Improvement in Learning Associated with Increase in Hippocampal Formation Volume

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Background: *Patients with spontaneous Cushing's syndrome are exposed to elevated levels of endogenous cortisol for months to years. We previously reported that hippocampal formation volume (HFV) increased in such patients after treatment lowered cortisol to normal concentrations. In the present study, we examined whether the structural increase was associated with improvement in cognition.*

Methods: *Twenty-four patients with Cushing's disease were studied before treatment and following treatment. Magnetic resonance imaging was used to measure HFV and caudate head volume. Neuropsychologic tests of verbal cognition, learning, and memory were also administered.*

Results: *Patients showed variability in improvement on neuropsychologic test performance. After partialing out age, education, duration of illness, and time since surgical treatment, greater improvement in word list learning, as measured by the Selective Reminding Test was associated with greater increase in HFV (*$r = .59$, $p < .02$*). There were no significant associations between improvement in paragraph or paired-word learning or memory tasks and increase in HFV. Improvement in other verbal tasks not strongly dependent on the hippocampus were not significantly associated with increase in HFV.*

Conclusions: *After cortisol levels decline to normal concentrations, structural volumetric increase in HFV is accompanied by functional improvement in learning of unrelated words.* Biol Psychiatry 2003;53:233–238 © *2003 Society of Biological Psychiatry*

Key Words: Learning, memory, hippocampus, cortisol, Cushing's syndrome, imaging

Introduction

In a series of studies, we have used spontaneous Cushing's syndrome as an experimental opportunity to explore the neuropsychiatric effects of elevated cortisol (Starkman et al 1981, 1986; Shipley et al 1992) and to better understand its pathophysiologic role in conditions such as major depressive disorder, Alzheimer's disease, and normal aging. Patients with spontaneous Cushing's syndrome are exposed to elevated levels of endogenous cortisol, the naturally occurring glucocorticoid, for months to years. Re-examination of patients after treatment has restored cortisol concentration to normal levels provides a unique opportunity to study reversibility of glucocorticoid-induced alterations of brain structure and function.

In prior studies, we found that during hypercortisolemia many cognitive tasks were negatively affected before treatment (Starkman et al 2001; Whelan et al 1980). We also showed that before treatment hippocampal formation volume (HFV) was negatively correlated with plasma cortisol concentration and positively correlated with scores for verbal learning and recall (Starkman et al 1992).

We demonstrated that HFV increased in patients after treatment lowered cortisol to normal concentrations. The degree of increase in HFV was significantly correlated with the degree of decrease in cortisol concentration (Starkman et al 1999).

In the present study, we examine whether the structural increase in HFV after treatment is associated with improvement in cognition. Because learning and memory are the cognitive functions most clearly dependent on the hippocampus, we used a group of tasks measuring these functions. As comparison, we used verbal tasks that previously showed decrements in patients with untreated Cushing's disease (CD) (Starkman et al 2001) but that are not considered dependent predominantly on hippocampus. Caudate head volume (CHV) was used as a structural comparison for HFV. The hypotheses tested were that the degree of improvement in learning/memory is associated with the degree of increase in HFV, and that there is selectivity for task (verbal learning/memory vs. other tasks) and for brain structure (HFV vs. CHV).

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Methods and Materials

Subjects

The study included 24 consecutive patients with CD (i.e., the most common form of spontaneous Cushing's syndrome, resulting from hypersecretion of adrenocorticotropic hormone [ACTH] by a benign pituitary microadenoma) who received both brain imaging and neuropsychologic tests. Of the participants, 20 were women and 4 were men, approximating the gender ratio usually seen in CD. Nineteen of the patients were subjects in our earlier article reporting an increase in HFV volume following treatment of CD (Starkman et al 1999).

The study was approved by the University of Michigan's Institutional Review Board for Medical Experimentation, and all patients provided written informed consent. Mean age ($\pm$ 1 SD) for patients at entry was 33.7 $\pm$ 13.1 years. Mean estimated duration of illness was 2.7 $\pm$ 2.1 years, based on an assessment of the patient's history and old photographs. Patients were admitted to the University of Michigan General Clinical Research Center for diagnostic studies and were restudied at the same facility following clinical and biochemical remission.

Diagnostic clinical and biochemical criteria for CD have been described previously (Starkman et al 1999). All patients received a magnetic resonance imaging (MRI) scan and neuropsychological testing at the time of diagnosis to determine the presence of a pituitary tumor and to obtain volumetric measurements of the brain structures of interest.

Approximately 1 month after diagnosis (mean = 1.3 $\pm$ .7), patients underwent transsphenoidal pituitary surgery with resection of a pituitary microadenoma. Surgical access to the pituitary used an incision between the lip and the gum, avoiding any invasion of the brain. Immediately following surgery, all patients exhibited the expected complete suppression of ACTH and cortisol secretion and required replacement therapy with cortisol for at least 6 months. This replacement therapy was adjusted at regular intervals to ensure that cortisol levels remained normal until recovery of spontaneous hypothalamic–pituitary–adrenal (HPA) function occurred. (The patient who had a total hypophysectomy also received thyroid hormone replacement.)

Patients received a repeat MRI scan of the brain and repeat neuropsychological testing after an interval of 15.7 $\pm$ 8.8 months after surgery. Because there is individual variability in the rate at which HPA function recovers, at the time of their reimaging, 18 patients were maintaining normal cortisol spontaneously, and six were still receiving replacement therapy with cortisol. For analyses evaluating the extent of brain volume changes, the full sample of 24 subjects was used. For analyses examining the relationship of these volume changes with changes in cortisol concentrations, the six patients receiving replacement were excluded. Of the 18 remaining patients, a laboratory value for urinary free cortisol (UFC) at the time of imaging was unavailable for three participants (n = 15).

The medications being taken by the CD patients before and after treatment were similar. Before treatment, six patients were receiving no medication, whereas at the posttreatment examination, six were not, except for cortisol supplementation where necessary. The following classes of medications were received (pretreatment;posttreatment): insulin or oral hypoglycemic agents (3;2), antihypertensive agents (14;7), gonadal steroids (4;5), thyroid hormone (2;3), nonsteroidal antiinflammatory (2;2), antidepressant (4;4), and benzodiazepine (1;0).

Cortisol Measurement

24-hour UFC was determined by radioimmunoassay using the Coat-a-Count Diagnostic Products Corporation (Los Angeles, CA) kits. This assay has a detection limit of 0.2 μg/dL. The antiserum used is highly specific for cortisol, with an extremely low ($<$1.4%) cross-reactivity to other naturally occurring steroids. Intraassay and interassay coefficients of variability are 2% and 5%, respectively. For plasma cortisol concentration, the mean of 12 samples taken every 2 hours during a 24-hour period was used in the analyses.

Magnetic Resonance Brain Imaging

All MRI was performed on a 1.5-Tesla superconducting MR unit (General Electric, Milwaukee, WI). Daily use of quality control phantoms, biweekly calibrations for magnetic field homogeneity, and system stability are regular features for the MR units. Although we presently use contiguous three-dimensional gradient echo technology for current research with new CD patients, in the studies reported here, we used a T1-weighted, off-axis, spin-echo sequence to use consistent methodology before and after treatment in patients with this rare disease who were entered into the study over a period of years. Technical details have been reported previously (Starkman et al 1999).

Image Processing and Analysis

One neuroradiologist (SSG) analyzed all the images without knowledge of the patient's clinical or treatment status or endocrine test results. In addition to HFV, CHV was measured as a comparison to examine specificity of changes in learning and memory to HFV. The caudate head was selected because it is also a gray matter nucleus, contains nearly the same neuronal density as the HFV, and has a concentration of glucocorticoid (GC) receptors comparable to the remainder of the brain (Reul and deKloet 1985, 1986). Because HFV and CHV are proportional to overall head size, total intracranial volume was also determined and used to normalize each volume (Free et al 1995). Technical details have been reported previously (Starkman et al 1999).

Neuropsychological Tests

Neuropsychological tests were administered by trained examiners from the University of Michigan Neuropsychology Division. The examiners tested a variety of patients with clinical presentations suggestive of potential CD, some of whom were subsequently confirmed to have the disease and some who were not. They tested patients whose surgical treatment for CD was both successful and unsuccessful. At the time of testing, the examiners had no knowledge as to the diagnostic category, treatment status, imaging results, or cortisol concentrations of the patients.

To understand the relationship between change in cortisol concentration, HFV, and cognition, we chose tasks that were

representative of two primary areas of cognitive decrements in CD that we previously demonstrated in patients with CD: learning/memory and verbal ability.

Learning/Memory

Three learning tasks were used. From the Wechsler Memory Scale-Russell Modification (Russell 1975), we chose two tasks. Logical Memory is a single presentation of a contextually dependent, paragraph-learning task. This paragraph-learning task measures the ability to freely learn "ideas" presented in two literary passages read aloud to the subjects. We also used the Paired Associates task, which is a three-trial, word-pair learning task. After each presentation, the patient was asked to recall and state the associated word when the other member of the pair was given as the stimulus. We also used the Selective Reminding Test (SRT), a six-trial, word-list learning task of unpaired words (Buschke et al 1974). In this test, after the first trial, in which all 12 words were read to the patient, they were asked to state the words they remembered, without regard to order. In each of the subsequent five trials, after being asked to state all 12 words, patients were selectively reminded only of the words they did not remember from the previous trials. Because the SRT was a new addition to our prior standard protocol, not all subjects received the SRT ($n = 19$).

Two delayed memory tasks were utilized. For the Logical Memory and Paired Associates word subtests noted above, patients were instructed that they would be asked to recall the material following a 30-min delay from initial presentation. (One person was not retested for Logical Memory and Paired Associates due to time constraints, resulting in $n = 23$.)

Thus, there were three tasks of learning: Paragraphs, paired words, and single unrelated words; and two tests of memory at 30 minutes: Paragraphs and paired words. Learning and memory have been demonstrated by lesion studies to be primarily dependent on hippocampal and other temporal lobe areas.

Verbal Cognitive Tasks

Vocabulary and arithmetic were used as two verbal tasks without a strong active learning component and likely dependent on brain regions other than hippocampus, such as prefrontal cortex. In our prior studies, patients with untreated CD showed lower scores on these subtests than did normal control subjects (Starkman et al 2001).

Vocabulary measures general mental ability by having the patient give definitions for up to 40 words of increasing difficulty presented both orally and visually (Wechsler 1981). Increased glucose metabolism has been found to occur predominantly in and around the left temporal lobe during performance of this test (Chase et al 1984).

Arithmetic measures the ability of subjects to solve mental arithmetic problems, evaluating both concentration and arithmetic reasoning (Wechsler 1981). Strong, generalized left hemisphere increases in cerebral metabolism have been associated with this task (Chase et al 1984).

Mood

Because patients with CD characteristically have symptoms consistent with a depressive syndrome, the symptoms checklist, SCL-90-R (Derogatis 1994), was obtained both pre- and posttreatment, and its Depression subscale used.

Analysis

Regression analyses to examine the relationships between changes in neuropsychological test scores with changes in brain volume or cortisol were computed, partialing out the effects of age, education, duration of illness, and the number of months from surgical treatment to the posttreatment MRI. SPSS version 10 (SPSS, Inc., Chicago, IL) statistical package was used.

Results

The means and standard deviations for UFC, brain volumes, and neuropsychological variables, pre- and posttreatment, are shown in Table 1.

Changes in Brain Volume and Association with Change in UFC

All 24 patients had an increase in HFV. The change in UFC concentration was significantly negatively correlated with change in HFV: the greater the decrease in UFC after treatment, the greater the percentage increase in mean HFV ($r = -.62$, $p < .01$). Eighteen patients had an increase in CHV, whereas six patients had no change or decrease in CHV. The relationship between change in UFC and in CHV did not reach statistical significance ($r = -.40$, $p = .14$).

Improvement in Learning, Memory and Verbal Cognitive Tasks

Some, but not all, patients showed improvement in neuropsychologic test performance. For Logical Memory learning, 12 of 23 (52%) showed an increase in learning score (immediate recall); for Paired Associates learning, 14 of 23 patients (61%) showed increased scores, and on the SRT list-learning task, scores for 10 of 19 patients (53%) increased. As for the two tests of memory, for Logical Memory recall, 14 of 23 patients (61%) showed increased scores, as did 14 patients (61%) for Paired Associates recall. Although there were overlaps between individuals whose scores increased on several tests of learning and memory, patients with increased scores on one particular test did not necessarily show increases in all the others. For Vocabulary, 6 of 24 subjects (25%) had increases in their scores, and for arithmetic, 12 subjects (50%) had increased scores.

Table 1. Means and Standard Deviations for Variables at Pre- and Posttreatment

	Pretreatment		Posttreatment	
	Mean	SD	Mean	SD
Urinary Free Cortisol	389.47	260.33	29.90	5.89
Hippocampal Formation Volume[a]	1.77	1.41	1.83	.12
Caudate Head Volume[a]	3.77	2.52	3.84	.29
Learning				
Logical Memory	8.13	3.06	8.89	3.19
Paired Associates	15.70	4.22	17.39	3.50
Selective Reminding Task	66.58	12.04	69.53	13.68
Memory				
Logical Memory Delay	6.50	2.67	7.48	3.04
Paired Associates Delay	8.83	1.40	9.26	1.10
Verbal Tasks				
Vocabulary	9.95	2.82	10.18	2.70
Arithmetic	9.91	2.45	10.50	2.79
SCL-90-R Depression Scale	47.52	9.81	38.39	7.73

SCL-90-R, Symptom Checklist-90-R.
[a]For clarity of presentation, intracranial volume–corrected values for means (cm^3) and SDs have been multiplied by 1000.

To rule out the possibility that the initial pretreatment level of cognitive performance affected the ability to increase scores (ceiling effect), we compared for each subtest the pretreatment cognitive scores of patients who demonstrated a posttreatment increase to the pretreatment scores of patients not showing a posttreatment increase. No significant differences were found in the pretreatment scores of the two groups.

The change in the SCL-90-R Depression subscale from the pre- to posttreatment examination was not significantly correlated with change in any of the cognitive variables.

Association of Change in HFV and Change in Tests of Learning and Memory (Cognition)

We first tested the hypothesis that change in learning and memory is associated with change in HFV. For all tasks, in the analyses here and to follow, we covaried the effects of age, education, estimated duration of illness, and time since surgery. These results are presented in the text below and in Table 2.

Of the learning tasks, greater improvement on the SRT was significantly associated with greater increases in mean HFV ($r = .59$, $p < .02$). Post hoc examination of right and left HFV separately showed that change in each was significantly associated with change in the SRT (right: $r = .56$, $p < .03$; left: $r = .59$, $p < .02$).

The degree of improvement in the other two learning tasks was not significantly associated with degree of increase in HFV (Logical Memory $r = .20$, $p = .43$; Paired Associates $r = .14$; $p = .57$).

For the two tests of recall at 30 min, neither was significantly associated with change in mean HFV (Logical Memory $r = .27$, $p = .26$; Paired Associates $r = .24$, $p = .33$).

Association of Change in CHV with Changes in Learning or Memory

We next tested the hypothesis that change in learning and memory is not associated with change in caudate head volume, a gray matter structure not considered to play a major role in learning and memory. The SRT, the learning task that was significantly correlated with increase in HFV, was not significantly correlated with change in CHV ($r = .41$, $p = .13$). There were also no correlations for change in CHV and change in Logical Memory learning ($r = .02$, $p = .95$) or Paired Associate learning ($r = .13$, $p = .61$).

Association of Change in Hippocampal Formation Volume and Change in Verbal Tasks

We next tested the hypothesis that that change in verbal tasks not considered strongly dependent on the hippocam-

Table 2. Partial Correlations of Change in Neuropsychological Tests with Change in Brain Volumes

	Hippocampal Formation Volume (*r*)	Caudate Head Volume (*r*)
Learning		
Logical Memory	.203	.017
Paired Associates	.141	.126
Buschke Selective Reminding Task	.586[a]	.413
Memory		
Logical Memory Delay	.274	.184
Paired Associates Delay	.237	.098
Verbal Tasks		
Vocabulary	−.025	.302
Arithmetic	−.352	−.063

[a]$p = .02$.

pus are not associated with change in HFV. There was no significant association between change in HFV and change in either arithmetic ($r = -.35$, $p = .13$) or vocabulary ($r = -.02$, $p = .92$).

Association of Changes in Cortisol, HFV, and Learning

We examined the association of change in cortisol with change in the SRT, again covarying for age, education, estimated duration of disease, and time since surgery. The degree of decrease in cortisol concentration and the degree of increase in performance of the SRT were significantly associated ($r = -.63$, $p < .04$).

Discussion

This study was designed to extend our series of investigations using CD as an experimental model to demonstrate and explore the negative effects of cortisol on brain structure and function. In this enlarged sample, change in HFV (but not CHV) again was significantly associated with the degree of decline in cortisol concentration after treatment. In all cases, the change in volume was positive, indicating HFV increased consistently in response to normalization of cortisol concentrations. This increase in HFV over time contrasts with the decrease in HFV over time reported for normal subjects (Laakso et al 2000).

Consistent with the selective region hypothesis, the degree of improvement in the SRT learning task was significantly associated with the degree of change in HFV but not CHV. Consistent with the selective task hypothesis, improvements in the two verbal tasks known not to be strongly dependent on hippocampal function (i.e., vocabulary and arithmetic) were not significantly associated with change in HFV.

A relationship between HFV and the SRT learning task is consistent with data from other studies. For example, in a study analysis combining subjects with normal aging and patients with Alzheimer's disease, mean HFV predicted performance on both the SRT learning measure and paragraph learning; however, when the abnormal group only (the Alzheimer's disease patients) were analyzed separately, learning on the SRT remained significantly associated with HFV, but paragraph learning (immediate recall) was not significantly associated (Peterson et al 2000).

In our study, whereas change in the SRT learning task was significantly associated with the change in HFV, change in the two other learning tasks (Paired Associates and Logical Memory) were not. Possible explanations for the differences we observed using various learning tasks include differences in relative difficulties of the tasks, the nature of the tasks, their degree of relative challenge to hippocampal function, and the ability of each test to tap the specific disruption of hippocampal function as reflected by alterations in HFV. The SRT likely includes a greater working memory component than the other two tasks and may be more affected by elevated cortisol, given the demonstration that acutely administered cortisol in normal subjects affects frontal lobe–based working memory, as well as hippocampus-based declarative memory (Lupien et al 1999). Of the three learning tasks we used, the SRT, composed of single, unrelated words, is the learning task least dependent on context. The other two tests involved predominantly related word pairs (Paired Associates) or the context of an overall theme (Logical Memory). We hypothesize that unrelated words represent a greater challenge to the hippocampus in pathophysiologic conditions, such as hypercortisolemia, that manifest themselves with decreases in HFV. Evidence from the early stages of Alzheimer's disease lends support to this hypothesis. Alzheimer's disease produces subtle changes in the neuroanatomy and volume of the hippocampus years before diagnosis (Braak and Braak 1995; de Leon et al 1997a; Jack et al 1999). In a study of cognitive decline in presymptomatic Alzheimer's disease patients, significant differences from normal subjects were found for unrelated word list learning and recall but not for story immediate recall (learning) or delayed recall (Chen et al 2001). Unrelated word lists may be a learning task more sensitive to the changes in hippocampal structure and function elicited by elevated cortisol concentration and manifested by changes in HFV. These alterations may be different than those produced by anatomically destructive lesions of the hippocampus, such as are produced by a stroke or by neurosurgical interventions for epilepsy.

The role of cortisol concentration per se is of importance. In our study, greater decreases in cortisol concentration after treatment, indicative of higher levels of cortisol before treatment, were associated with improved scores in learning of unrelated words. There are several potential biochemical mechanisms by which elevated cortisol before treatment and subsequent normalization of cortisol might contribute to such a result. For example, the animal literature indicates direct effects of glucocorticoids at neuronal glucocorticoid receptors, and modulation of brain excitatory amino acids, serotonin, nerve growth factors, neurogenesis, electrolytes, and glucose utilization (for review, see McEwen 2000). Although other regions of the brain are also undoubtedly impacted by such mechanisms, the hippocampus is especially vulnerable to the effects of cortisol. For example, positron emission tomography studies in normal elderly humans indicate that cortisol reduces glucose uptake selectively in the hippocampus as compared with other brain regions (de Leon et al 1997b).

In summary, we previously reported that HFV increased in Cushing's syndrome patients after treatment lowered cortisol to normal concentrations. In this study, we examined whether structural increase in HFV after treatment is associated with improvement in cognition. After partialing out age, education, duration of illness, and time since surgical treatment, greater improvement in word list learning as measured by the SRT was associated with greater increase in HFV. Thus, after cortisol levels decline and remain at normal concentrations, the structural volumetric increase in HFV is accompanied by functional improvement in learning of unrelated words.

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