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Subjective memory complaints in aging are associated with elevated cortisol levels

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Abstract

The origin and clinical significance of subjective memory complaints among middle aged and older individuals is not well understood. Associations with objective memory impairments, personality traits or mood disturbances have been reported. Elevated cortisol levels occur in aging and depression and causal links to cognitive or emotional problems have been suggested. The goal of this study was to investigate the associations between basal and feedback indices of cortisol regulation and subjective memory impairment in a sample of healthy middle aged and older subjects (mean age 61.8 years) with ($n = 27$) and without ($n = 19$) subjective memory complaints. Participants with memory complaints had both higher basal cortisol levels and higher cortisol levels after dexamethasone. There was a significant group by gender interaction for basal cortisol levels, where women without memory complaints showed significantly lower cortisol levels, whereas no such difference was found for the men. All effects were not due to slight differences in depression scores. Differences in personality traits or in stress susceptibility might underlie the present findings. Future studies of memory complaints should take a comprehensive approach including relevant endocrine parameters.

Keywords: Aging; Hormones; HPA axis; Subjective memory complaints; Cognition; Depression; Cross-sectional study

1. Introduction

Subjective memory complaints in the absence of verifiable cognitive dysfunction are common among midlife and older individuals, yet the reasons for these memory complaints remain unclear. Our understanding of the predictive value of subjective memory complaints for future cognitive decline is still rudimentary. Subjective memory complaints are prevalent in 25–50% folder individuals [17]. Cross-sectional studies relating subjective memory complaints to objective memory impairment have resulted in inconsistent findings, with about 50% of reports finding an association and the remaining finding none [17]. Despite the lack of consistent cross-sectional associations between subjective and objective memory complaints, the majority of community-based studies observed longitudinal associations between subjective memory complaints and future cognitive decline (e.g. [7,18,35,36,40]).

The hypothalamus–pituitary–adrenal (HPA) axis and its role in stress regulation have been of particular interest in the study of neuroendocrine influences on cognition in aging. It has been suggested that repeated or prolonged 'hits' to this system (the so-called allostatic load) will have a negative impact on multiple physiological systems, including some in the brain [25,27]. Alterations of this neuroendocrine axis have been associated with normal aging, however causal links of HPA axis dysregulation to impaired cognition and mood disturbances also have been established (see below), and thus the interactions of age, memory complaints, and mood disturbances are not easy to disentangle. Age is linked to higher basal cortisol levels [41] and reduced feedback sensitivity of

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the axis to pharmacological challenges [14,20,43,45]. However, the literature on the feedback sensitivity of the axis is somewhat mixed and a large inter-individual variance appears to exist [38]. In addition to the cross-sectional individual variability, there may be variability that is only apparent with longitudinal observation. For example, in one longitudinal study, Lupien et al. demonstrated the existence of subgroups of elderly subjects with stable versus increasing basal cortisol levels after tracking this cohort over a period of years [21].

Hyperactivity of the HPA axis is also often observed in depressive disorder and a causal role has been suggested [15,28]; similar associations between self-reported depressive symptoms and higher cortisol levels have been observed in normal healthy volunteers [32]. Subjective memory complaints in younger people often are associated with depression (e.g. [6,29]) or anxiety [5], both of which are stress-related disorders. The influence of stress-related increases in plasma cortisol levels and acute cortisol administration on memory has been demonstrated in both animals [4,34] and humans [22,44]. While the consolidation of emotional material is enhanced by cortisol, it also can impair declarative memory retrieval and working memory [34,44]. Chronically elevated cortisol levels due to stress, aging, or disease lead to memory impairments and structural alterations in the brain [24]. Studies in rodents have demonstrated that chronic stress is associated with elevations in endogenous corticosterone (the rat equivalent of cortisol), resulting in impaired spatial memory [2], dendritic atrophy [26], and reduced neurogenesis in the hippocampus [10]. Moreover, old animals with elevated corticosterone levels show impaired memory while older animals with stable levels do not [16].

Taken together there is evidence that cortisol levels and HPA axis control are associated with memory during aging and may play a role in the correlation of mood symptoms with subjective memory complaints in younger people. However, we are not aware of any reports examining the relationship between subjective memory complaints, HPA axis function, and mood among older subjects. We examined the associations between several measures of HPA activity and subjective memory complaints in a cohort of healthy midlife and elderly subjects. Since the HPA axis has been linked to both memory impairments and depression/anxiety, we measured mood symptoms so as to assess the relationship between subjective memory complaints and enhanced HPA axis activity, while being able to account for mood symptoms.

2. Methods

2.1. Patient recruitment

Sixty-seven consecutively screened healthy community-residing middle-aged and elderly non-demented individuals were initially selected for evaluations. Subjects represent a typical research clinic population and were not drawn randomly from the general population. They are volunteers responding to media coverage of our research program, individuals with concerns about their memory, relatives of demented individuals being evaluated in our NIH Aging and Dementia Core Center, or individuals responding to advertisements on the web. Study subjects underwent medical, neurological, psychiatric, neuropsychological MRI, and endocrine evaluations. Individuals with significant neurological, medical, or psychiatric disease were excluded as were those currently taking glucocorticoids or who had received them in the prior 6 months. This study was approved by the Institutional Board of Research Associates of the New York University School of Medicine. All study subjects gave written informed consent to participate.

Out of the initial 67 subjects, 10 were excluded due to the presence of mild cognitive impairment (for definition see below) and another 11 were excluded due to the presence of diabetes. Individuals were considered diabetic if they had a fasting blood glucose level greater than 125 mg/dl on two separate occasions or if they were being treated with hypoglycemic agents. Individuals with a history of elevated glucose levels that were well controlled by diet alone were not considered diabetic. Therefore, we included 46 subjects in the current analyses. The use of anti-hypertensives ($n = 8$), statins ($n = 8$), diuretics ($n = 2$) or estrogens ($n = 2$) was permitted. Subjects using those medications were evenly distributed between the two groups (all p's $> .50$).

2.2. Definition of subjective memory complaints

The Global Deterioration Scale (GDS) [33] was used to assign subjects into groupings consistent with their overall level of functioning. The GDS is a structured clinical assessment administered by a trained clinician, which is used to determine levels of impairment in memory, concentration, motor ability, language production and self-care in older populations. The scale has been shown to have very high inter-rater reliability [9]. Individuals being evaluated are assigned a rating of 1 through 7 using clearly operationalized criteria, with higher numbers indicating greater impairment. Individuals with a score of 1 or 2 are functioning in the normal range; those with a GDS score of 1 have no subjective memory complaints (they feel their memory is no different than it was when they were in their 20s) and on careful evaluation have no memory deficits. Those individuals with a GDS score of 2 have subjective memory complaints, but on careful evaluation are found not to have objective memory deficits. Subjects assigned a score of 3 on the GDS, have both subjective memory complaints and functional deficits, but do not fulfill diagnostic criteria for dementia. This group has been referred to as having Mild Cognitive Impairment (MCI). A GDS of 4 or higher is given to subjects with dementia [33].

2.3. Subjective memory questionnaire

In a subset of subjects, memory complaints were further characterized using the Memory Assessment Clinics Ques-

tionnaire (MAC-Q), a 6-item questionnaire requiring the subjects to rate their memory (in comparison to what it was like when they were in high school) in specific situations on a 5-point scale [3]. Higher test scores reflect greater memory complaints.

2.4. HPA measures

The assessment of cortisol level and HPA axis regulation entailed the measurement of nocturnal (12 h) urinary free cortisol excretion and an evaluation of HPA axis feedback inhibition by means of the combined DEX/CRH test.

2.4.1. 12 h night-time (8:00 p.m. to 8:00 a.m.) free cortisol

This measurement of basal HPA activity was chosen because it has been associated with memory performance in a population of elderly humans [37] and avoids some of the variability inherent in 24 h determinations due to individual differences in daytime activity patterns. This measure provides a global index of the total amount of cortisol produced when the subject is not very active, and therefore, is more reflective of basal secretion. The 12 h night sample has been shown to correlate fairly well with 24 h urine samples [37]. The total overnight 12 h cortisol excretion was used as an independent variable in the analyses.

2.4.2. DEX/CRH challenge test

The combination of dexamethasone and corticotropin releasing hormone (CRH) has been shown to be particularly sensitive in unmasking subtle HPA alterations, which may not be detected by baseline cortisol levels. Elderly subjects as well as depressed patients show larger cortisol and ACTH responses to CRH after dexamethasone pretreatment [13,14,20]. In this study we carried out the simplified DEX/CRH test, which uses only five blood samples and is more cost effective [13]. We used the average baseline levels and the incremental change (last sample minus baseline) for cortisol and ACTH as variables of interest.

Subjects took 1.5 mg of dexamethasone orally at 23:00 h the day before they came into the laboratory for the CRH test. On the day of the test subjects arrived to the laboratory by 13:00 h and were provided with a standardized lunch. After lunch, an intravenous catheter was placed in the forearm between 13:30 and 13:45 h and kept patent with a heparin lock. The subject was asked to sit quietly (but not allowed to sleep) in an easy chair in a quiet room. The subject was allowed to read. No blood samples were drawn for at least 1 h after the placement of the IV catheter to allow sufficient time for cortisol levels to return to baseline after the stress of the catheter insertion. Two baseline blood samples were drawn at 14:50 and 14:55 h. At 15:00 h, 100 μg of CRH (ACTHREL, Ferring Pharmaceuticals, Inc.) was given intravenously. After the CRH injection the catheter was flushed with 10 cm^3 of normal saline solution. Subsequently blood samples for cortisol and ACTH analysis were drawn at 15:30, 15:45, 16:00, and 16:15 h. Six milliliters of blood was collected into two chilled 3 cm^3 EDTA tubes at each time point. Bloods were kept on ice and immediately spun down in a refrigerated centrifuge. Plasma and serum were separated into aliquots and frozen at −80 °C.

2.5. Hormone assays

Total blood plasma cortisol was measured with a commercial enzyme immunoassay (EIA; IBL, Hamburg, Germany) with a sensitivity of 0.1 μg/dl. Adrenocorticotropin (ACTH) was measured with a RIA (Nichols Institute, Bad Nauheim, Germany) with a sensitivity of 2 pg/ml. Free urinary cortisol was measured with a radioimmunoassay that utilizes a double antibody (Diagnostics Product Corporation (DPC)). All assays had inter- and intra-assay coefficients of variance below 12%.

2.6. Neuropsychological measures

The cognitive battery included, among other tests, an assessment of intelligence using the Shipley Intelligence Quotient [46], the declarative memory tests of immediate and delayed recall of two paragraphs from the Guild Memory Test [8], and Digit Span forwards and backwards taken from the Wechsler Adult intelligence Scale (WAIS-R) [42]. In order to allow comparison to other studies, the Mini Mental State Exam (MMSE) [1] was also used.

2.7. Psychological measures

Given the links between HPA axis function, depression, and memory dysfunction [15,28], we administered the Hamilton Psychiatric Rating Scale for Depression [12] in order to assess for objective symptoms of depression.

3. Results

3.1. Demographic and neuropsychological measures

There were 19 subjects with no subjective memory complaints and 27 with such complaints but with no evidence of cognitive impairment. The two groups did not differ in age, gender distribution, MMSE scores, education, IQ, paragraph recall (immediate and delayed), or digit span. They also did not differ in current or past antidepressant use. They did, however, differ in Hamilton depression scores (see additional analysis below) and body mass index (BMI). Means, standard errors, and p levels are presented in Table 1.

3.2. Subjective memory questionnaire

Data from the MAC-Q was available for 29 out of the 42 subjects (11 without and 18 with memory complaints). Subjects without memory complaints had a significantly lower

Table 1
Demographic and cognitive data of subjects without and with memory complaints

	No memory complaints ($n = 19$)	Subjective memory complaints ($n = 27$)	p level (t tests or Chi-square)
Age	60.34 ± 2.14	62.86 ± 1.57	$t = -0.98$, $p = .34$
MMSE	29.37 ± 0.21	29.07 ± 0.23	$t = 0.92$, $p = .36$
Gender (F/M)	(9/10)	(16/11)	$\chi = .64$, $p = .43$
Antidepressant use (no/history of/yes)	(13/0/6)	(20/2/5)	$\chi = 2.25$, $p = .32$
BMI (kg/m^2)	28.05 ± 1.11	25.49 ± 0.58	$t = 2.20$, $p = .03$
Hamilton (maximum possible score is 52)	1.21 ± 0.36	3.37 ± 0.53	$t = -3.09$, $p = .003$
Education (years)	16.16 ± 0.39	16.27 ± 0.44	$t = -0.18$, $p = .86$
Shipley IQ	116.28 ± 1.73	116.25 ± 1.67	$t = 0.01$, $p = .99$
Digits forwards	9.16 ± 0.46	9.30 ± 0.44	$t = -0.21$, $p = .83$
Digits backwards	8.26 ± 0.46	7.81 ± 0.53	$t = 0.61$, $p = .55$
Guild paragraphs immediate	7.66 ± 0.51	7.41 ± 0.44	$t = 0.38$, $p = .71$
Guild paragraphs delayed	9.08 ± 0.79	9.08 ± 0.55	$t = 0.00$, $p = .99$

total complaint score (21.27 ± 1.09 versus 25.22 ± 1.10; $t = -2.4$, $p < .05$). Looking at the individual items, subjects with subjective memory complaints reported a significantly poorer performance in remembering the name of a person they had just met (item 1), recalling where they had put objects (item 3), as well as in the general comparison of their overall current memory relative to their high school years (item 6). Two additional items revealed trends with subjects with subjective memory complaints having more trouble to recognize people who recognize them (item 4) and remembering items they intended to buy (item 5). Both groups were similar in recalling phone numbers or zip codes that they used on a daily or weekly basis (item 2).

3.3. HPA axis measures

Subjects with no memory complaints had lower ($p = .05$) 12 h urinary cortisol levels. In addition they tended ($p < .10$) to have lower cortisol as well as ACTH levels during the dexamethasone/CRH challenge. Although subjects with subjective memory complaints had higher basal cortisol values after dexamethasone pre-treatment, there were no statistically significant difference between the groups in cortisol or ACTH increase after CRH injection, (see Table 2 for means, standard errors as well as p levels).

3.3.1. Influence of gender and depression

3.3.1.1. Univariate analysis with t tests. For those HPA axis variables that differed between subjects with and without memory complaints (urinary cortisol, cortisol after dexamethasone, or ACTH after dexamethasone), there were no gender differences. However, women tended to show a more pronounced cortisol and ACTH increase in response to CRH administration ($p < .10$).

Subjects with current or past antidepressant use ($n = 13$) did not differ significantly from the rest of the subjects in any of the assessed HPA axis measures (data not shown).

3.3.1.2. Associations between age, BMI, Hamilton depression scale scores, and HPA axis measures. Subjects with and without memory complaints differed in BMI, Hamilton scores, and age. We have no explanation for the higher BMI for those subjects without subjective memory complaints. Given the group differences for BMI, Hamilton scores, and age, we ascertained whether there were any associations between those variables and the HPA measures. Analysis using Pearson's correlations indicated that none of these measures was associated with any of the five HPA axis measures (all p's $> .10$).

3.3.1.3. Analysis of covariance. Since study participants with subjective memory complaints endorsed a slight, but significantly, higher number of items in the Hamilton depression scale (see Table 1), we performed additional analyses in order to exclude the possibility that the observed associations between memory complaints and HPA axis measures were not simply reflecting differences in depression. Two factorial ANCOVAs (memory complaints and gender as independent factors and Hamilton score as covariate) were computed for the three HPA axis measures that had differed between the groups in the initial t-test analysis.

Table 2
HPA measures of subjects without and with memory complaints

	No memory complaints ($n = 19$)	Subjective memory complaints ($n = 27$)	p level (t tests)
Urinary cortisol (μg)	18.67 ± 4.08	30.49 ± 4.04	$t = -2.00$, $p = .05$
Cort after dexamethasone (μg/dl)	1.19 ± 0.14	1.92 ± 0.30	$t = -1.95$, $p = .06$
ACTH after dexamethasone (pg/ml)	3.50 ± 0.72	7.31 ± 1.75	$t = -1.75$, $p = .09$
Cort increase after CRH (μg/dl)	6.38 ± 1.54	9.60 ± 1.96	$t = -1.20$, $p = .24$
ACTH increase after CRH (pg/ml)	18.24 ± 3.98	27.45 ± 4.97	$t = -1.35$, $p = .18$

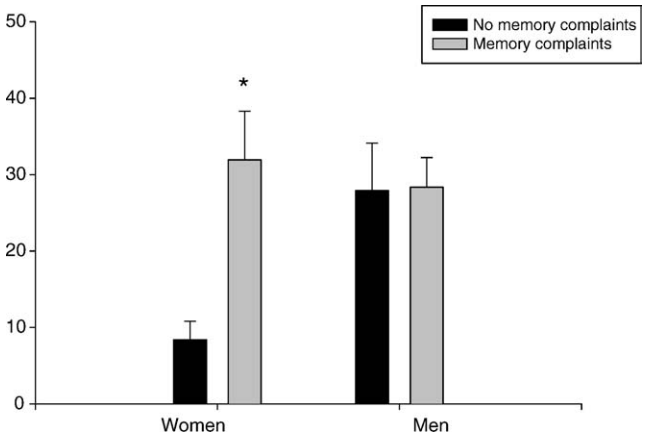

Fig. 1. Effects of memory complaints and gender on 12 h urinary cortisol levels. $^{*}p < .05$ in Student's t test.

Analyses of the urinary cortisol measure revealed a trend for a main effect for memory complaint group ($F = 2.81$ $p = .10$), in the absence of an effect of gender or the covariate (Hamilton score). In addition, a significant interaction was observed between memory complaint group and gender ($F = 4.13$, $p < .05$), with women showing a stronger difference in urinary cortisol values between those with and without subjective memory complaints than men did (see Fig. 1).

Analysis of cortisol levels after dexamethasone treatment detected significantly higher levels for the group with subjective memory complaints ($F = 7.47$, $p < .01$), no main effect for gender and no group × gender interaction between the two groups. In addition, a significant effect of the covariate (Hamilton depression scores) occurred ($F = 4.1$, $p = .05$). The mean cortisol levels after dexamethasone treatment for the women were $1.12 \pm .13$ μg/dl (for the group without memory complaints) and $1.79 \pm .32$ μg/dl (for the group with subjective memory complaints). The values for the men were $1.27 \pm .25$ μg/dl (group without memory complaints) and $2.12 \pm .57$ μg/dl (group with subjective memory complaints).

Analysis of the ACTH levels after dexamethasone treatment detected no significant effect for the subjective memory complaint group ($F = 2.15$, $p = .15$), no main effect for gender, no interaction between the two, and no effect of the covariate (data not shown).

Our results were unchanged when we repeated the analyses without using the Hamilton depression score as a covariate, namely an ANOVA with subjective memory complaints and gender as factors.

4. Discussion

In the present study we observed that middle aged and older subjects with subjective memory complaints, in the absence of observable memory deficits, had higher basal urinary cortisol levels and higher CRH-induced cortisol and ACTH levels following dexamethasone administration. While subjects with subjective memory complaints endorsed more items on the Hamilton depression scale, the observed differences in basal and feedback measures of the HPA axis remained significant after controlling for the depression scores in analyses of covariance.

We did not find any differences in objective memory measures between subjects with and without subjective memory complaints, which is in line with several other reports (for review see [17]). Our findings diverge from previous studies showing an association between cortisol levels and memory in aging [11,21,37]. Those previous studies had tested older subjects (mean age between 69 and 75), so it is possible that they may have included participants with incipient dementia. Moreover, in those studies only objective memory scores were assessed, while subjective memory complaints were not assessed and/or reported. We studied a younger cohort with an average age of 61 years and carefully excluded individuals with MCI. Only the longitudinal observation of our study participants will allow us to determine whether or not subjective memory complaints and their associated HPA axis hyperactivity lead to future objective cognitive decline.

The lack of memory performance differences between our subjects with and without subjective memory complaints may reflect our testing conditions, which were designed to minimize stress during test administration. If the cognitive tests were administered under more stress-inducing circumstances, memory performance differences between the groups may be uncovered and might prove to be related to the abnormalities in HPA axis regulation seen in the subjective impairment group. This would be analogous to findings in a recent study, in which memory performance was impaired by the acute administration of cortisol for those subjects showing rising basal cortisol levels over the last years, but the effects were smaller for older subjects showing stable cortisol levels [23]. One could speculate that individuals with subjective memory complaints might actually have a higher incidence of memory problems under situations of daily stress, concomitant with the level of dysregulation of their HPA axis functioning. This is consistent with our group differences on the MAC-Q, where subjects with memory complaints reported problems in tasks of daily life that rely on working or declarative memory. However, this hypothesis would need to be put to the test.

Our participants with subjective memory complaints endorsed a slightly higher number of items on the Hamilton depression scale. Even though scores in both groups were very low (3.37 versus 1.21), this observation is in keeping with previous studies, which observed associations between memory complaints and depression [17]. Since elevation in cortisol levels is often present in depression [15,28], this could conceivably be one mediating factor for our findings. However, arguing against such an interpretation of our data, in addition to the very low Hamilton scale scores, is the fact that the group with memory complaints still had significantly higher cortisol levels, after controlling for those scores.

We found that the associations between subjective memory complaints and urinary cortisol levels varied by gender. Women without subjective memory complaints had significantly lower cortisol levels than women with memory complaints, while no such differences were observed among the men. In contrast, no gender differences were seen for HPA feedback inhibition when dexamethasone was given; both women and men without subjective memory complaints showed lower post-dexamethasone cortisol levels. Seeman et al. have observed in a large study that higher 12 h urinary cortisol measures were associated with poorer memory in older women, but not in older men [37]. Our study finds parallel associations, but for subjective memory complaints. Several studies have suggested that older women have more pronounced basal cortisol elevations [41] and also show a more pronounced ACTH and cortisol response to CRH in the dexamethasone/CRH challenge test [14]. In contrast, older women are less reactive to a standardized psychosocial laboratory stressor than older men [19]. In the current sample we observed no overall sex differences for basal cortisol levels as well as for cortisol levels after dexamethasone administration. However, the cortisol and ACTH response to CRH tended to be more pronounced in older women, a finding in agreement with work by others [14]. Clearly gender differences are of major interest in neuroendocrine aging research and future studies should continue to characterize similarities as well as differences in age associated HPA axis alterations and their associations to objective as well as subjective memory assessments.

It is possible that older individuals without subjective memory complaints differ in personality trait measures from those with complaints [17]. These personality differences could be another factor explaining our findings. Indeed, some of these same personality traits have also been associated with the HPA axis function. For example, studies have observed a reduced HPA responsiveness in subjects with high self-esteem, high internal locus of control or strong self-enhancing biases [30,31,39]. Unfortunately, we have no personality questionnaire data available on our participants, but a more detailed psychometric evaluation is warranted in future studies on this topic.

In sum the results of our study indicate that individuals who complain about memory impairments (in the absence of measurable impairments) have enhanced HPA axis activity. We are aware that the cross-sectional nature of our study does not allow us to resolve the issue of cause and effect. Since the two groups in our study did not differ in any objective memory measure it appears possible that HPA axis dysregulation exerts an independent effect on subjective memory complaints. The longitudinal follow up of this cohort will allow us to test whether subjective memory complaints in combination with enhanced HPA activity leads to future objective cognitive decline. Our novel observation should be considered in future study designs aimed at resolving the inconsistencies in the literature regarding the associations between subjective memory complaints and cognitive decline.

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