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Basal Hypothalamo-Pituitary-Adrenal Axis Activity and Corticotropin Feedback in Young and Older Men: Relationships to Magnetic Resonance Imaging-Derived Hippocampus and Cingulate Gyrus Volumes

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Abstract
Alterations in basal cortisol secretion and feedback sensitivity are reported in aging. However, it is not known whether these hypothalamus-pituitary-adrenal (HPA) axis alterations are related to structural brain changes. This study was designed to investigate these relationships in the human. Nine young (24.0 ± 1.2 years; mean ± SE; range: 19–30) and 11 older (69.0 ± 1.8 years; range: 59–76) men, in addition to having standardized magnetic resonance imaging of their brains, were given 0.5 mg/kg cortisol or placebo intravenously in a double-blind, crossover study. As expected, older men had significantly smaller volumes for all brain regions. Although the groups did not differ in baseline HPA axis activity, there were significant and specific relationships between the brain volumes and the baseline measures of HPA activity. Namely, for young and older subjects combined and after controlling for age and cerebral vault size, hippocampal volumes were inversely associated with 24-hour urinary cortisol and basal corticotropin (ACTH) levels, and the anterior cingulate gyrus volume was negatively correlated with baseline ACTH. Elderly subjects had a slower decrease in ACTH levels (percent of baseline level) during the first 30 min after cortisol administration. However, no associations were observed between the ACTH feedback indices and any brain measure. This report, although based on a small number of subjects, supports previous studies showing a blunted ACTH fast feedback during normal aging. Hippocampal atrophy appears to be related to increased basal measures of HPA axis activity, but not to fast ACTH feedback. It remains possible that age-associated changes in fast feedback may be related to changes to other brain sites, such as hypothalamus or pituitary.

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Introduction

Aging is accompanied by increases in basal cortisol levels and reductions in feedback sensitivity of the hypothalamus-pituitary-adrenal (HPA) axis in both animals and humans [1–3]. In humans, the age-associated increased basal cortisol secretion is especially prominent in the evening (higher nadir) [4, 5]. Moreover, with aging, a blunted corticotropin (ACTH) feedback has been observed after administration of cortisol [6–8] or dexamethasone (DEX) [9, 10]. However, this literature is not in complete agreement [11–13], especially with respect to DEX (for a review, see ref. [3]).

Rodent studies have documented that the hippocampus [14] and the cingulate gyrus [15–17] are involved in the control of the HPA axis. However, the precise role of the hippocampus is still under debate. Some rodent studies suggest that hippocampal pathology is associated with increased stress reactivity and blunted negative feedback, which leads to prolonged glucocorticoid secretion after stress [14, 18–20]. Research from other laboratories, using different research strategies, has failed to support this hypothesis, suggesting a rather limited role for the hippocampus in fast ACTH feedback [21–23]. Instead, these studies point to a key role for the paraventricular nucleus (PVN) of the hypothalamus in fast feedback control.

Human studies have reported an association between magnetic resonance imaging (MRI)-derived hippocampal volume reductions and elevated cortisol levels during aging [24] or as a result of Cushing's disease [25, 26]. In addition, an early study from our laboratory revealed that Alzheimer patients had an exaggerated cortisol response to a glucose challenge, and that this was linked to qualitative hippocampal atrophy [27]. Also, a failure to suppress cortisol secretion after DEX administration has been associated with atrophy of the hippocampus in patients with Alzheimer's disease [28]. More recently, we have shown that the administration of a cortisol bolus selectively reduces hippocampal glucose utilization [29], thereby demonstrating in the human that an acute cortisol elevation affects the hippocampus directly.

The present study was carried out in order to replicate previous reports documenting that with aging there is a blunted or delayed ACTH fast feedback (after exogenous cortisol administration) and to investigate whether age-related structural changes in the hippocampus and/or anterior cingulate gyrus may be related to known age-related changes in basal HPA axis activity or fast feedback. In order to ascertain whether the hypothesized relationships between HPA axis activity or fast feedback and hippocampal and/or cingulate gyrus are specific, we also assessed two control regions (parahippocampal gyrus and orbitofrontal region) and a measure of global atrophy.

Method

Subjects

Subjects were 9 young (24.0 ± 1.2 years; mean ± SE; range 19–30) and 11 elderly (69.0 ± 1.8 years; range 59–76) males, who were recruited through the Center for Brain Health, Neuroimaging Laboratory of the New York University School of Medicine. The study was approved by the institutional review board. All participants gave written informed consent and were compensated for their time. All subjects were nondiabetic (fasting glucose <126 mg/dl), nondemented, and nondepressed. Moreover, none of the subjects was receiving any kind of treatment (e.g. steroidal medication) known to influence the parameters investigated in the current study. Subjects underwent a thorough medical and neurological evaluation, which included a complete blood analysis after an overnight fast. The psychiatric screening used the NIMH Quick Diagnostic Interview Schedule [30] and the Mini-Mental Status Examination [31]. The two groups did not differ in body mass index (BMI: kg/m^2; young 26.0 ± 1.0; old: 25.6 ± 1.3), Mini-Mental Status scores (young: 29.6 ± 0.3; old: 28.9 ± 0.4), and years of formal education (young: 15.5 ± 0.9; old: 15.8 ± 0.6).

Endocrine Challenge Paradigm

The study was designed as a placebo-controlled, double-blind, crossover study. In a first experimental session, subjects randomly received an intravenous injection of either 0.5 mg/kg cortisol (hydrocortisone sodium succinate; Pharmacia and Upjohn, Kalamazoo, Mich., USA) or placebo. This was followed by a second session 7–14 days later, during which the injection (placebo or hydrocortisone) not utilized in the first test session was administered. The subjects arrived at the laboratory at 8:00 a.m. after fasting overnight. A 20-gauge catheter was placed in each forearm, one was used for administration of the drug and the other for blood sampling. Both sites were kept patent using heparin locks. The lines were placed at 8:30 a.m., 45 min prior to collection of baseline bloods and 1 h prior to drug administration. Baseline bloods were obtained at 15 and 10 min prior to injection. The mean of these two samples was taken as the baseline value. Postinjection blood samples were taken at 15, 30, 45, 90 and 180 min after injection. Six milliliters of blood were collected into chilled EDTA tubes with each blood draw. Blood samples were kept on ice and then spun down in a refrigerated centrifuge (4°C). Plasma was separated into aliquots and kept frozen at –70°C until assayed. The subjects performed several cognitive tests during the course of the experimental sessions. The results of this part of the experiment were reported elsewhere [32].

Baseline HPA activity was measured using two different approaches. First, to characterize resting ACTH and cortisol levels, a mean of the two baseline values was computed and then these were averaged across the two test sessions. Second, basal urinary free cortisol levels were assessed by having subjects collect their urine during a 24-hour period on the day prior to the second experimental session. ACTH reactivity was assessed by measuring the percent reduction

(relative to baseline) in ACTH levels after exogenous cortisol administration.

Hormone Assays

Total blood plasma cortisol was measured with a commercial radio immunoassay (IBL, Hamburg, Germany). ACTH was measured with a two-site chemiluminescence assay (Nichols Institute, Bad Nauheim, Germany). Free urinary cortisol was measured with a radio immunoassay that utilizes a double antibody (Diagnostics Product Corporation). All assays had inter- and intra-assay coefficients of variance below 12%.

MRI Evaluations

The subjects were scanned using a 1.5 T GE Advantage MR system (GE Medical Systems, Milwaukee, Wisc., USA). Fast spin echo axial images (T_1, T_2) were used to ensure the subjects met the inclusion and exclusion criteria. Subjects with MR evidence of infarct, hydrocephalus, intracranial masses, or significant white matter lesions were excluded. For the anatomical measurements, a three-dimensional spoiled gradient recalled (SPGR) sequence in a sagittal plane was acquired utilizing TR 35/TE 9 ms, 60° flip angle and 1 signal average, 1.2 mm slice thickness with no gap, a 25-cm field of view and a 256 × 128 matrix. These SPGR sagittal scans were used to create coronal images reformatted orthogonally to the plane of the anterior and posterior commissures at 1.5- and 2-mm-thick sections for the hippocampal and frontal volume measurements, respectively. Details about the MRI acquisition and image reformatting are provided elsewhere [33]. The scans were acquired prior to this study by 8.6 ± 1.4 months (mean ± SE). Except for 1 young subject, who was scanned 24 months prior to the experimental sessions, all other subjects were scanned within 14 months of the sessions. Studies from other laboratories have shown that during such short time intervals, minimal structural changes occur in the brain of healthy elderly subjects [34–36]. We do not anticipate any changes during that short interval among young normal subjects.

To correct for head size variations across individuals, a cerebral vault volume was obtained by measuring the volume of the compartment bounded by the dura and the tentorium cerebri. The cerebral vault volume was measured by following the dural and tentorial margins every fifth sagittal image (mid-points every 6 mm) in the original sagittal SPGR images. A measure of global brain atrophy was determined using a threshold procedure to segment the CSF (see [37] for details).

The hippocampus, parahippocampal gyrus, orbitofrontal region, and cingulate gyrus were manually outlined on the standardized reformatted coronal images. The hippocampus (cornu amonnis, dentate gyrus, and subiculum) was measured in its entire anterior posterior extension combining our original method [37] with the use of multiple planes to reliably separate the hippocampus from the adjacent amygdala (for details see [33]). The parahippocampal gyrus was measured in the same sections as the hippocampus.

The anterior cingulate gyrus was defined as the region contained between the cingulate and pericallosal sulci and was measured using a method reported in [38]. The cingulate gyrus region had as its anterior boundary the cingulate sulcus, which is easily seen on mid-sagittal view, and as its posterior boundary the coronal plane that bisects the distance between the anterior cingulate sulcus and precentral sulcus (see [38] for details). To include a standard amount of white matter in the cingulate measurements across the subjects, we devised a method that uses an anchor point in the geometric center of each hemisphere to define the point of origin for each region [37]. When corpus callosum was present, the superior and inferior cingulate portions seen on coronal orientation were combined into one volume. Similarly, for the orbitofrontal region, the same anterior and posterior boundaries and anchor point were used. The medial boundary for the orbitofrontal region is the cingulate sulcus. The lateral boundary of the orbitofrontal region is difficult to ascertain on coronal orientation. On lateral sagittal views, the horizontal extension of the circular sulcus (also called the anterior horizontal ramus of the Sylvian fissure) is readily seen and can be used to identify the lateral boundary of the orbitofrontal region. This method has been described in detail elsewhere [38]. We have obtained a high level of reproducibility between two independent raters (ICC = 0.90, n = 55) for these measurements. For all anatomical regions, hemispheres were averaged, and this average was the volume utilized in the analyses. In addition, all regions, including the global atrophy measure, were corrected for individual differences in head size by creating a ratio [(structure/cerebral vault) × 1,000].

Statistical Analyses

For analyses involving the baseline measures of HPA axis activity (24-hour urinary cortisol and baseline plasma ACTH and cortisol levels), we created an overall basal measure by averaging across all four baseline samples taken during the two test sessions. These overall baseline measures were compared across the age groups using t tests. To assess if differences in each of the brain/cerebral vault ratio measures (hippocampus, parahippocampal gyrus, cingulate gyrus, orbitofrontal region, and global atrophy) existed between the age groups, we again used t tests.

The ACTH levels after either cortisol or placebo were analyzed in two ways. First, we used the raw data, and second, we expressed the ACTH levels as percent of the mean baseline ACTH levels from the placebo and cortisol day, respectively. This second approach was used in order to reduce the individual variability in the data, for it to reflect the feedback, and in order to make the results more easily comparable to previous studies that used a similar approach [6–8]. The raw ACTH data as well as the transformed variables were analyzed utilizing analyses of variance (ANOVAs), with age as the grouping factor (young versus old) and treatment and time as the within-subject factor. All significant ANOVA results for the repeated-measurement factor time are corrected with the Huynh-Feldt procedure in order to adjust for violation of the ANOVA sphericity assumption in the repeated-measurement design. The Huynh-Feldt procedure, which is similar to the Greenhouse Geisser procedure, but less conservative, results in less of a reduction in degrees of freedom, and was thus selected for this small data set. Post hoc testing was performed using the Tukey (HSD) test.

Finally, the relationships between the structural brain measures and the endocrine measures were investigated using partial correlations in order to control for age or for age and BMI. If two or more brain measures were related to the same HPA parameter, stepwise linear regression analyses (controlling for age and inverting the order of entry for the brain measures) were performed in order to investigate whether the two brain measures provided independent contributions.

Results

Brain Measures

The young and old subjects did not differ in cerebral vault volumes. However, the old subjects had significantly smaller hippocampal, parahippocampal gyrus, orbitofrontal region, and anterior cingulate gyrus ratios and significantly more global atrophy ratio (table 1).

Endocrine Measures

Basal HPA Measures. The young and old subjects did not differ in their 24-hour free cortisol levels (young: 79.89 ± 11.72 μg; old: 86.91 ± 11.59 μg). They also did not differ in their overall (average of the two sessions) baseline cortisol (young: 10.93 ± 1.34 μg/dl; old: 8.11 ± 0.94 μg/dl); or overall baseline ACTH levels (young: 40.20 ± 8.52 pg/ml; old: 27.23 ± 3.93 pg/ml), although the younger subjects had numerically higher overall baseline ACTH levels.

Cortisol Increase in Response to Hydrocortisone Injection. Hydrocortisone administration significantly increased the measurable total serum cortisol levels, giving rise to a significant treatment main effect [$F(1, 18) = 270.53$, $p < 0.01$] and a significant treatment by time interaction [$F(2.15, 38.66) = 73.87$, $p < 0.01$]. Relative to baseline, cortisol levels were significantly elevated 15 min after hydrocortisone injection and declined thereafter ($p < 0.05$), but were significantly elevated from placebo levels during the entire course of the experiment ($p < 0.05$). No significant age main effect, age by treatment, or age by treatment by time interaction was observed (table 2).

ACTH Levels on the Placebo Day. The young and old subjects did not differ in their ACTH levels on the placebo day (table 2). There was no significant age main effect or age by time interaction. However, as expected, there was a significant reduction in ACTH levels indicating the typical circadian decline obvious in the raw ACTH levels [$F(3.09, 55.65) = 2.71$, $p = 0.05$] as well as in the transformed variables [percent from baseline: $F(2.4, 43.19) = 2.51$, $p = 0.08$].

ACTH Levels after Cortisol Administration. Analysis of the raw ACTH data (table 2) indicated a significant

Table 1. MRI-derived volumetric brain measurements in young and old subjects

	Young subjects (n = 9)	Old subjects (n = 11)	p value
Intracranial vault, cm^3	1,292.31 ± 22.86	1,297.47 ± 21.36	n.s.
Hippocampus ratio	2.30 ± 0.04	1.98 ± 0.05	<0.01
Parahippocampal gyrus ratio	4.26 ± 0.20	3.45 ± 0.16	<0.01
Cingulate gyrus ratio	9.17 ± 0.5	7.74 ± 0.4	<0.05
Orbitofrontal ratio	27.02 ± 1.12	23.61 ± 0.82	<0.01
Global atrophy ratio	102.98 ± 11.50	191.32 ± 15.65	<0.01

Means ± SE. p values are based on two tailed t tests.

Table 2. Cortisol (C) and ACTH levels after cortisol or placebo (P) injection in young and old subjects

Time	Young (n = 9)				Old (n = 11)			
	C, μg/dl		ACTH, pg/ml		C, μg/dl		ACTH, pg/ml	
	after P	after C	after P	after C	after P	after C	after P	after C
Base	10.0 ± 1.1	11.8 ± 1.9	32.1 ± 6.3	48.3 ± 11.7	7.6 ± 0.7	8.6 ± 1.3	23.7 ± 2.7	30.8 ± 6.6
+15 min	8.2 ± 0.9	54.8 ± 6.1	24.1 ± 4.2	32.3 ± 6.8	7.5 ± 0.7	54.5 ± 3.0	22.8 ± 3.4	26.2 ± 4.3
+30 min	7.5 ± 0.8	47.9 ± 6.2	20.7 ± 2.5	24.0 ± 5.0	6.8 ± 0.6	42.8 ± 1.1	22.3 ± 2.9	19.2 ± 2.6
+45 min	6.8 ± 0.8	46.9 ± 5.3	23.5 ± 4.3	18.4 ± 3.9	6.5 ± 0.5	40.2 ± 1.1	21.9 ± 2.4	14.5 ± 1.9
+90 min	6.6 ± 0.9	36.0 ± 1.3	28.3 ± 5.3	9.6 ± 2.0	6.2 ± 0.5	34.7 ± 1.8	23.4 ± 3.3	7.0 ± 0.7
+180 min	5.9 ± 0.7	26.6 ± 1.3	25.6 ± 2.1	6.2 ± 1.0	6.9 ± 0.7	26.2 ± 2.0	25.7 ± 4.2	4.4 ± 0.5

Means ± SE; details of the statistical analysis are provided in the text.

main effect of time, reflecting the cortisol-induced decrease in ACTH levels [F (1.2, 22.06) = 31.17, $p < 0.01$]. However, there was no main effect of age [F (1, 18) = 1.34, p = 0.20] and no significant age by time interaction [F (1.2, 22.06) = 1.56, p = 0.23].

A different picture of the data emerged when the transformed ACTH variables [percent from baseline (average of the –15-min and –10-min samples during the cortisol session)] were used in order to reduce the variance in mean baseline ACTH levels and to adjust for baseline differences in ACTH levels. Again, there was a time main effect, indicating that cortisol induced a decrease in ACTH levels [F (2.6, 46.7) = 299.29, $p < 0.01$]. Each postinjection time point showed significantly lower ACTH levels than the preceding one. In addition, a significant age by time interaction was observed [F (2.6, 46.7) = 4.29, $p < 0.05$] (fig. 1). Older subjects had significantly ($p < 0.05$) higher ACTH levels (or a significantly smaller percent ACTH decrease) at 15 and 30 min after hydrocortisone administration and also tended to have higher levels 45 min after treatment (p = 0.08). No ACTH differences between the two age groups were apparent at 90 and 180 min after cortisol administration (fig. 1). Relative to baseline levels, young subjects showed a significant ACTH decrease 15 min after hydrocortisone administration ($p < 0.05$). Old subjects, on the other hand, did not show ACTH reductions at 15 min after cortisol injection (p = 0.20), but started to show a significant decrease starting 30 min after cortisol administration ($p < 0.05$).

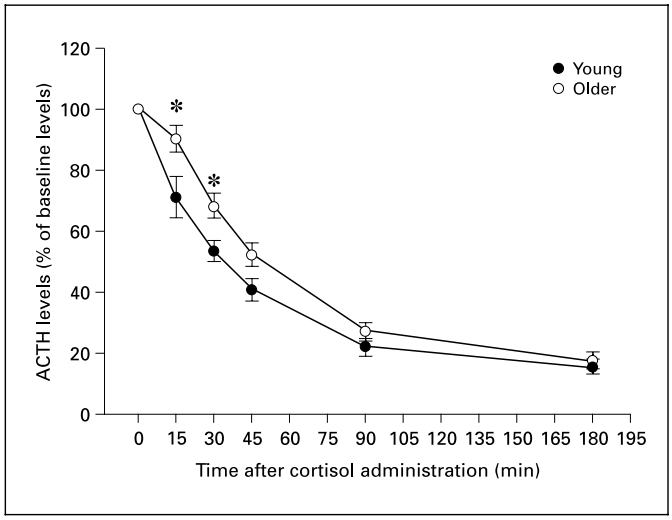

Fig. 1. ACTH decrease, expressed as percent of the mean baseline level (average of the –15- and –10-min sample) in young and old men after a bolus injection of 0.5 mg/kg cortisol. * $p < 0.05$ for the comparison between young and old subjects.

Relationships between Endocrine and Brain Measures. The results of the associations between endocrine and brain measures, after accounting for age (partial correlations), are presented in table 3.

Elevated basal cortisol secretion (24-hour free urinary cortisol) and elevated overall baseline ACTH levels were both significantly associated with smaller hippocampi

Table 3. Relationship between MRI-derived brain measures and measures of basal HPA activity and HPA fast feedback

	Hippocampus ratio	Parahippocampal gyrus ratio	Cingulate gyrus ratio	Orbitofrontal ratio	Global atrophy ratio
24-hour cortisol	**r = –0.45** **p = 0.05**	r = 0.15 p = 0.45	r = –0.14 p = 0.57	r = –0.22 p = 0.37	r = –0.08 p = 0.74
Average baseline ACTH	**r = –0.46** **p = 0.04**	r = –0.28 p = 0.24	**r = –0.50** **p = 0.03**	r = –0.27 p = 0.26	r = –0.04 p = 0.88
Average baseline cortisol	r = –0.34 p = 0.16	r = –0.12 p = 0.63	r = –0.07 p = 0.77	r = –0.08 p = 0.76	r = 0.24 p = 0.33
ACTH 15 min after cortisol injection, %	r = 0.09 p = 0.73	r = 0.04 p = 0.87	r = 0.13 p = 0.60	r = –0.23 p = 0.34	r = –0.20 p = 0.41
ACTH 30 min after cortisol injection, %	r = 0.14 p = 0.56	r = 0.05 p = 0.85	r = 0.14 p = 0.58	r = –0.14 p = 0.57	r = –0.22 p = 0.38

Partial correlations including the entire sample (n = 20), controlling for age. Significant correlations are printed in bold.

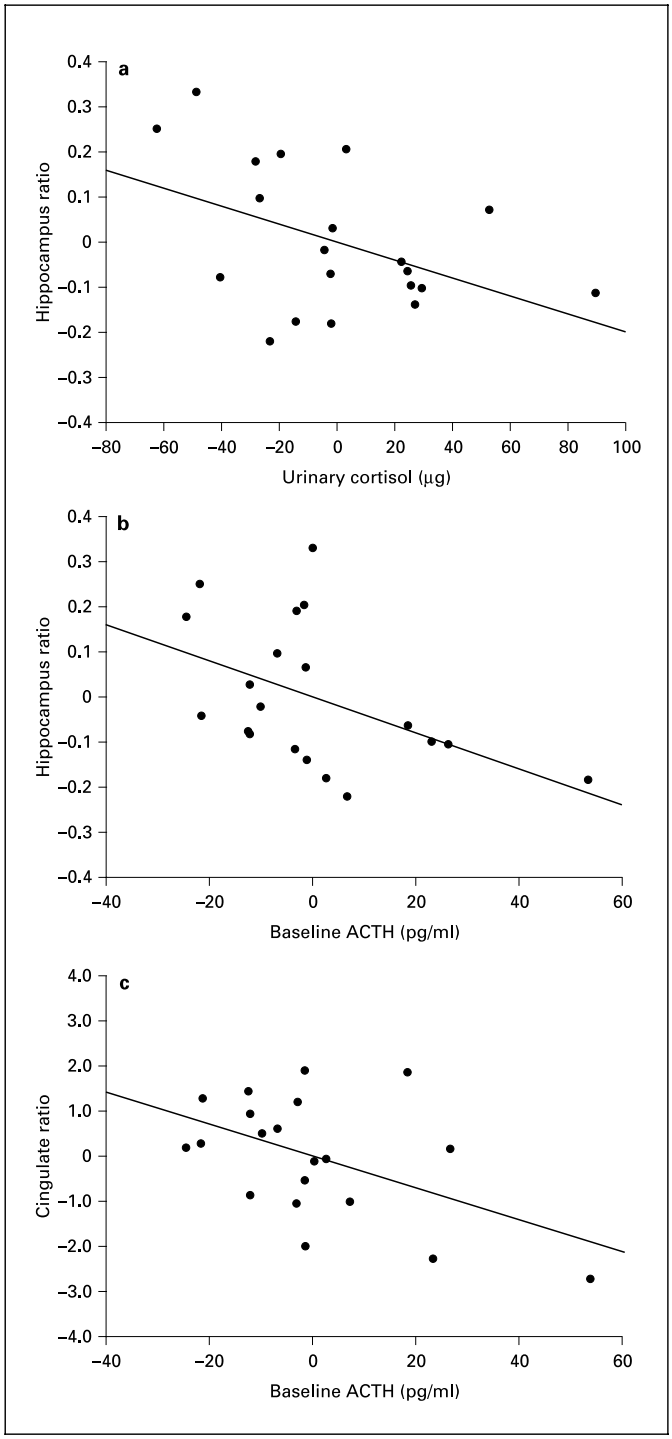

Fig. 2. Scatterplot showing the partial correlation (controlling for age) between hippocampus/head size ratio and 24-hour urinary cortisol ($r = -0.045$, $p = 0.05$) (a) hippocampus/head size ratio and average baseline ACTH levels ($r = -0.46$, $p = 0.04$) (b) and the cingulate/head size ratio and average baseline ACTH levels ($r = -0.50$, $p = 0.03$ (c).

(fig. 2a, b). We also found a significant inverse association between cingulate gyrus volume and baseline ACTH levels (fig. 2c). However, no associations were found between cingulate gyrus volume and 24-hour urinary free cortisol. In contrast to the basal measures, ACTH levels after exogenous cortisol administration were not related to hippocampal or cingulate size. The two control regions (orbitofrontal region and parahippocampal gyrus) as well as the amount of global atrophy were not associated with either basal HPA axis activity or HPA axis feedback (table 2). Identical results were found whether the baseline ACTH values were averaged across the two experimental sessions or whether only the cortisol day baseline values were used. Moreover, the results were also unchanged when both age and BMI were controlled for in the partial correlations (data not shown).

Finally, the individual contributions of the hippocampus and the cingulate in explaining variance in the baseline ACTH levels were investigated using stepwise regression analysis, with age entered first and the two brain regions entered second and third in alternating order. The variance (R^2 change) in the baseline ACTH level explained by the two brain regions ranged from 15 to 21% and were significant ($p < 0.05$) for both orders of entry.

Discussion

To the best of our knowledge, this is the first study in the human seeking to link basal and feedback measures of the HPA axis to volumetric measures of brain structures known to be involved in the regulation of the axis. In line with previous studies on older subjects [7, 8], we observed that after adjusting for baseline levels, there was a delay in the reduction in ACTH levels after cortisol administration. During the first 30 min after injection, ACTH levels were higher in older subjects, but this difference was no longer apparent at later time points, which is similar to findings from a previous report [6]. No such effects existed for the absolute ACTH values. We decided to adjust for individual baseline differences in ACTH because the young subjects had numerically higher baseline levels. Moreover, there was a substantial individual variability in all baseline ACTH levels. A similar approach had been taken in previous studies demonstrating a blunted ACTH fast feedback to cortisol administration after metyrapone pretreatment [7, 8].

Basal measures of HPA axis activity were not significantly different between young and older subjects. Subtle alterations in baseline cortisol levels may require larger

numbers of subjects or perhaps the use of a standardized laboratory setting [5] for detection.

The older subjects in our study had significantly smaller hippocampi, parahippocampal gyri, and orbitofrontal regions, as well as more global cortical atrophy, which is in line with previous studies from this and other laboratories [38–43]. In contrast to previous findings from this and one other group, the cingulate gyrus was also found to be reduced with age [38, 43]. It is possible that these age effects are only detectable by contrasting groups with large age differences, as was the case in this study.

We observed, using healthy young and older men, that elevations in 24-hour urinary free cortisol and baseline ACTH levels were associated with smaller hippocampal volumes after accounting for age. These findings are similar to those of previous studies of older subjects and Cushing patients [24–26]. In the present study, the resting period between catheter insertion and the two baseline samples was only 45 and 50 min. This is an equivalent [6] or longer [7, 8] rest period than used in previous studies. However, we cannot exclude the fact that baseline ACTH levels were influenced by the physiological and psychological stress of catheter insertion (see also discussion below).

We also observed an association between baseline ACTH levels (but not the 24-hour urinary free cortisol measure) and cingulate volume. The association between cingulate and baseline ACTH was independent from the association between hippocampus and baseline ACTH levels. The explanation for this finding is likely complex, and may involve the possible effect of cingulate reductions on the stress response. For example, there are animal studies reporting that cingulate lesions modulate the HPA axis response to a stressor [15, 17]. Based on this animal literature, one could speculate that the relationship between higher baseline ACTH levels (45–50 min after catheter insertion) and volume losses in the cingulate gyrus might reflect an exaggerated HPA response to the stress of catheter insertion among those subjects with smaller cingulate gyrus volumes. This would be in line with some of the results obtained in rats [15]. However, the reported direction of associations has varied across different studies [15, 17]. Therefore, there is a clear need for more animal as well as human research on the role of the medial prefrontal cortex in HPA axis regulation. The orbitofrontal, parahippocampal gyrus and global atrophy measures were not related to basal HPA indices, suggesting that the observed hippocampal and cingulate effects are specific and not simply the result of global age effects on the brain.

Although the hippocampus, and to a lesser degree the cingulate gyrus, seem to be associated with basal measures of HPA activity, we did not find an association between blunted ACTH fast feedback and reduced hippocampal volumes. This lack of association has not been previously reported and suggests that hippocampal atrophy may not be central to this age-associated alteration. If this observation is replicated in other human studies utilizing larger sample sizes, our results would stand in contrast to several observations made in rodents [14, 18–20].

We did not ascertain nonhippocampal brain regions that may play a role in fast ACTH feedback. For example, it is likely that the hypothalamus or the pituitary gland may be responsible for the changes in fast ACTH feedback inhibition seen during normal aging. The notion that the hypothalamus and the pituitary are key structures in fast feedback has been supported so far by previous studies in rodents [21–23]. Indeed, age-associated alterations have been described for these brain regions. While there appears to be no neuronal loss with aging in the PVN of the hypothalamus, an increase in neurons containing corticotropin-releasing hormone has been reported [44–46]. In contrast, the pituitary has been reported to undergo a reduction in volume with aging [47, 48]. These regions should be included in future MRI structural studies investigating the neural correlates of fast feedback inhibition [47–51]. Another possibility suggested by Boscaro et al. [6] is the fact that vascular factors could be contributing to the feedback alterations.

In sum, the present study utilizing a small sample of young and older men replicates previous findings demonstrating an age-associated blunted ACTH feedback inhibition response after exogenous cortisol administration. Moreover, this study has also demonstrated that volumes of the hippocampus, and to a lesser degree the cingulate gyrus, were negatively correlated with basal HPA axis measures. The changes we observed in ACTH fast feedback sensitivity were not associated with those brain measures, suggesting that alterations in other brain structures might be responsible for these age-related changes. Clearly more research is needed trying to understand the association between the HPA axis and structural brain measures in the human.

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