsychological measures. Predicted significant correlations between cortisol slope and final memory measures were not demonstrated. However, positive cortisol slopes were significantly associated with poor performance on both Trail Making Part B and Stroop tests—two measures of executive function.

In all 79 subjects with at least one full evaluation, an even broader array of significant correlations emerged between the final cortisol measure and cognitive tests scores. In this particular analysis, the final cortisol levels refer to those measured in the subjects' last visit, regardless of how many evaluations were made. Higher final cortisol concentration was significantly associated with poorer global cognitive performance (MMSE score) as well as with poorer delayed performance on the paragraph recall, proactive interference, trails B, and Stroop tasks (Table 1).

4. Discussion

These results are the first demonstration that higher cortisol concentrations predict declines in the verbal recall component of memory during subsequent years in initially cognitively normal older persons. In addition, these results demonstrate that the subgroup of subjects with increasing

cortisol concentrations over time (positive cortisol slope) consistently had the poorest verbal recall scores during the 3 year study. Because verbal recall depends on the integrity of hippocampal function [29] these findings are consistent with the hypothesis that increased brain exposure to glucocorticoids lowers the threshold for aging-associated deficits in hippocampal neuronal function [27,38,58].

These results generally confirm and extend earlier findings from studies examining the longitudinal relationships between cortisol concentrations in plasma or urine and hippocampally-mediated cognitive function [21,35,62]. That increasing 23:00 h salivary cortisol over time (positive slope) is associated with poorer delayed recall scores is consistent with Lupien et al.'s demonstration that increasing plasma cortisol concentrations over time predict poorer memory performance at the end of the study [35]. The present results extend Lupien et al.'s findings by demonstrating that subjects with a positive slope of 23:00 h salivary cortisol not only have reduced memory function at the end of the study, but also at initial and at intermediate evaluations (see Fig. 3).

In Lupien et al.'s study, a small subgroup with positive cortisol slope and high cortisol had the poorest memory function [35]. Although our analogous group was too small to perform a similar statistical analysis, final 23:00 h cortisol levels were negatively correlated with memory function for study completers and for all subjects combined, and the subject subgroup with increasing cortisol slope consistently demonstrated the poorest delayed recall performance. However, we were unable to replicate a significant inverse correlation between cortisol slope and memory function at the end of the study observed by Lupien et al. [35]. Although the current results generally are consistent with the overall finding of modest inverse correlations between urinary cortisol concentrations and memory function demonstrated by Seeman et al. in their subgroup of older women [62], the specific patterns of relationships show differences from that study and gender differences were not detected in the current study.

The current findings do not agree with those of Kalmijn et al. who failed to find a significant relationship between initial total or free serum cortisol and subsequent decline in memory performance [25]. Kalmijn et al. sampled cortisol only at 8:00–9:00 h. This sampling time is subject to high measurement variability because the time of the morning peak of cortisol secretion is related to the time of awakening [7,61]. In addition, only the MMSE, a global measure of cognition, was used by Kalmijn et al., rather than a specific index of hippocampally-mediated memory functions.

The significant association between higher cortisol and poorer performance on the Stroop and the Trail Making Part B at the end of the study suggest interactions of cortisol with brain areas in addition to the hippocampus. In contrast to the predominantly hippocampally-mediated delayed recall task, the Stroop and the Trail Making Part B involve executive functions mediated in large part by other brain regions including the prefrontal cortex. The longitudinal studies in humans described by Lupien et al. [35] also found increasing cortisol slope associated with poorer selective attention. Thus, in that study also, there is the suggestion of an inverse relationship between cortisol and cognitive function beyond hippocampally-mediated memory. Recent studies of the location of glucocorticoid (GC) receptors in primates provide an anatomic rationale for possible deleterious effects of cortisol on prefrontal cortex. Although GC receptors in rodents are localized predominantly in the hippocampus [56], GC receptors in primate brain are expressed more heavily in prefrontal cortex [57]. The prefrontal cortex, in addition to the hippocampus, has also been implicated in inhibitory regulation of the HPA axis [13,15], and glucocorticoid administration has been shown to induce dendritic reorganization and glutamatergic tone in this area [43,51,75]. These changes in prefrontal cortical dendritic morphology and glutamate activity are also characteristic of aging and chronic stress. If the hypothesized neurotoxicity of excessive neuronal exposure to cortisol is mediated by GC receptors, then the neuroanatomic localization of GC receptors in the prefrontal cortex should be relevant to cortisol's adverse effects on executive function.

Although these results demonstrate that high cortisol concentrations predict future longitudinal cognitive decline and show an association between higher cortisol levels and poorer memory function, they do not establish that increased brain exposure to cortisol is a causative mechanism contributing to neuronal damage underlying cognitive impairment in later life. Additional potential explanations of the observed inverse associations between cortisol and both memory and executive function are that stressful compensatory adaptation to impaired cognition results in higher secretion of cortisol or that deficits in hippocampal and/or prefrontal cortical function result in partial release from glucocorticoid feedback inhibition. These explanations are somewhat plausible with regard to the inverse association between cortisol and cognition measured at the end of the study. However, they are not concordant with the finding that the group comprising the top quartile of initial cortisol levels also had the highest initial delayed paragraph recall scores. Furthermore, the large majority of subjects (17 of 23) with high initial cortisol concentrations exhibited decreasing cortisol levels over time as their delayed recall scores declined.

The possibility suggested by this and other correlational studies [35,62] that increased brain exposure to cortisol in later life contributes to dysfunction or degeneration of neurons critical for cognitive function is consistent with the observed relationship between apolipoprotein E genotype and cortisol concentrations in CSF of older persons [49]. In this study, brain exposure to cortisol as indicated by CSF cortisol is significantly higher both in cognitively intact older persons and those with AD who carry the APOE-ε4 allele. As in the current study, this APOE-ε4 effect on CSF cortisol was not demonstrated on peripheral cortisol levels. Although presence of the APOE-ε4 allele is the strongest genetic risk factor for the expression of AD, the mechanism by which APOE-ε4 increases risk for AD remains unclear. Increased brain exposure to cortisol in those older persons with an

APOE-ε4 allele is one candidate mechanism. In another study providing some support to deleterious effects of GC, persons with AD were randomized for one year either to the synthetic GC, prednisone, or placebo [1]. The prednisone group showed greater deterioration in behavior and a trend toward worsening on a global rating of dementia severity.

Another possible link between high cortisol and cognitive decline is through insulin abnormalities. In AD patients, raising insulin while maintaining fasting glucose increased plasma cortisol levels [12]. Conversely, high cortisol levels induce insulin resistance and hyperinsulinemia. There is increasing evidence that hyperinsulinemia and insulin resistance are associated with increased risk of AD and cognitive decline [34,72].

In the current study, there was a trend toward a decline in salivary cortisol values over time, although the change was not statistically significant. This result was not unexpected, because consistent findings of age-related increases in circulating cortisol in cross-sectional studies have generally required large numbers of subjects and an age span of three or more decades [3,31,32,52,68]. Longitudinal follow-up for a considerably longer period may be necessary to confirm the relatively subtle aging-related increases in circulating cortisol found in cross-sectional studies. Seeman et al. found a similar tendency toward a decline in nighttime urinary cortisol concentrations in non-demented older subjects in their eighth decade followed over 2.5 years [62]. This downward trend may be related to a significant sequence effect found in four measurements of salivary cortisol from subjects between 20 and 70 years of age made at 3-month intervals. The downward effect was attributed to a blunting of anticipatory stress or novelty responses, and this explanation may explain the trend in our relatively short-term longitudinal study [28]. Longer-term follow-up of urinary cortisol and cognition in the initially nondemented older persons sample in the MacArthur study of normal aging cited by Seeman et al. [62] should provide a more robust description of within subject cortisol changes over time with human aging.

Almost half of the original sample failed to complete the full 3 years of the study. However, it is unlikely that the findings were influenced by differential relations between cortisol and cognitive function in completers and non-completers. In fact, the associations between higher final cortisol concentrations and lower cognitive function observed among the 46 completers were strengthened and broadened when all 79 subjects were included in the correlation analysis. In this whole-group analysis of final available measures, inverse correlations remained significant between cortisol levels and delayed paragraph recall, proactive interference, and Trail Making Part B; and additional significant inverse correlations emerged between cortisol and both the Stroop and global cognitive function as estimated by the MMSE. This whole-sample analysis is not consistent with limited adverse effects of cortisol on hippocampally-mediated cognitive functions. Rather, it suggests adverse effects of cortisol on a broader range of brain regions and functions.

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