Published in final edited form as:

Psychosom Med. 2016 ; 78(2): 182–191. doi:10.1097/PSY.0000000000000249.

Endogenous cortisol exposure and declarative verbal memory: A longitudinal study of healthy older adults

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Abstract

Objective—Exposure to endogenous cortisol is associated with hippocampal degeneration and may contribute to problems with declarative memory, but effects of persistent vs. phasic cortisol elevations have not been established. The present longitudinal investigation examined persistent individual differences and phasic changes in cortisol as they related to verbal memory, executive functions, and subjective cognitive function.

Methods—Older adults ($N = 132$, aged 60 to 93 years) were followed for up to 5 years. They were assessed annually for verbal memory and every 6 months for executive functions, subjective cognitive function, and cortisol area under the curve (averaged over 3 days).

Results—In multilevel models, persistently but not phasically higher cortisol was associated with worse verbal memory in both learning ($t(181)=2.99, p=.003$) and recall ($t(280)=3.10, p=.002$). This effect withstood adjustment for stress, depression, metabolic health, and age. There was evidence for attenuated primacy in learning with higher persistent cortisol. Phasic increases in cortisol were not associated with changes in memory, and cortisol was not related to executive functions or subjective cognitive function.

Conclusions—Higher secretion of cortisol may, over time, contribute to memory dysfunction in older adults.

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Conflicts of Interest:

The authors have no financial interests to disclose.

Keywords

aging; cortisol; verbal memory; serial position; executive cognitive function

Introduction

Declines in declarative memory, among other cognitive functions, accompany aging (e.g., 1). However, average decline obscures significant heterogeneity: some individuals maintain good function, whereas others decline quickly (2). One contributing factor to individual differences in declarative memory is exposure to endogenous cortisol. A steroid hormone product of the hypothalamic-pituitary-adrenal axis, cortisol acts on receptors in the hippocampus and prefrontal cortex and can contribute to neuronal loss in these regions (3). A number of studies have obtained negative correlations between endogenous cortisol production and performance on declarative memory tests, and a 2003 meta-analysis identified a small but statistically significant negative correlation between cortisol and memory, primarily from cross-sectional studies (4). Later-emerging studies have yielded similar results (5–7).

An important development in this literature is a move from cross-sectional to longitudinal assessments of cortisol and/or memory. Characterizing both persistent and phasic cortisol effects aids in identifying who is at higher risk for declarative memory deficits and when. Three longitudinal studies of older adults have examined levels and/or slopes in mean cortisol, measured annually, as related to memory change across the study and/or memory at the end of the study. Study lengths ranged from 3 to 5 years. Larger declines in memory performance (paragraph recall) in one study ($N = 52$, aged 65–97) correlated with higher cortisol levels at study beginning and increases in cortisol over time, but not higher average cortisol across the study (6). However, another study ($N = 46$, aged 63 and older) found that larger declines in memory (verbal learning) did correlate with higher average cortisol (7). Poorer memory performance (paragraph recall, cued recall) at study end was not significantly correlated with higher average cortisol in two studies ($N = 52$ and 19 [aged 60–80], respectively) (6, 8); only one found a significant correlation between larger increases in cortisol and poorer memory performance at study end (8).

Therefore, the extant research is inconsistent with regard to the effects of persistent cortisol elevations versus changes in cortisol on memory. Small sample sizes and limited cortisol sampling protocols may have contributed to these inconsistencies. Approximately 50% of the variance in a single day's cortisol measurement is idiosyncratic to that day (9–10). However, all longitudinal studies have assessed cortisol on a single day at each assessment (6–8). This measurement protocol limits the ability to detect effects due to longer-term cortisol exposure and contributes to heterogeneity in estimates (4, 9–10). These studies also focused on long-term changes in cortisol (i.e., slope over years). However, phasic increases in cortisol can also occur, for example, with temporary increases in stress. Increases in cortisol lasting only a few days can result in memory decrements (11). Importantly, these decrements are reversible, suggesting that phasic increases in cortisol may temporarily affect memory.

The present study was designed to build on these previous reports both substantively and methodologically by testing the relationship between cortisol and verbal declarative memory (1) measuring cortisol on multiple days at each time point, (2) in a sample of healthy older adults that had adequate power (.80) to detect a small-to-medium effect size ($r=.23$), and (3) considering both persistent and phasic cortisol elevations in a multi-year longitudinal design.

The primary hypothesis of the study was that cortisol elevations, both persistent and phasic, would be associated with poorer verbal declarative memory. Several supplemental analyses explored the nature of this relationship. First, whether cortisol mediates a relationship between stress and memory is not resolved, with some studies suggesting independent effects of stress or depression and cortisol (7,12). Therefore, supplemental analyses included stress or depression in the model. Second, whether elevated cortisol is a proxy for metabolic ill health or aging, both of which may be associated with neurocognitive decline, is not resolved. Therefore, supplemental analyses included age and an index of metabolic dysregulation in the model. Finally, some studies suggest that effects of cortisol on cognition are not limited to memory but also apply to other functions, particularly executive functions (e.g., 5–6) and subjective complaints (13). Therefore, whether cortisol also affected these functions was also tested.

We tested two parameters of declarative verbal memory: total learning (number of words recalled across 5 consecutive trials) and delayed recall (number of words recalled after a 20-minute delay). We performed supplemental analyses on memory for words in different list positions. Better recall of words in the first part of the list comprises a primacy effect, which is attributed to more rehearsals and long-term memory encoding; better recall of words in the latter part of the list comprises a recency effect, which is attributed to occupation of short-term memory (14–15). It has been suggested that exposure to endogenous cortisol is associated with attenuated primacy, a reduced ability to recall items from the beginning of a word list (16). Attenuated primacy is associated with dysfunctional memory and brain pathologies (14; 17–18) but is not characteristic of normal aging (14).

Method

Participants

Participants were 132 community-dwelling older adults recruited through a volunteer subject pool. The sample mean age was 74 years at enrollment (range = 60–93), 58% female, and predominantly white (96%), with the remainder African-American (4%). The sample was well educated on average within the context of a large range in education ($M=16$ years, range=11–22 years). All participants were married at enrollment, although only one member of the couple was enrolled in order to avoid dyadic dependency in the data. Some study participants ($N=18$) were excluded from the present analysis for severe illness (bladder tumor and bone cancer) or use of acetylcholinesterase inhibitors or topical corticosteroids.

Procedures

All procedures were approved by the University of Kentucky Institutional Review Board. Older adults who had expressed interest in participating in research were contacted and screened. Inclusion criteria were: age 60 or older; married. Exclusion criteria were: diseases affecting the immune system; chemotherapy/radiation in the 5 years prior to enrollment; opiates or systemic steroids use; or use of more than two of the following medication classes: psychotropics, antihypertensives, hormone replacement, thyroid supplements. These restrictions were meant to ensure a relatively healthy sample of older adults.

After complete description of the study to the participants, written informed consent was obtained. Participants were interviewed at semi-annual visits in their homes for up to 10 visits. All cognitive testing took place in the home, with the interviewer ensuring the best possible testing environment (e.g., ensuring that phones were silenced, household members were not present, etc.). In advance of each interview, participants collected saliva three times per day (with target times of waking, 5 pm, and 9 pm) on three consecutive days. Participants completed a saliva collection log including exact time of collection. Mean interval between saliva collection and interview was 2.6 days ($SD = 8.4$), with 79% of interviews taking place within one week of collection. Saliva was stored at approximately 4°C until collected by study personnel. Participants received a \$20 gift card following each interview. Interviews took place between August, 2006, and May, 2011.

For verbal memory, 419 person-visits were available for analysis ($M=3$ annual administrations of memory testing for each participant, range = 1 to 5; 63% of all possible administrations). For executive functions and subjective cognitive function, 793 person-visits were available for analysis ($M=6$ semiannual administrations for each participant, range = 1 to 10; 60% of all possible administrations). Data were primarily missing at later visits due to dropouts ($N=49$; $M=5$ visits completed) and end of study (i.e., people who entered the study later did not complete as many visits before study end as those who entered the study earlier, $N=46$; $M=8$ visits). Some missing data were also due to deaths ($N=4$; $M=4$ visits). Multi-level analysis (see below) accommodated the use of all available data without listwise deletion.

Measures

Demographics—Participants reported date of birth, years of education, race, and gender.

Verbal memory—The Rey Auditory Verbal Learning Test (RAVLT; 19) consists of eight trials: Trials 1–5 ask participants to immediately recall a 15-word list read aloud by the interviewer. Trials 6–8 assess the effects of interference and delay. The primary outcome measures for this study were total learning (TL; sum of words recalled over Trials 1–5, range = 0–75) and delayed recall (DR; sum of words recalled in Trial 8, range = 0–15). In addition, exploratory analyses tested position-related recall: primacy (recall of first 5 words), middle (middle 5), and recency (last 5). A single form of the RAVLT was administered every other visit on odd-numbered visits (i.e., annually). At baseline, the mean percentile, normed for age and sex, for TL was 72 ($SD = 31$) and for DR, 64 ($SD = 35$). Therefore, this was a generally high-functioning sample, although there was a large range in normed

performance (percentile range = 1 – 100 for both TL and DR). Raw scores (i.e., not normed scores) were employed in analysis so that effects of age could be explicitly included in the statistical model.

Medications—A medication list was provided to the interviewer at each visit. Each medication was coded by a registered nurse into medication classes. Corticosteroid use was examined due to its effect on endogenous cortisol production. A composite of use of lipid-lowering medication, blood pressure medication, and glucose regulation medication provided an index of metabolic health, ranged from 0–3, and was normally distributed in the sample.

Perceived stress—The Perceived Stress Scale (PSS; 20) assesses the degree to which life circumstances over the past month are appraised as stressful. The PSS was administered at each visit and demonstrated good internal consistency at all visits ($\alpha=.78-.89$).

Depressive symptoms—The Geriatric Depression Scale (GDS; 21) assesses depressive symptoms excluding somatic complaints commonly associated with aging. The GDS was administered at each visit and demonstrated good internal consistency at all visits ($\alpha=.69-.82$).

Executive functions—The Trail Making Test Forms A and B (TMT; 22) were used to assess executive functions. For Form A, participants are asked to connect numbers (1–25) on a page in ascending order, assessing abilities including visual scanning and motor speed. For Form B, participants are asked to connect numbers and letters on a page, alternating between a number and a letter. The TMT was administered at each visit and operationalized as seconds to complete B minus seconds to complete A, an index of the additional demands of cognitive flexibility and executive control in Form B (23–24). Raw scores (i.e., not normed scores) were employed so that effects of age could be explicitly included in the model.

Subjective cognitive function—Cognitive function from the Medical Outcomes Study consists of a six-item self-report measure assessing the amount of time in the past month the respondent was confused, reacted slowly to things, had difficulty reasoning, was forgetful, had trouble keeping attention, and had trouble concentrating (25). Higher scores reflect better subjective cognitive function. The scale was administered at each visit and demonstrated good internal consistency at all visits ($\alpha=.76-.86$).

Cortisol area under the curve (AUC)—Saliva samples were collected in pre-labeled Salivettes (Walter Sarstedt Inc., Newton, North Carolina), centrifuged, aliquoted, and frozen at -80°C . Cortisol levels were assessed using an enzyme immunoassay (Salimetrics, Inc., State College, PA). Assay sensitivity was 0.003 ug/dL. Data from the low and high control samples yielded average inter-assay CVs of 9.40% and 5.49% and intra-assay CVs of 5.31% and 3.13%. Data were excluded if reported collection time was outside a window 4 SD earlier or later than mean collection time. All time points had > 98% valid data. In cases in which participants provided saliva but did not record the collection time for the sample, time values were imputed using the expectation-maximization algorithm in SPSS. Cortisol values were not imputed.

Diurnal area under the curve (AUC) is an integrated measure of cortisol exposure across the day. Unlike a raw mean across collection times, AUC incorporates duration of exposure and change over time and thus may provide a more accurate estimate of total exposure. The area under the curve (AUC) calculation used mean raw cortisol values (C_x) and within-person mean collection times (T_x) for each targeted time of collection (wake, 5pm, 9pm). AUC was calculated by trapezoidal estimation using the formula: $AUC = .5[(C_{wake} + C_{5pm}) \times (T_{5pm} - T_{wake})] + .5[(C_{5pm} + C_{9pm}) \times (T_{9pm} - T_{5pm})]$. The distribution of AUC was skewed and therefore log transformed before analysis. Previous analyses indicated that 3 days of diurnal data were sufficient to create reliable measures of AUC change within people (.58) and of stable differences between people (.90) (10).

Data Analysis

Data analysis was primarily conducted in multi-level models with visits at Level 1 and people at Level 2 using SAS PROC MIXED with maximum likelihood estimation (for detailed description of multilevel models, see (26)). Indices of model quality included variance estimates at Level 1 and Level 2, Aikake's information criterion (AIC), and Bayes's information criterion (BIC). The latter two consider both model fit and parsimony. The percent variance accounted for by a predictor was calculated by dividing the residual variance (at the appropriate level for the predictor) from the model with that predictor by the residual variance from the model without that predictor and subtracting the result from 1. All tests were two-tailed with $\alpha=.05$.

To separate out influences of cortisol on verbal memory at Level 1 (phasic, within-person influences) and Level 2 (persistent, between-person influences), cortisol AUC was person-centered (27): A mean across visits for each person comprised the Level 2 predictor, and a deviation from this mean at each visit comprised the Level 1 predictor. The Level 2 predictors were grand mean centered.

The first model was a null model with no predictors. The following equations demonstrate how the multilevel model was constructed. Level 1 characterizes the outcome Y_{ij} (e.g., total learning for person j at visit i) *within* person j : For person j 's visit i , Y_{ij} can be modeled as person j 's average across all visits (β_{0j}) plus the deviation from that average at visit i (e_{ij}). Level 2 characterizes the outcome *across* people: There is an average of β_{0j} 's across the sample (γ_{00}) and a deviation from that average for person j 's β_{0j} (U_{0j}).

$$\text{Level 1: } Y_{ij} = \beta_{0j} + e_{ij}$$

$$\text{Level 2: } \beta_{0j} = \gamma_{00} + U_{0j}$$

This null model provided the sample intercept γ_{00} (analogous to a mean across all people and visits) and variance estimates at Levels 1 (within-person variance, i.e., of e_{ij}) and 2 (between-person variance, i.e., of U_{0j}) that permitted calculation of the intraclass correlation (ICC; the ratio of between-person variance to total variance).

The second model added number of administrations of the RAVLT to account for changes over time and practice. Model testing indicated a significant random effect of

administrations ($\chi^2=23.7, p<.0001$); therefore, number of administrations was included as a random effect in all further models.

The third model added cortisol AUC at Level 1 (phasic, within-person) and Level 2 (persistent, between-person). The following equations illustrate this model. For person j 's visit i , the outcome Y_{ij} was a function of number of previous administrations at visit i and within-person phasic changes in cortisol at Level 1 and of between-person differences in persistent cortisol across visits at Level 2. The U_{1j} term reflects individual differences in the effects of administrations (i.e., the random effect). There was no evidence for individual differences in the effects of phasic cortisol, and so no random term was included in the models.

Level 1:	$Y_{ij} = \beta_{0j} + \beta_{1j}(\text{administrations}) + \beta_{2j}(\text{phasic cortisol}) + e_{ij}$
Level 2:	$\beta_{0j} = \gamma_{00} + \gamma_{01}(\text{persistent cortisol}) + U_{0j}$
Level 2:	$\beta_{1j} = \gamma_{10} + U_{1j}$
Level 2:	$\beta_{2j} = \gamma_{20}$

By substitution, these equations can be combined as:

$$Y_{ij} = \gamma_{00} + \gamma_{01}(\text{persistent cortisol}) + \gamma_{10}(\text{administrations}) + \gamma_{20}(\text{phasic cortisol}) + U_{0j} + U_{1j}(\text{administrations}) + e_{ij}.$$

The estimates in the Tables correspond to these model elements as follows: fixed effects included the intercept (γ_{00}), administrations (γ_{10}), persistent cortisol (γ_{01}), phasic cortisol (γ_{20}); random effects included Level 2 variance (the variance of U_{0j}), administrations slope variance (the variance of U_{1j}), and Level 1 variance (the variance of e_{ij}).

The remaining models tested whether covariates affected the cortisol estimates. Covariates were included individually. Because results of Model 3 suggested effects of cortisol at Level 2, these models focused on covariates measured at Level 2 (means across visits), except for metabolic index, which was included as a single time-varying covariate at Level 1. Table 1 shows the means of and correlations between Level 2 variables in the model(s) and the metabolic index at the first visit. Model 3 was repeated for exploratory analyses to determine whether effects on verbal memory were (1) stronger for different serial positions and (2) extended to other cognitive functions (executive functions and subjective cognitive complaints).

Supplemental Digital Content 1 contains zero-order correlation tables among the primary study variables for each measurement visit.

Results

Verbal memory

Table 2 shows the result of the model predicting total words recalled during the 5 verbal memory learning trials (i.e., total learning). Each fixed effect shows the number of additional words recalled per one unit change in the predictor; units are shown in the second

column. Model 1 indicated that most variance in total learning (74%) was at Level 2 (between people), with less (26%) at Level 1 (within people). Model 2 included the effect of administrations, which was positive but not statistically significant.

Model 3 indicated that higher average cortisol AUC at Level 2 predicted poorer total learning, supporting the primary hypothesis. One SD higher persistent cortisol was associated with 3.3 fewer words recalled across the learning trials (Table 2, Model 3, persistent cortisol effect, $t(181)=2.99, p=.003$). This effect accounted for 6% of the Level 2 variance. Contrary to prediction, upward phasic deviations from a person's own average were associated with better total learning at that visit (Table 2, Model 3, phasic cortisol effect, $t(181)=0.94, p=.35$), but this effect was not statistically significant and accounted for only 1% of the Level 1 variance.

Among the covariates (Table 2, Models 4–7), only perceived stress and age were associated with total learning above and beyond the effects of persistent cortisol AUC. Higher perceived stress was associated with better total learning, accounting for an additional 5% of the Level 2 variance (Table 2, Model 5, perceived stress effect, $t(180)=2.14, p=.034$); however, the cortisol AUC estimate was only slightly reduced, and model fit estimates were improved for AIC but not BIC. Older age at study entry predicted poorer total learning, accounting for an additional 5% of the Level 2 variance (Table 2, Model 7, age effect, $t(181)=2.68, p=.008$). In this case, the cortisol AUC effect estimate was more substantially reduced, and model fit was improved by both AIC and BIC. Age and persistent cortisol AUC were significantly positively correlated (Table 1). Therefore, it is useful to characterize their predictive validity together and individually. Together, age and cortisol AUC predicted 10% of the variance in total learning (Level 2 variance in Table 2, Model 2 vs. Model 7). The effect of age independent of cortisol AUC predicted 5%; the individual effect of cortisol AUC independent of age predicted 3% (calculated by reversing the order of entry); therefore, their shared variance predicted 2% of the variance in total learning.

Table 3 shows the same models for delayed recall. (Note that there was no significant random effect of administrations on delayed recall. The fixed effect was included, but was not statistically significant in any model.) The results paralleled those for total learning. Higher persistent cortisol AUC predicted poorer delayed recall, accounting for 8% of the variance (Table 4, Model 3, persistent cortisol effect, $t(280)=3.10, p=.002$). However, the best predictor of delayed recall was the number of words encoded during total learning, accounting for 88% of the Level 2 variance (residual Level 2 variance in a model with only administrations and total learning = 1.07, SE = 0.32, compared with Table 3, Model 2). Therefore, a model in which cortisol predictors were tested for their effects on delayed recall above and beyond total learning was added (Table 3, Model 8). In this model, persistent cortisol AUC continued to predict fewer words recalled during delayed recall, accounting for 5% of the variance in delayed recall above and beyond total learning.

Verbal memory: Serial position

Model 3 was repeated with the outcome variable being the number of words recalled in the primacy positions (1 to 5 of 15), middle positions (6 to 10 of 15), and recency positions (11 to 15 of 15). Persistent cortisol AUC was significantly related to total learning only for

words in the primacy and middle positions (Table 4, persistent cortisol effect; $t(181)=3.38$, $p<.001$ and $t(181)=2.82$, $p=.005$, respectively). Although there remained a negative relationship with persistent cortisol AUC for words in the recency positions, this effect was substantially smaller and not statistically significant (Table 4, persistent cortisol effect, $t(181)=1.65$, $p=.10$). For delayed recall, persistent cortisol AUC associated with fewer words recalled from all three positions: primacy (effect = $-.33$, $t(285)=2.53$, $p=.012$), middle (effect = $-.48$, $t(283)=2.95$, $p=.003$), and recency (effect = $-.41$, $t(284)=2.77$, $p=.006$). In addition, as shown in the last 3 columns of Table 4, cortisol AUC was associated with worse delayed recall above and beyond total learning (i.e., greater retention loss) for the middle and recency positions.

Executive functions and subjective cognitive health

In order to test the specificity of the relationship between cortisol and verbal memory, Model 3 was repeated for executive functions and subjective cognitive function. Because these measures were taken semiannually rather than annually, Models 1 and 2 were re-estimated for each. (Note there was no significant random effect of “administrations” on subjective cognitive function, and so this effect was not included in Models 2 or 3 for this outcome. The fixed effect was included and shows a decrease in subjective cognitive function over time.) As shown in Table 5, there was not a significant effect of cortisol AUC at either Level 1 or Level 2 for either outcome: fixed effects were not statistically significant, there was not a substantial amount of variance accounted for, and model fit was not improved.

Discussion

Cortisol has been implicated in degeneration of the hippocampus and other brain regions involved in memory (3). In the present study, older adults (aged 60–93) with higher average cortisol AUC across a period of up to 5 years had poorer learning and recall in declarative verbal memory. In contrast, increases in cortisol AUC at a particular time point were not associated with decreases in memory performance. These results suggest that although short-term exposure to cortisol may affect cognitive performance (11), long-term exposure may be more important. Higher cortisol was also specifically related to memory; it did not significantly predict performance on the TMT or subjective cognitive function (c.f., 5–6, 13). It should be noted that persistently high cortisol AUC and, to a lesser degree, phasic increases in AUC were both associated with slower performance on the TMT (B-A; Table 5, Model 3), suggesting poorer executive function and cognitive flexibility. However, these effects were not statistically significant due to relatively high standard errors. In future, a battery of executive cognitive functions may provide a more reliable assessment of executive function and a clearer picture of its relationship to endogenous cortisol exposure.

Neither stress nor depression accounted for the relationship between cortisol and memory. Likewise, Peavy and colleagues (7) found cortisol effects on verbal declarative memory that were independent of stressful life events; cortisol and stress were themselves not significantly correlated. A lack of relationship between cortisol and stress might call into question the quality of measurement of one or both. However, further investigation revealed

that in the present sample, although persistently higher cortisol AUC was not related to persistently higher perceived stress, there was a significant within-person relationship: Visits with higher-than-usual cortisol AUC were characterized by significantly higher perceived stress scores (Level 1 effect=0.5, SE=0.2, $p<.005$). Therefore, phasic, within-person changes in cortisol related to changes in stress, whereas persistent, between-person cortisol differences related to memory performance. Cross-sectional data would not be able to yield this differentiation, further emphasizing the importance of the use of longitudinal studies to answer questions regarding stress, cortisol, and memory.

Older people have higher cortisol AUC (Table 1; 28). However, cortisol and age predicted memory relatively independently, with age accounting for 5% of the memory performance variance; cortisol, 3%; and their overlap, 2%. Therefore, cortisol can account for individual differences in declarative memory above and beyond age.

Persistently elevated cortisol was associated with a pattern of learning characteristic of dysfunctional memory: attenuated primacy (14–16, 29). Attenuated primacy was observed during the learning trials, suggesting cortisol relationships with long-term memory rather than short-term memory. Cortisol was not related to recall of words in the recency positions, which are retrieved from short-term memory during learning. However, persistently elevated cortisol was related to worse recall of words in all three positions after delay, which relies on encoding. For primacy positions, this effect was largely attributable to poorer learning; however, for middle and especially recency positions, the effect persisted after adjustment for learning. Persistently elevated cortisol was therefore associated with greater “retention loss” from the learning to delayed recall trials. Words in the recency positions may be the most susceptible to cortisol-mediated retention loss because they are rehearsed the least and have the weakest memory trace (14). Overall, the pattern of findings suggests that cortisol influences multiple parameters of declarative memory (encoding, retrieval, retention) in older adults. These data suggest the need for studies that evaluate declarative memory components to further elucidate the impact of cortisol levels on memory processes and associated brain regions (30,31).

The present sample constituted fairly homogenous, healthy, and well-educated older adults. Future research should investigate these relationships in more diverse samples. Effects of phasic cortisol changes on neuropsychological performance might have been larger if cortisol had been sampled on the day of testing. However, even 3 days of sampling resulted in a minimally reliable measurement of AUC change, and sampling over more days around the testing day might be even better for detecting within-person relationships. These limitations were offset by significant strengths, including multiple assessments of both cortisol and cognitive function over up to 5 years; distinguishing between persistent and phasic differences in cortisol AUC; and a large sample size relative to previous investigations that provided reasonable power to detect effects. These strengths contribute to the conclusion that among older adults, higher secretion of cortisol may, over time, contribute to memory dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding:

The work was supported by the Dana Foundation (to SCS) and the National Institute on Aging (R01-AG026307 and K02-AG033629 to SCS, F31-AG048692 to IAB, P30-AG028383 to Linda J. Van Eldik, and R01-AG038651 and R01-AG019241 to Frederick A. Schmitt). The authors thank David T.R. Berry, Ph.D. for his helpful comments on a previous version of this work.

Abbreviations

AIC	Aikake's information criterion
AUC	area under the curve
BIC	Bayes's information criterion
CV	Coefficient of variability
GDS	Geriatric Depression Scale
ICC	Intraclass correlation
PSS	Perceived Stress Scale
RAVLT	Rey Auditory Verbal Learning Test
TMT	Trail Making Test

References

1. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. *Psychol Aging*. 2002; 17:299–320. [PubMed: 12061414]
2. Mungas D, Beckett L, Harvey D, Tomaszewski Farias S, Reed B, Carmichael O, Olichney J, Miller J, DeCarli C. Heterogeneity of cognitive trajectories in diverse older persons. *Psychol Aging*. 2010; 25(3):606–619. [PubMed: 20677882]
3. McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol*. 1995; 5:205–216. [PubMed: 7620309]
4. Sauro MD, Jorgensen RS, Teal Pedlow C. Stress, glucocorticoids, and memory: a meta-analytic review. *Stress: The International Journal on the Biology of Stress*. 2003; 6(4):235–245.
5. Lee BK, Glass TA, McAtee MJ, Wand GS, Bandeen-Roche K, Bolla KI, Schwartz BS. Associations of salivary cortisol with cognitive function in the Baltimore memory study. *Arch Gen Psychiatry*. 2007; 64(7):810–818. [PubMed: 17606815]
6. Li G, Cherrier MM, Tsuang DW, Petrie EC, Colasurdo EA, Craft S, Schellenberg GD, Peskind ER, Raskind MA, Wilkinson CW. Salivary cortisol and memory function in human aging. *Neurobiol Aging*. 2006; 27(11):1705–1714. [PubMed: 16274857]
7. Peavy GM, Salmon DP, Jacobson MW, Hervey A, Gamst AC, Wolfson T, Patterson TL, Goldman S, Mills PJ, Khandrika S, Galasko D. Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry*. 2009; 166(12):1384–1391. [PubMed: 19755573]
8. Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ. Basal cortisol levels and cognitive deficits in human aging. *J Neurosci*. 1994; 14(5):2893–2903. [PubMed: 8182446]

9. Hellhammer J, Fries E, Schweisthal OW, Schlotz W, Stone AA, Hagemann D. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: state-and trait components. *Psychoneuroendocrinol.* 2007; 32(1):80–86.
10. Segerstrom SC, Boggero IA, Smith GT, Sephton SE. Variability and reliability of diurnal cortisol in younger and older adults: Implications for design decisions. *Psychoneuroendocrinology.* 2014; 49:299–309. [PubMed: 25137484]
11. Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry.* 1999; 56(6):527–533. [PubMed: 10359467]
12. Sephton SE, Studts JL, Hoover K, Weissbecker I, Lynch G, Ho I, McGuffin S, Salmon P. Biological and psychological factors associated with memory function in fibromyalgia syndrome. *Health Psychol.* 2003; 22(6):592–597. [PubMed: 14640856]
13. Wolf OT, Dziobek I, McHugh P, Sweat V, de Leon MJ, Javier E, Convit A. Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiol Aging.* 2005; 26(10): 1357–1363. [PubMed: 16243606]
14. Capitani E, Della Sala S, Logie RH, Spinnler H. Recency, primacy, and memory: Reappraising and standardising the serial position curve. *Cortex.* 1992; 28:315–342. [PubMed: 1395637]
15. Squire LR, Knowlton B, Musen G. The structure and organization of memory. *Ann Rev Psychol.* 1993; 44:453–495. [PubMed: 8434894]
16. Suhr J, Demireva P, Heffner K. The relation of salivary cortisol to patterns of performance on a word list learning task in healthy older adults. *Psychoneuroendocrinology.* 2008; 33(9):1293–1296. [PubMed: 18774653]
17. Bayley PJ, Salmon DP, Bondi MW, Bui BK, Olichney J, Delis DC, Thomas RG, Thal LJ. Comparison of the serial position effect in very mild Alzheimer's disease, mild Alzheimer's disease, and amnesia associated with electroconvulsive therapy. *Journal of the International Neuropsychological Society.* 2000; 6(03):290–298. [PubMed: 10824501]
18. Moser B, Deisenhammer EA, Marksteiner J, Papousek I, Fink A, Weiss EM. Serial position effects in patients with mild cognitive impairment and early and moderate Alzheimer's disease compared with healthy comparison subjects. *Dement Geriatr Cogn Disord.* 2013; 37(1–2):19–26. [PubMed: 24107650]
19. Schmidt, M. *Rey Auditory Verbal Learning Test: A handbook.* Los Angeles, CA: Western Psychological Services; 1996.
20. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;385–396. [PubMed: 6668417]
21. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1983; 17:37–49. [PubMed: 7183759]
22. Reitan, RM.; Wolfson, D. *The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation.* Tucson, AZ: Neuropsychology Press; 1985.
23. Crowe SF. The differential contribution of mental tracking, cognitive flexibility, visual search, and motor speed to performance on Parts A and B of the Trail Making Test. *J Clin Psychol.* 1998; 54:585–591. [PubMed: 9696108]
24. Sánchez-Cubillo I, Periañez JA, Adrover-Roig D, Rodríguez-Sánchez JM, Rios-Lago M, Tirapu J, Barcelo F. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society.* 2009; 15:438–450. [PubMed: 19402930]
25. Hayes, RD.; Sherbourne, CD.; Mazel, RM. *User's manual for the Medical Outcome Study (MOS) core measures of health-related quality of life.* Santa Monica, CA: RAND; 1995.
26. Myers ND, Brincks AM, Ames AJ, Prado GJ, Penedo FJ, Benedict C. Multilevel modeling in psychosomatic medicine research. *Psychosom Med.* 2012; 74:925–936. [PubMed: 23107843]
27. Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. *Psychological Methods.* 2007; 12(2):121–138. [PubMed: 17563168]
28. Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH. Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition,

- leptin levels, and aging in adult men and women. *J Clin Endocrinol Metab.* 2004; 89(1):281–287. [PubMed: 14715862]
29. Morris JC, McKeel DW Jr, Storandt M, Rubin EH, Price JL, Grant EA, Ball MJ, Berg L. Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology.* 1991; 41(4):469–478. [PubMed: 2011242]
30. Budson AE, Price BH. Memory dysfunction. *N Eng J Med.* 2005; 352(7):692–699.
31. Rugg MD, Vilberg KL. Brain networks underlying episodic memory retrieval. *Curr Opinion Neurobiol.* 2013; 23(2):255–260.

Table 1

Descriptive statistics and correlations between person-level variables (N = 132)

	Mean	SD	1	2	3	4	5	6	7	8
1. RAVLT total learning	43.6	9.7	-							
2. RAVLT delayed recall	9.2	3.2	.91**	-						
3. Cortisol AUC (log (ug/dL)/hr)	0.72	0.36	-.24*	-.24*	-					
4. Depressive symptoms	4.2	3.6	-.08	-.05	-.04	-				
5. Perceived stress	11.8	5.6	.16	.20*	-.06	.74**	-			
6. Metabolic index at study entry	1.25	0.79	.00	.03	.02	.04	-.05	-		
7. Age at study entry	74.6	6.2	-.35**	-.32*	.28*	.14	-.11	-.03	-	
8. TMT B-A	60.5	32.1	-.48**	-.48*	.01	.15	.08	.00	.32**	-
9. Subjective cognitive function	5.0	0.6	.20*	.13*	.06	-.54**	-.45**	.06	-.14	-.27*

Note: RAVLT = Rey Auditory Verbal Learning Test; AUC = area under the curve; TMT = Trail-Making Test*
 $p < .05$.**
 $p < .001$.

Table 2

Effects of cortisol AUC on RAVLT total learning (419 person-visits; estimates with standard errors)

Fixed effects	Increase in words recalled per:	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Intercept		43.9 (0.9)	43.5 (0.8)	43.6 (0.8)	43.7 (0.8)	43.5 (0.8)	43.7 (1.5)	48.8 (2.1)
Administrations	1 administration		0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Persistent cortisol log AUC (Level 2)	1 SD			-3.3* (1.1)	-3.4* (1.1)	-3.2* (2.2)	-3.3* (1.1)	-2.5* (1.1)
Phasic cortisol log AUC (Level 1)	1 SD			0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Depressive symptoms	1-point increase (0–30)				-0.2 (0.2)			
Perceived stress	1-point increase (0–40)					0.3* (0.1)		
Metabolic index	1 indicator						-0.05 (1.0)	
Age at study entry	1 year							-0.4* (0.1)
Level 2 variance		83.0 (11.7)	68.7 (11.3)	64.7 (10.7)	64.6 (10.7)	61.1 (10.3)	64.7 (10.7)	61.6 (10.3)
Administrations slope variance			3.3 (1.1)	3.3 (1.2)	3.3 (1.1)	3.2 (1.2)	3.3 (1.2)	3.4 (1.2)
Level 2 –slope covariance			3.7 (2.9)	2.8 (2.8)	2.5 (2.8)	3.2 (2.8)	2.8 (2.8)	1.7 (2.8)
Level 1 variance		29.9 (2.5)	23.1 (2.4)	22.8 (2.3)	22.8 (2.3)	22.9 (2.3)	22.8 (2.3)	22.8 (2.3)
ICC		.74						
AIC		2906.0	2882.1	2876.5	2877.7	2874.0	2878.5	2871.7
BIC		2914.7	2899.4	2899.6	2903.6	2900.0	2904.4	2897.6

Note: AUC = area under the curve; RAVLT = Rey Auditory Verbal Learning Test; ICC = intraclass correlation; AIC = Akaike's information criterion; BIC = Bayes's information criterion.

* $p < .05$.

Table 3

Effects of cortisol AUC on RAVLT delayed recall (414 person-visits; estimates with standard errors)

Fixed effects	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Intercept	9.33 (0.28)	9.01 (0.14)	9.06 (0.30)	9.19 (0.45)	7.72 (0.64)	8.89 (0.52)	10.72 (0.74)	10.67 (0.19)
Administrations		0.14 (0.07)	0.14 (0.08)	0.14 (0.08)	0.14 (0.08)	0.14 (0.08)	0.13 (0.08)	0.05 (0.07)
Persistent cortisol log AUC (Level 2)			-1.19* (0.38)	-1.20* (0.38)	-1.13* (0.38)	-1.19* (0.28)	-0.91* (0.39)	-0.41* (0.19)
Phasic cortisol log AUC (Level 1)			0.09 (0.12)	0.09 (0.12)	0.09 (0.12)	0.09 (0.12)	0.09 (0.12)	0.01 (0.12)
Depressive symptoms				-0.92 (2.34)				
Perceived stress					1.14* (0.49)			
Metabolic index						0.14 (0.35)		
Age at study entry							-0.11* (0.05)	
Total learning								0.24** (0.01)
Level 2 variance	9.27 (1.30)	9.26 (1.25)	8.56 (1.21)	8.56 (1.21)	8.10 (1.17)	8.55 (1.21)	8.12 (1.16)	1.02 (0.32)
Level 1 variance	3.20 (0.27)	3.17 (0.27)	3.16 (0.27)	3.16 (0.26)	3.17 (0.27)	3.16 (0.27)	3.16 (0.27)	3.28 (0.29)
ICC	0.74							
AIC	1953.5	1951.8	1946.0	1947.8	1942.6	1947.8	1942.2	1767.2
BIC	1962.2	1963.3	1963.3	1968.0	1962.8	1968.0	1962.4	1787.4

Note: AUC = area under the curve; RAVLT = Rey Auditory Verbal Learning Test; ICC = intraclass correlation; AIC = Akaike's information criterion; BIC = Bayes's information criterion.

*
p < .05.

**
p < .001

Table 4

Effects of cortisol AUC on total learning and delayed recall for different word positions (419 person-visits; estimates with standard errors)

	Total learning			Delayed recall		
	Primacy	Middle	Recency	Primacy	Middle	Recency
Fixed effects						
Intercept	13.3 (.3)	13.2 (.4)	17.2 (.8)	3.44 (.08)	3.00 (.08)	2.59 (.11)
Administrations	0.3 (.1)	0.1 (.2)	0.0 (.3)	0.0 (.04)	0.01 (.04)	0.06 (.04)
Persistent cortisol log AUC (Level 2)	-1.3** (.4)	-1.5* (1.1)	-0.7 (.4)	-0.11 (.09)	-0.21* (.09)	-0.32* (.13)
Phasic cortisol log AUC (Level 1)	0.03 (.2)	0.3 (.2)	-0.05 (.2)	0.00 (.06)	-0.05 (.06)	0.06 (.07)
Total learning				0.19** (.01)	0.20** (.01)	0.12* (.02)
Level 2 variance	7.9 (1.5)	13.1 (2.8)	8.7 (2.0)	0.23 (.07)	0.12 (.06)	0.57 (.13)
Administrations slope variance	0.4 (.2)	1.1 (.8)	0.8 (.3)			
Level 2 –slope covariance	-0.5 (.5)	0.5 (.4)	-1.0 (.7)			
Level 1 variance	5.2 (.5)	9.7 (1.0)	7.6 (.7)	0.75 (.06)	0.92 (.08)	1.14 (.10)

Note: AUC = area under the curve.*
 $p < .05$.**
 $p < .001$.

Table 5

Effects of cortisol AUC on executive functions (TMT B – A) and subjective cognitive function (793 person-visits; estimates with standard errors)

	TMT B - A			Subjective cognitive function		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Fixed effects^a						
Intercept	58.3 (2.4)	56.5 (2.8)	56.8 (2.8)	5.04 (0.05)	43.5 (0.8)	43.6 (0.8)
Administrations		0.6 (0.4)	0.4 (0.5)		–0.01* (0.006)	–0.01* (0.006)
Persistent cortisol log AUC (Level 2)			1.9 (3.4)			0.06 (0.07)
Phasic cortisol log AUC (Level 1)			1.0 (1.4)			–0.01 (0.02)
Level 2 variance	578.1 (98.7)	552.5 (125.5)	554.8 (126.0)	0.29 (0.04)	0.29 (0.04)	0.29 (0.04)
Administrations slope variance		8.4 (4.5)	8.6 (4.5)			
Level 2 –slope covariance		–10.2 (22.2)	–12.0 (22.5)			
Level 1 variance	880.9 (48.8)	827.9 (49.0)	827.1 (49.0)	0.15 (0.01)	0.15 (0.01)	0.15 (0.01)
ICC	.40			.65		
AIC	7826.9	7828.5	7831.7	1084.7	1080.2	1083.0
BIC	7841.5	7844.8	7854.7	1093.3	1091.8	1100.3

Note: AUC = area under the curve; ICC = intraclass correlation; AIC = Akaike's information criterion; BIC = Bayes's information criterion.

* $p < .05$.