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Subjective Memory Complaints are Associated with Diurnal Measures of Salivary Cortisol in Cognitively Intact Older Adults

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Abstract

Objective—To investigate the relationship between subjective memory complaints (SMC) and the stress hormone cortisol using diurnal measures in older, cognitively intact subjects.

Methods—This cross-sectional study conducted at a university research center included 64 volunteers (with or without SMC) with a mean age of 78.6 years (± 6.3) and diagnosis of cognitively normal based on objective neuropsychological testing. Measures of diurnal salivary cortisol, depressive symptomatology, episodic memory performance, level of anxiety, and Apolipoprotein E (APOE) e4 allele status were obtained.

Results—In multivariate logistic regression analyses with SMC as outcome, averaged post-peak cortisol, the cortisol awakening response, and depressive symptomatology were significant predictors, while gender, memory performance, anxiety and APOE-e4 status were not.

Conclusions—Significant associations between SMC and diurnal measures of cortisol in cognitively intact elderly suggest that HPA axis dysfunction may contribute to early neuropathological changes in older adults who complain of memory decline undetected on neuropsychological testing.

Keywords

dementia; chronic stress; Alzheimer's disease; depression; Apolipoprotein E

OBJECTIVE

Subjective memory complaints (SMC) have been associated with progressive cognitive decline (1), as well as depression (1, 2) and self-report measures of stress (3). Chronic stress in older adults can lead to dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) axis

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that regulates response to stress, subsequently affecting the hippocampus, a brain region critical for memory (4).

A previous study found an association between nocturnal measures of the stress hormone cortisol and SMC in groups of cognitively intact, middle-aged to young-elderly individuals (mean age 61.8 years) (5). To further investigate the relationship of SMC with **measures of cortisol that may be related** to chronic stress, we investigated the degree to which specific aspects of the diurnal cortisol cycle predict SMC in a sample of older, cognitively normal individuals, taking variables previously found to be associated with SMC into account.

METHODS

Participants

Volunteers over age 65 and living independently were recruited from the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC) longitudinal cohort and the UCSD ADRC Memory Screening Clinic. Senior neurologists assigned a diagnosis based on medical, functional, neurological, and neuropsychological information. Only cognitively normal individuals (n=64) were included. Exclusions included significant medical disorders (e.g., insulin-dependent diabetes), prominent psychiatric conditions (e.g., severe depression), and use of medications that could affect daily cortisol production. Topical corticosteroids were permitted, as were steroidal inhalants if discontinued the day before and day of sampling. Other medications were allowed if participants maintained a stable dose for at least six months prior to baseline.

Trained psychometrists administered a neuropsychological battery assessing memory, attention, executive function, visuospatial ability, and language. Study personnel, including reviewing neurologists, were blind to cortisol measures. The subject and a knowledgeable study partner signed separate written informed consents approved by the UCSD Human Research Protections Program.

Measures

Subjective Memory Complaint was determined by a yes/no response to a verbal question of problems with memory representing a change from previous abilities. **The Geriatric Depression Scale** (GDS) (6) is a reliable, valid self-rating questionnaire designed for elderly. **The Mattis Dementia Rating Scale** (DRS) (7) estimates global cognition. **The California Verbal Learning Test** (CVLT) (8) assesses episodic memory including long delay free recall. **The State-Trait Anxiety Inventory** (STAI) (9) measures trait anxiety, a relatively stable tendency to perceive stressful situations as threatening.

Cortisol Levels—Saliva samples ("Salivettes" by Sarstedt) were used to assess circulating cortisol levels. The samples were frozen (−20°C) until delivered to the UCSD General Clinical Research Core Laboratory. Cortisol EIA kits (Cat# 1-3002) were purchased from Salimetrics LLC, State College, PA. Samples, standards, controls and Cortisol-HRP conjugate were added to a micro-plate coated with mAb to cortisol and incubated at room temperature for 1 hour; unbound components were washed and bound cortisol-HRP was measured using tetramethylbenzidine (TMB) substrate. The color was read on a Spectramax M-5 Plate reader equipped with SoftmaxPro v5.2, and a 5-parameter sigmoid minus curve fit to the calibration standards determined sample concentrations. The intra and inter assay precisions were 0.01-2.5% and 3.0-8.0% respectively. The CV of duplicates varied from 0.01 to 2.5%.

Subjects provided saliva samples in their home at awakening, 30 minutes later, 2 pm, 4 pm and just before sleep. We calculated the mean of all five measures (diurnal average), the post-peak mean of 2 pm, 4 pm, and bedtime measures, and the change from awakening to 30 minutes later (cortisol awakening response or CAR). Post-peak average and CAR were used in statistical modeling based on previous studies (10) supporting an association of higher post-peak average and/or decreased CAR rise with HPA axis dysfunction.

Statistical analyses—Univariate comparisons of subjects with and without SMC were by t-test (age, CVLT recall, CAR) or the nonparametric **Mann-Whitney U test** (education, DRS, GDS and STAI scores, diurnal average and post-peak cortisol). Chi-square analyses were used to compare SMC groups by gender and the presence of at least one Apolipoprotein E, e4 allele (APOE-e4). Multivariate logistic regression analysis was used to test the association between simultaneously entered predictor variables, GDS, CAR, and post-peak cortisol, and the outcome variable SMC after controlling for potential co-variables. Only terms with p-values < 0.10 in univariate comparisons were included in the multivariate logistic model. Analyses were performed using SPSS 16.0; statistical significance of multivariate model terms was set at p<.05.

RESULTS

Thirty-nine of the 64 subjects (60.9%) reported SMC at baseline. Mean age of the total sample was 78.6 years (SD±6.3; range 65-97), education, 15.9 years (±3.1;6-20), DRS total score, 138.7 (±3.9;128-144), GDS score, 5.1 (±5.1;0-22), and STAI score, 33.5 (±10.1;20-61). T-tests revealed no significant differences between SMC groups on age [with SMC: 78.5(±5.4), without SMC: 78.7(±7.7)]; subjects with SMC scored lower on the CVLT long delay free recall z-score [-0.31(±0.87), 0.30(±1.0)] (t=2.57; df=62;p<.02). There were no significant differences between SMC groups on mean education [16.0(±3.5), 15.7(±2.4)], anxiety score [34.3(±10.6), 32.1(±9.4)], or DRS total [138.2(±3.6), 139.6(±4.1)]. Subjects with SMC, however, acknowledged more depressive symptomatology [6.2(±5.6), 3.4(±3.8)] (U=312.5;p<.03). There were equal numbers of women with and without SMC, but a higher proportion of men (79.2 percent) with complaints than without (Chi-square=5.36; df=1;p<.03). A comparison of SMC for APOE-e4 carriers (41.2%, 58.8%) and non-carriers (68.1%, 31.9%) did not reach significance (**Chi-square=3.80; df=1;p<.06**).

Subjects with SMC had a lower CAR [-0.83(±4.2), 3.1(±5.9)] (t=2.9; df=52;p<.01) than subjects without SMC. There were no significant differences between SMC groups on cortisol diurnal average [6.3(±4.2), 4.6(±3.5)], but subjects with SMC showed higher levels of post-peak cortisol [4.1,(±3.3), 2.0(±1.4)] (U=222.0;p<0.01) than those without SMC.

In the logistic regression model predicting SMC, significant variables after controlling for gender, memory performance, and APOE-e4 status included depressive symptomatology, post-peak cortisol, and CAR slope. Each point increase in GDS score and each unit (nmol/L) increase in post-peak cortisol was associated with increased odds of SMC of 1.28 (**CI: 1.03-1.58**) and 1.83 (**CI: 1.10-3.05**), respectively (see Table). Each unit (nmol/L) increase in CAR was associated with a 0.78 decreased odds of SMC (CI: 0.62-0.98); for example, a 2 point difference in CAR predicts a $0.78^2 = 0.61$ **decreased odds of SMC, etc.** Removing APOE-e4 status from the regression did not change the model appreciably. Trait anxiety, when added as a predictor, did not reach significance and did not appreciably modify other terms. When an APOE-e4 by depression interaction term was added, it did not reach significance and did not appreciably modify other terms.

CONCLUSIONS

We found that measures of cortisol (post-peak, CAR) and depressive symptomatology independently contributed to the prediction of SMC in older adults intact on neuropsychological testing. Like Wolf et al. (5), we carefully excluded subjects with MCI and dementia. However, our study measured diurnal cortisol in an older cohort, while Wolf and colleagues measured nighttime cortisol in a somewhat younger sample. The consistency in the association between SMC and cortisol measures found in both studies, however, is notable and strengthens existing evidence of a meaningful relationship between SMC and HPA axis dysfunction. While these studies cannot establish causality, it is plausible that perception of memory loss in older individuals contributes to persisting distress and anticipation of further loss of memory and independence. These responses may initiate and sustain a vicious cycle in which chronic stress leads to HPA axis dysfunction resulting in neuropathological changes and further cognitive decline.

Subjects with SMC in our sample acknowledged significantly more depressive symptomatology than those without SMC as in previous studies (11). The association of gender with SMC has been inconsistent in previous studies (1, 11, 12). In our study, male gender was associated with SMC in a univariate analysis, but was not a significant predictor of SMC in the regression model controlling for co-variables. Among the men, the high proportion with complaints (79.2%) could be related to a tendency for men to volunteer primarily due to concern about memory loss.

Previous studies also have reported inconsistent findings concerning the relationship between objective memory performance and SMC (1, 12). In our study, the delay recall score was significantly lower for subjects with SMC in univariate analysis, but not in the logistic regression model co-varying for gender, depression, and cortisol variables. Limitations that may have influenced our findings include the relatively small sample size, sampling method requiring volunteer participants, and restricted assessment of SMC. Differences in broader methodological issues such as statistical analyses applied, choice of co-variables, and presence and length of follow-up also may account for inconsistencies (1).

In summary, we found an association between SMC and specific measures of the cortisol diurnal rhythm that may reflect HPA axis dysfunction in older, cognitively intact adults. Longitudinal studies will improve speculation concerning causative links. However, our findings suggest that specific behavioral markers may reflect changes that are associated with a neuropathological process, and if so, may aid in preclinical identification of heightened risk for dementia. Easily acquired, inexpensive methods can reduce harmful responses to chronic stress. Therefore, targeting HPA axis dysfunction in the earliest stages of neurodegeneration could lead to disease modification prior to clinical manifestations and loss of independence.

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REFERENCES

1. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry*. 2000; 15:983–991. [PubMed: 11113976]
2. Reid LM, MacLulich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord*. 2006; 22:471–485. [PubMed: 17047326]
3. Potter GG, Hartman M, Ward T. Perceived stress and everyday memory complaints among older adult women. *Anxiety Stress Coping*. 2009; 22:475–481. [PubMed: 19337885]
4. Lupien SJ, Maheu F, Tu M, et al. The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain Cogn*. 2007; 65:209–237. [PubMed: 17466428]
5. Wolf OT, Dziobek I, McHugh P, et al. Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiol Aging*. 2005; 26:1357–1363. [PubMed: 16243606]
6. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982; 17:37–49. [PubMed: 7183759]
7. Mattis, S. DRS: Dementia Rating Scale professional manual. Psychological Assessment Resources; New York: 1988.
8. Delis, D.; Kramer, J.; Kaplan, E., et al. The California Verbal Learning Test. The Psychological Corporation; New York: 1987.
9. Spielberger, C. Manual for State-Trait Anxiety Inventory. Consulting Psychologists Press; Palo Alto: 1983.
10. Evans PD, Fredhoi C, Loveday C, et al. The diurnal cortisol cycle and cognitive performance in the healthy old. *Int J Psychophysiol*. 2011; 79:371–377. [PubMed: 21185883]
11. Slavin MJ, Brodaty H, Kochan NA, et al. Prevalence and predictors of “subjective cognitive complaints” in the Sydney Memory and Ageing Study. *Am J Geriatr Psychiatry*. 2010; 18:701–710. [PubMed: 21491631]
12. Benito-Leon J, Mitchell AJ, Vega S, et al. A population-based study of cognitive function in older people with subjective memory complaints. *J Alzheimers Dis*. 2010; 22:159–170. [PubMed: 20847410]

Multivariate logistic regression analysis of subjective memory complaint testing the simultaneous influence of GDS score and salivary cortisol measures (Post-peak cortisol, CAR slope) after controlling for gender, CVLT long delay free recall score, and APOE-e4 status.

Table

Significant Variables	Wald Chi-square	df	p-value	Odds Ratio	95.0% C.I.
GDS score	5.02	1	< 0.03	1.28	1.03 1.58
Post-peak cortisol	5.41	1	0.02	1.83	1.10 3.05
CAR Slope	4.47	1	< 0.04	0.78	0.62 0.98

Model: Chi-square=29.22; df=6; p<.001

GDS = Geriatric Depression Scale

Post-peak cortisol = mean of 2 PM, 4 PM and bedtime samples (nmol/L)

CAR = Cortisol Awakening Response, Slope=30 minute after awakening - awakening (nmol/L)

CVLT = California Verbal Learning Test

APOE-e4 = Apolipoprotein E, e4 allele

C.I. = Confidence Intervals for Odds Ratio