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Cognitive decline in patients with Cushing's syndrome

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Abstract

Chronic exposure to elevated glucocorticoid levels in Cushing's syndrome (CS), is associated with deficits in cognitive function and in emotion. The hippocampus plays a crucial role in the behavioral manifestations of the syndrome as it is richest in glucocorticoid receptors and is thus particularly vulnerable to glucocorticoid excess. The wide distribution of glucocorticoid receptors throughout the cerebral cortex, however, suggests that several cognitive functions can also be affected by the dysregulation of glucocorticoids. In this study, we investigated how an excess of glucocorticoid hormones affects cognitive processes. Nineteen patients with chronic hypercortisolemia due to CS were compared to healthy controls matched for age, sex, education, and occupation in tests of processing of visual and spatial information, memory, reasoning and concept formation, language and verbal functions, and attention. Multivariate and univariate analyses revealed overall differences in tests of treatment of visual and spatial information, reasoning and concept formation as well as in verbal and language performance, with poorer performance from CS patients. Differences were also observed in nonverbal aspects of memory and in attention tasks. The results suggest that chronic exposure to elevated levels of cortisol is associated with deficits in several areas of cognition, particularly those involving processing of selective attention and visual components. This study also shows that hormones play an important role in the modulation of cognitive function and that their influence on cerebral structure and function merits closer scrutiny. (*JINS*, 2000, *6*, 20–29.)

Keywords: Glucocorticoids, Cushing's syndrome, Cognition

INTRODUCTION

It is now well established that the brain is a major target of circulating adrenal hormones. The steroid hormones secreted by the adrenal cortex—principally the glucocorticoids—have morphological and functional repercussions on the central nervous system. Chronic exposure to high glucocorticoid levels, such as those seen in Cushing's syndrome (CS), Alzheimer's disease, and prolonged physical and psychological stress, modify neurotransmitter function and neuronal structure of the nervous system by altering expression of particular genes (Beato, 1989; Landfield et al., 1992; McEwen, 1988; McEwen et al., 1992; Starkman et al., 1992; Uno et al., 1994). Young rats exposed to chronically elevated glucocorticoid levels develop hippocampal degeneration, affecting mainly pyramidal cells; hippocampal degeneration was due, in part, to a loss of neurons (Sapolsky et al., 1985). Exposure to high levels of glucocorticoids (GC) also reduces denditric length and branching morphology of adult hippocampal pyramidal cells (Woolley et al., 1990). Elevated glucocorticoid levels, through inhibition of compensatory axodendritic sprouting, also impair neuronal capacity to recover from injury (DeKosky et al., 1984). Prolonged exposure to high levels of GC is associated with impaired hippocampal long-term potentiation (Foy et al., 1987; Kerr et al., 1991) and can decrease hippocampal synaptic plasticity (Bodnoff et al., 1995). Finally, hypercortisolemia may also be associated with cognitive impairment and mood dysregulation (Dorn et al., 1995; Jensen et al., 1982; Ling et al., 1981; Newcomer et al., 1994; Starkman et al., 1986; Wolkowitz, 1994; Wolkowitz et al., 1990).

Cushing's syndrome is a disease characterized by an overproduction of steroid hormones, principally cortisol, from the cortex of the adrenal gland. The major endogenous cause of CS is secondary to excessive secretion of adrenocorticotropic hormone (ACTH) by pituitary corticotrope adenomas (Cushing's disease; CD) or by other tumors at some ectopic site; alternatively, excess cortisol production re-

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sults from benign or malignant tumors of adrenal gland. The etiology of the syndrome can be exogenous, for example as a result of the administration of GC in the treatment of patients with inflammatory rheumatic diseases. Inhaled glucocorticoids and topical use may also induce CS (Fisher, 1995). The rationale for treatment with GC is their potent immunosuppressive and antiinflammatory action (Schteingart, 1989). The clinical manifestations of CS involve many organ systems and biochemical processes. The most common clinical observations are central obesity, muscle weakness and osteoporosis, hypertension, cutaneous atrophy, hyperglycemia. In women, hirsutism and menstrual disorders and, in men, impotence are observed (Krieger, 1983). Elevation of cortisol has been documented to cause cerebral atrophy and ventricular enlargement in patients with CS and in those receiving exogenous GC (Bentson et al., 1978; Leclerc et al., 1996; Momose et al., 1971). Starkman et al. (1992) have also suggested that reduced hippocampal volume is associated with elevated cortisol production in patients with CS.

Neuropsychiatric disorders and personality changes have been observed in most patients with CS. In 53 verified cases of CS, Starr (1952) reported that 60% of these patients showed personality changes. Severe depression is the commonest mental disturbance, followed by psychosis, nervousness, and irritability. Trethowan and Cobb (1952) reported that depression associated with retardation was the most frequent mental change in their group of CS patients. Cohen (1980) observed that 25 of 29 consecutive unselected patients were significantly depressed; removal of the tumor or hyperplastic glands was followed by a reduction of depressive symptoms. Haskett (1985), in the context of a longitudinal study, noted that 25 of 30 patients with CS met diagnostic criteria for mood disorders: 20 patients suffered from major depressive disorder and 8 from bipolar disorder. More recently, Dorn et al. (1995) reported that patients with CS presented with significant psychiatric disturbances expressed primarily by atypical depression. Taken together, the biological and psychological aspects of CS provide us with a natural model for studying the interaction between endocrinology and neuropsychology. An examination of the relationship between overproduction of steroid hormones and neuropsychological function may help elucidate the interaction between endocrinological and cognitive functioning.

Few studies however, have investigated the neuropsychological correlates of CS. The first such investigation evaluated 35 unselected CS patients using the Michigan Neuropsychological Test Battery (Whelan et al., 1980). The study revealed diffuse bilateral cerebral dysfunction in 2/3 of the patients. Impairment was, however, more frequent and more severe in nonverbal visual–ideational and visual memory functions. Starkman et al. (1981) also reported generalized impairment including disturbances in affect (depressed mood and crying), in cognitive functions (decreased concentration and memory; perceptual distortions), and in vegetative functions (insomnia and decreased libido). More recently, Starkman et al. (1992) observed moderate-to-severe deficits in a wide variety of language and nonverbal subtests in more than 1/3 of their CS patients ($N = 35$). The studies cited here suggest that cognitive deficits are a characteristic feature of CS. The lack of appropriate control groups in these studies, however, limits our understanding of this interaction between hormones and cognition and may weaken the conclusions drawn here. Adequate comparison with a control group is present in the study by Mauri et al. (1993) who found moderate impairment in several aspects of memory such as logic, both learning and retrieval, serial learning, backward digit span, visual reproduction, and digit symbol substitution. The results of these four studies indicate that cognitive impairment—more specifically in learning and memory and in nonlanguage functions—may be a hallmark of CS.

The modulation of brain function by GC is relatively well understood. Glucocorticoids act, in a large part, by binding to intracellular receptors for adrenal steroids—mineralocorticoid (MR, type I) and glucocorticoid (GR, type II) receptors (McEwen et al., 1986). These receptors are differentiated by glucocorticoid affinity and neuroanatomical distribution. Type I—high affinity MR binding sites—are almost exclusively localized in the hippocampus and septum. Within the hippocampus, they are widespread but most plentiful in the CA1, CA3 and dentate regions (Reul & de Kloet, 1985). In contrast, type II GR are lower affinity sites that are activated during stress and at the peak of the circadian cycle (Reul et al., 1987; Spencer et al., 1990). GR are widely distributed throughout the brain, but are found in greater concentration in the hippocampus, septum, amygdala, paraventricular nucleus of the hypothalamus, areas of the cerebral cortex—in layers II, III and VI of the frontal, frontoparietal and occipital cortex—and in the brainstem (Aronsson et al., 1988; Reul & deKloet, 1986; Van Eekelen et al., 1988). The presence of glucocorticoid receptors outside the hippocampal formation strongly suggests a pathophysiologic role of the glucocorticoid hormones in cognition—which likely extends beyond its common specific reported effects on memory and learning and may include, among others, processing of visual information.

The cerebral regions known to be involved in visual processing are the posterior areas of the brain, especially posterior parietal, inferior temporal, and occipital regions for the perceptual recognition and organization of visuospatial skills, and prefrontal regions, between parietal and frontal lobes, for facial recognition (Scalaidhe et al., 1997) and for the planning and foresight aspects of spatial function. Patients with damage to the posterior parietal cortex, for example, demonstrate a constellation of spatial impairments—such as an inability to make comparative judgments of line length or difficulty in organizing the parts of a pattern (Mishkin et al., 1982; Ungerleider & Brody, 1977). Overproduction of GC has been reported in Alzheimer's disease, where during its early course both episodic memory failure and visual processing abnormalities are commonly apparent (Geldmacher et al., 1995; Kaskie & Storandt, 1995; Mendez et al., 1990). Moreover, visuospatial impairment fol-

lowing posterior cortex injury can be attenuated following administration of an ACTH 4-9 analog (Wells et al., 1995).

Given the wide range of reported effects of increased levels of GC, we evaluated several aspects of cognitive function in a group of CS patients to determine whether high levels of GC hormones are associated with limited or wide ranging neuropsychological impairment. The choice of tests allowed us to explore specific dimensions of information processing: visual perceptual and constructional aspects, concept formation and reasoning, attention and language as well as verbal and nonverbal memory.

METHODS

Research Participants

Patients who had been referred to the Division of Endocrinology of the Notre-Dame, Hôtel-Dieu and St-Luc hospitals in Montreal were tested prior to surgical treatment. Etiology of CS had been established by usual clinical criteria and biochemical findings—lack of normal cortisol circadian rhythm, excessive cortisol secretion as indicated by high plasma cortisol and urinary free cortisol concentrations, and failure to suppress cortisol normally after dexamethasone administration. In addition, participants were screened for hypomania by members of the research team, who were asked to indicate whom they thought might by suffering from this condition. Two CS patients with severe depressive disorder (Beck Depression Scale score greater than 17[1]; Beck, 1987) and another with visual field damage (as assessed with Vision Tester, Model 2000, Group 1 standards–administrative and clerical) were excluded from the study. In all, 19 CS patients with ACTH-dependent CD ($N = 11$) or ACTH-independent CS ($N = 8$) due to adrenal disease agreed to participate in the study. The mean estimated duration of disease (time ranging from the estimated symptom onset to diagnosis confirmation) was 42.7 ± 26.9 months (range: 15–120 months). Urinary free cortisol concentrations ranged from 198 to 11510 nmol/24 hr (normal range is 55–195 nmol/24 hr); range of AM plasma cortisol levels was 279–3153 nmol/l and range of PM plasma cortisol levels was 354–3858 nmol/l (normal range is 165–695 nmol/l). Plasma ACTH levels ranged from zero to 24 pmol/l (normal values are 4–16 pmol/l).

Control participants, selected from the patients' social environments, were carefully matched, one to one, with CS patients for age (47.11 years ± 11.73; 46.79 years ± 10.97; respectively), education (13.0 year ± 3.89; 12.16 year ± 4.06), sex (18 women and 1 man in each group) as well as for type of occupation. All were fully oriented in space and time and a few patients reported only a mild impairment in memory and attention in everyday life tasks.

[1]Items 18, 19, and 20, which are not appropriate for CS patients (e.g., weight loss), were omitted.

Tests and Procedure

A battery of tasks including tests to assess attention (Visual target detection, Stroop Test, Digit Symbol Substitution Test, Trail Making Test), visuospatial processing of information (Judgment of Line Orientation, Bells Test, Hooper Visual Organization, Gollin Figures, Block Design, Object Assembly, Visual Reproduction–Copy), memory performance (California-Verbal Learning Test, Logical Memory, Digit Span, Visual Memory, Benton Visual Retention Test), reasoning and concept formation (Comprehension, Picture Completion, Picture Arrangement, Arithmetic, Similarities, Raven's Standard Matrices) and verbal fluency (Vocabulary, Letter, and Category Fluency).

Visual target detection was tested via a letter-cancellation task adapted from the *d*2 cancellation test (Richer et al., 1993). The selective attention task includes three conditions gradually increasing in difficulty: detecting occurrences of a target letter randomly interspersed among *d*s, detecting occurrences of a target letter among other distractor letters; detecting occurrences of three different target letters among distractors. The *Stroop* task (Stroop, 1935) measures intentional attention, the inhibition of a response to the salient detail and attention to the less salient detail. The test includes reading words (color names), color naming of colored patches, and color naming of the ink in which words representing incompatible color names are typed. Number of items completed in 45-s and errors in each of the three conditions were recorded. The *Digit Symbol Substitution* (DSS) test, a subtest of the WAIS–R, is a test of incidental learning, ability to learn new material, rapid and systematic visual scanning, memory, response speed, visuomotor coordination, and selective attention. Participants are asked to fill, as quickly as possible, rows of small blank spaces with the number that is paired with the symbol above the blank space. Finally, the *Trail Making Test* measures visual scanning, mental tracking, and the ability to keep track of two simple concepts (Lezak, 1995). The participant must first draw lines to connect consecutively numbered circles (Trails A) and then connect the same number of consecutively numbered and lettered circles by alternating between the two sequences (Trails B). *Judgment of Line Orientation* (Benton et al., 1978) examined the ability to estimate angular relationships between line segments by visually matching angled line pairs to a number of radii forming a semicircle. The test consists of 30 items, each showing a different pair of angled lines to be matched to the display cards. The *Bells Test* (Gauthier et al., 1989) is sensitive to visual inattention, visual exploration and detection of salient stimuli. It consists of 315 silhouetted objects distributed in a pseudorandom manner on a sheet of paper with 35 bells scattered among them. Participants were asked to circle bells as fast and as accurately as possible. In the *Hooper Visual Organization Test* (Hooper, 1983), the participant's task was to name each of 30 more or less readily recognizable cut-up objects. The test is designed to measure the ability to organize and integrate visual stimuli. The *Gollin*

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Figures Test (Gollin, 1960) evaluates the ability to extract meaning from incomplete visual information. The test consists of 18 picture series of five line drawings of common objects ranging in completeness from a barely suggestive sketch to a complete drawing of the figure. *Block Design*, a subtest of the WAIS–R (Wechsler, 1981) is a construction test where the participant uses white and red blocks to construct replicas. The test evaluates abilities in perception, at the conceptual level and in constructive execution. It also evaluates visuospatial organization, rapid detection of the underlying principles of organization and the ability to translate that detection into a replica. *Object Assembly*, also a subtest of the WAIS–R, contains four cut-up cardboard figures of common objects given in order of increasing difficulty. This is a test of visuospatial manipulation with great importance accorded to perceptual–conceptual and constructional abilities. *Visual Reproduction* (copy administration) test, a subtest of the Wechsler Memory Scale (WMS; Wechsler, 1974), is a drawing task. This test investigates both perceptual organization and construction skills. The test material consists of a reproduction of three figures and the subject is instructed to copy the figures. The *California Verbal Learning* test (CVLT; Delis et al., 1987) assesses various aspects of verbal learning and memory and includes three lists of words. The first list consists of five presentations with recall of 16 items from four semantic categories; the second has the same structure, with only two semantic categories being the same as in the first list and one presentation; the third, a recognition list, includes 16 target items from the first list, plus distractors that share or do not share semantic or phonological membership with items in that list. Administration and scoring were conducted according to the instruction manual. *Digit Span* forward and backward, a subtest of the WAIS, evaluates short-term verbal memory or working memory and brief attentional skills. *Logical Memory*, a subtest of WMS, is a story task; two stories are read to the participants and there are immediate and delayed free recalls. *Visual Memory*, also a subtest of WMS, is a visual memory task includes both immediate and delay recall. It consists of four items composed with more or less simple geometric designs. The *Benton Visual Retention* test evaluates short-term (15-s) visual memory for three geometric designs varying in size, form, and details of spatial location relative to each other. *Comprehension*, a subtest of the WAIS–R, evaluates verbal reasoning. The test includes open-ended questions that tap common-sense judgment and practical reasoning. *Picture Completion*, another subtest of the WAIS–R, consists of 20 incomplete pictures arranged in order of difficulty with instructions to tell what important part is missing. This test measures visual recognition, remote memory, logical reasoning and judgment about visually presented material with a social content. *Picture Arrangement*, a subtest of the WAIS–R, consists of 10 sets of cartoon pictures that make up stories. Each set is presented in scrambled order with instructions to rearrange the pictures to make the most sensible story. This test also evaluates concept formation, judgment and reasoning concerning visually presented material with a social content. *Arithmetic*, a subtest of the WAIS–R, is composed of 14 arithmetic reasoning problems. These problems evaluate logical mathematic abilities and resistance to distraction. *Similarities*, also a subtest of the WAIS–R, is a test of verbal concept formation. Participants are asked to explain in what ways the two words in a pair are alike. The word pairs range in difficulty from the simplest to the most difficult. *Raven's Standard Matrices* (Raven et al., 1976) consist of a series of visual pattern matching and analogy problems pictured in nonrepresentational designs. The test requires subjects to conceptualize spatial, design, and numerical relationships ranging from the very obvious and concrete to the very complex and abstract. *Vocabulary*, a subtest of the WAIS–R, is made up of 35 words arranged in order of difficulty. The score reflects both extent of recall vocabulary and the precision of speaking vocabulary. *Letter and Category Fluency* require the participant to produce within a 2-min period as many words as possible belonging to a specific category and words with a specific initial letter. Verbal and Performance IQ scores were also obtained with the WAIS–R.

Participants were individually tested in a quiet room. For CS patients, all tests were administered during hospitalization prior to surgery.

RESULTS

General Intellectual Functioning

Full Scale IQ scores were within the normal range for all participants. A *t* test was conducted to compare Verbal and Performance IQ and there was no significant Verbal–Performance disparity in either group. However, there were group differences, suggesting a better general performance on the part of control subjects. Verbal, performance, and full scale IQ scores are presented in Table 1.

Attention

Table 2 summarizes the results of the CS and control groups on attention tasks (speed and error rates). ANOVA results revealed no significant differences and there were very few errors in baseline and single-target detection conditions (Con-

Table 1. Comparison of IQ scores

Score	CS ($N = 19$) $M \pm SD$	Control ($N = 19$) $M \pm SD$	F	p*
Verbal IQ	91.32 ± 10.27	102.53 ± 9.12	8.63	.006
Performance IQ	92.95 ± 11.71	107.16 ± 10.76	8.54	.006
Full Scale IQ	91.26 ± 11.03	104.79 ± 10.29	9.42	.004

*All significant differences are between CS patients and controls. There are no differences between Verbal and Performance IQ scores within each group.

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Table 2. Speed and error rates in attentional tasks

	CS ($N = 19$)		Control ($N = 19$)	
Task	Speed (items/s) $M \pm SD$	Errors (%) $M \pm SD$	Speed (items/s) $M \pm SD$	Errors (%) $M \pm SD$
Target Detection Task				
Visual Detection Baseline (Condition A)	3.93 ± 0.67	–	4.45 ± 1.01	–
Single-target detection (Condition B)	2.01 ± 0.51	0.85 ± 1.37	2.24 ± 0.48	0.55 ± 0.55
Three-target detection (Condition C)	1.34 ± 0.38	7.96 ± 7.46	1.62 ± 0.34	4.32 ± 3.53
Trail Making Test*				
Trails A	0.70 ± 0.21	–	0.91 ± 0.34	–
Trails B	0.33 ± 0.12	–	0.46 ± 0.17	–
Stroop Task				
Word reading (W)	2.12 ± 0.3	0.26 ± 0.93	2.36 ± 0.37	–
Color naming (C)	1.55 ± 0.29	1.63 ± 1.46	1.74 ± 0.36	0.84 ± 1.01
Color naming with interference (CW)	0.82 ± 0.26	6.32 ± 6.91	0.98 ± 0.2	1.58 ± 1.43
DSS Test	0.49 ± 0.1	–	0.63 ± 0.15	–

*For the Trail Making Test Part A, time taken was 38 ± 10.17 s for Cushing patients *vs.* 31.47 ± 11.80 for controls [$F(1,36) = 3.76$, $p = .06$]; for Trails B it was 90.68 ± 44.82 s for Cushing patients *vs.* 61.47 ± 22.94 s for controls [$F(1,360 = 6.39, p = .016$].

ditions A and B, Fs < 1). However, CS patients were slower in the three-target detection task [Condition C; $F(1,36) = 5.47$, $p = .025$]. There was no significant difference between the two groups in error rates in Condition C [$F(1,36) = 3.69$, $p = .062$].

Performance in the Trail Making A and B tests, was significantly slower for CS patients [Trails A: $F(1,36) = 5.17$, $p = .029$; Trails B: $F(1,36) = 7.49$, $p < .01$]. The effect of alternating between the two sequences (Trails B) on performance speed was evaluated in an analysis of covariance (ANCOVA) on the Trails B scores, using Trails A scores as covariate. In this analysis, CS patients were not significantly slower than controls [$F(1,36) = 2.02$, $p = .164$]. Error rates were negligible in these two conditions.

In the Stroop task, CS patients were significantly slower than controls in Word Reading [W; $F(1,36) = 4.84$, $p = .034$] and in color naming with interference condition [CW; $F(1,36) = 4.41$, $p = .043$]. As with the Trail Making Tests, the reading interference effect of the Stroop on performance speed was examined in an ANCOVA on the CW scores, with W condition scores as covariate. In this ANCOVA, CS patients' performance was not significantly slower than controls' [$F(1,36) = 1.33$, $p = .256$]. However, error rates were significantly higher in CS patients than in controls in the CW condition [$F(1,36) = 7.97$, $p < .001$]. Finally, CS patients were significantly slower than controls in the DSS test [$F(1,36) = 10.81$, $p = .002$]. Table 2 shows speed and error performances of CS and control groups in attention tasks.

Visuospatial Processing

Multivariate analyses of variance (MANOVAs) were conducted to compare the overall performance profile between controls and CS patients in the treatment of visuospatial information. Results revealed a general difference in performance between the two groups, suggesting a poorer performance on the part of CS patients [Pillais's = .6090; $F(1,36) = 2.28$, $p = .038$]. Separate univariate F tests showed group differences in Hooper Visual Organization ($p < .01$), Block Design ($p < .05$), Object Assembly ($p < .05$) and Visual Reproduction ($p < .001$). Table 3 shows the performance of the two groups on visuospatial tasks.

Memory

A MANOVA was also conducted on CVLT scores (learning, immediate and delayed recall and recognition) to determine whether group differences also emerged in aspects of verbal memory. Results showed that controls' overall performance was not better than that of the CS group [Pillais's = .5956; $F(1,36) = 1.55$, $p = .174$]. *Post-hoc* univariate F tests showed a significant difference between the groups only in the recall of the second list ($p < .05$) and in the short-term primed recall ($p < .05$). Comparisons on intrusions and perseveration errors, clustering and other measures of recognition and organization of verbal information from the CVLT revealed no difference between the two groups. Mean performance scores for the various measures of the CVLT are presented in Table 3. There were no differences in logical memory scores (immediate, long-term) between the two groups. Digit Span forward performance was, however, poorer in CS participants ($p < .02$). Comparison of visual memory scores further revealed significant differences between the two groups, in both immediate and long-term recall (ps $< .01$). In contrast, BVRT performance was quite similar for the two groups (see Table 4).

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Table 3. Comparison of performance scores in visuospatial tasks

Task	CS ($N = 19$) $M \pm SD$	Control ($N = 19$) $M \pm SD$	F	p*
Simple perceptual recognition				
Judgment of Line Orientation	20.21 ± 4.91	22.47 ± 4.98	1.99	.167
Perceptual inattention				
Bells Test*	95.84 ± 37.13	80.69 ± 26.28	2.11	.153
Perceptual organization				
Hooper Visual Organization	24.42 ± 3.15	27.16 ± 1.61	11.37	.002
Gollin Figures*	1.86 ± 0.39	1.74 ± 0.31	1.22	.277
Construction tasks				
Block Design	7.89 ± 2.83	9.74± 2.00	5.66	.023
Object Assembly	7.74 ± 2.66	9.21± 1.58	5.38	.026
Visual reproduction	12.95 ± 1.48	14.55± 0.66	18.594	.001

*Scores on these tests are negatively correlated with performance.

Concept Formation

MANOVAS showed overall differences between controls and CS participants in concept formation [Pillais's = .2749; $F(1,36) = 6.64$, $p = .004$] and subsequent univariate F tests further showed that the performance of CS participants was poorer in the Similarities test and Raven's Progressive Matrices (ps < .02). Differences were also observed in reasoning abilities (Comprehension and Picture Completion; ps < .01). Table 5 shows mean performances on the tests used.

Table 4. Verbal and nonverbal memory performance scores

Test	CS ($N = 19$) $M \pm SD$	Control ($N = 19$) $M \pm SD$	F	p
CVLT				
First five trials	52.63 ± 12.98	59.37 ± 10.68	3.05	.089
Tuesday list	5.63 ± 2.22	7.63 ± 2.39	7.16	.011
SFR*	11.32 ± 3.58	12.47 ± 2.82	1.22	.275
SPR	11.68 ± 3.25	13.74 ± 1.82	5.76	.022
LFR	11.95 ± 3.06	13.47 ± 2.14	3.16	.084
LPR	12.32 ± 3.02	13.68 ± 1.92	2.78	.104
Recognition	15.11 ± 1.52	14.79 ± 1.23	0.49	.486
Intrusion errors	4.00 ± 4.51	2.63 ± 4.65	0.84	.363
Clustering	37.16 ± 23.45	46.11 ± 21.83	1.48	.231
Organization	4.21 ± 3.71	5.79 ± 4.74	1.31	.260
Logical memory				
Immediate recall	8.91 ± 3.33	10.38 ± 2.61	2.30	.138
Long-term recall	8.21 ± 3.13	8.70 ± 2.51	0.28	.600
Digit Span				
Forward	5.68 ± 1.57	7.37 ± 2.34	6.80	.013
Backward	5.21 ± 1.58	6.37 ± 2.09	3.71	.620
Visual memory				
Immediate recall	11.05 ± 2.50	14.24 ± 0.86	27.61	.001
Long-term recall	9.29 ± 4.00	12.34 ± 2.48	7.99	.008
BVRT				
Immediate recall	8.05 ± 1.39	8.26 ± 0.65	0.35	.555
Long-term recall	8.21 ± 1.27	8.68 ± 1.06	1.55	.220

*SFR: short-term free recall; SPR: short-term primed recall; LFR: long-term free recall; LPR: long-term primed recall.

Verbal Function and Language Skills

A MANOVA was also conducted to compare the overall performance profile between control subjects and CS patients in verbal functions and language skills. Results showed differences between the two groups [Pillais's = .3098; $F(1,36) = 3.70$, $p = .013$] and separate univariable F tests showed, again, that the CS group performance was poorer in all tasks (ps < .01; Table 6).

DISCUSSION

In this study, we were interested in determining to what extent chronic exposure to elevated glucocorticoid levels such as those seen in CS affects various aspects of cognitive function. Our findings revealed that CS patients manifest variable degrees of deficit on all standardized neuropsychological

Table 5. Concept formation and reasoning

Test	CS ($N = 19$) $M \pm SD$	Control ($N = 19$) $M \pm SD$	F	p
Concept formation				
Similarities	8.32 ± 2.47	10.74 ± 1.63	12.70	.001
Raven's Progressive Matrices	40.40 ± 9.20	48.80 ± 8.60	6.25	.019
Reasoning				
Comprehension	9.74 ± 3.41	11.74 ± 2.31	9.42	.004
Picture Completion	8.53 ± 2.48	11.00 ± 2.16	10.74	.002
Picture Arrangement	6.89 ± 2.54	8.53 ± 2.76	3.60	.066
Arithmetic	9.95 ± 3.61	9.68 ± 2.38	2.64	.113

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Table 6. Verbal functions and language skills

Test	CS ($N = 19$) $M \pm SD$	Control ($N = 19$) $M \pm SD$	F	p
Vocabulary	8.32 ± 2.60	11.11 ± 2.64	10.73	.002
Letter Fluency	30.00 ± 8.10	38.68 ± 10.09	8.56	.006
Category Fluency	35.63 ± 7.78	42.00 ± 7.75	6.38	.010

tests. There was a clear difference between CS and controls in both verbal and performance as well as Full Scale IQ. These results point to a general decline relative to a strictly matched, participant by participant, control group in most cognitive domains evaluated—perceptual and conceptual dimensions, as well as reasoning and constructional abilities, in visuospatial and verbal information processing—although all participants' IQ scores were within the normal range.

Performance on the cancellation task suggests that CS patients have more difficulty with visual multiple target detection than do their matched controls. This effect cannot be attributed to a nonspecific slowing, since it is observed in the multiple letter cancellation condition only (Condition C). Neither can it be attributed to a failure to remember the targets in the task, since all patients are able to recall them without error. Similarly, the CS group made more errors than their controls in the color-word interference trial of the Stroop test. Furthermore, the lower performance of CS patients in the Digit Symbol Substitution test also strongly suggests that attentional and visuomotor functions may also be impaired (see also Mauri et al., 1993). The coexistence of deficits in multiple target detection, Stroop and Digit Symbol Substitution tests also adds support to the notion that selective attention changes may be associated with chronic exposure to high levels of GC. These data are compatible with those of Lupien et al. (1994) who found that selective attention measures and levels of GC were negatively correlated in elderly participants.

Performance on the simple perceptual recognition of angles (Judgment of Line Orientation) and perceptual inattention (Bells Test) revealed no differences between the two groups. Newcomer et al. (1994) had also reported that visual recognition was not impaired in participants briefly exposed to GC. Differences start to appear with more complex measures and the weight of these tests would tend to indicate widespread changes involving both hemispheres, though the right hemisphere might be more affected than the left. In these visuospatial tasks, the performance of CS patients was significantly lower relative to that of controls, suggesting a problem in perceptual organization, conceptualization, and construction tasks, while perceptual attention and recognition abilities appeared preserved. Since disorders of visual attention are more apt to occur during the acute stages of a sudden-onset condition (e.g., Marsh & Kersel, 1993), it is probably the case that in chronic disease with insidious onset, as in CS, no disorders of visual attention are observed.

Performance of CS patients in the Gollin Figures Test was similar to that of controls. The Gollin Figures Test, as is the case with the Hooper Visual Organization Test, was used to evaluate perceptual organization abilities. It may be that the contrast in performance between the Gollin and Hooper tests is due to the nature of the stimuli used. In the Hooper Visual Organization Test, the stimuli are fragmented and unstructured. In the Gollin Figures Test, the stimuli are incomplete but structured, making them more readily identifiable (as with the Bells Test) and less vulnerable to the effects of brain damage (Lezak, 1995). Unlike the other tests, both the Gollin Figures and Bells Tests draw more heavily on object recognition than on the treatment of abstract spatial relations. Moreover, the Gollin Figures Test is probably easier since it was developed to investigate behavioral development and young children can accomplish the task without much difficulty. Finally, in contrast to Gollin figures, the Hooper test was found to be very sensitive to disease duration in Parkinson's disease patients (Levin et al., 1991). The performance of CS participants was poorer than that of controls in construction tasks combining perceptual activity, motor response, and a spatial component. CS patients appear unable to conceptualize the objects in the Object Assembly test. They can put the objects together in piecemeal fashion by matching lines and edges in a methodical manner, but they do not recognize what they are putting together until the puzzle is almost completely assembled (Lezak, 1995), much as left-brain-damaged patients do (Kaplan et al., 1991).

Verbal memory problems, however, appear less marked in CS. Differences in CVLT measures were observed only on measures of free recall of a second list and short-term primed recall as well as in digit span forward. There were no differences between CS patients and controls on all other measures of verbal immediate, delayed and primed recall, nor in learning and recognition. In contrast to our findings, Wolkowitz et al. (1990) had previously reported glucocorticoid treatment-related errors of commission during the word list recall task. Differences in methodology may account for this. In the Wolkowitz et al. (1990) study, free recall was tested after one presentation only of the word list while there were five presentations of the list in the present study.

No significant differences between the two groups were observed on the logical memory task. Our results agree with those of Lupien et al. (1994) who found no correlation between glucocorticoid measures and paragraph recall in aged subjects (but see Mauri et al., 1993; Newcomer et al., 1994). In contrast, both immediate and long-term recall of visual memory are significantly impaired in CS, suggesting that aspects of visuospatial processing are susceptible to the disease. The present results are in accord with those of Whelan et al. (1980) who found that there is a generally better preservation of verbal than nonverbal memory skills in CS patients. Digit span was shorter in CS, suggesting an impairment in short-term retention capacity and auditory attention. Systematic analyses of digit span error types have been conducted showing that CS patients, as is the case with multiple sclerosis and diffuse brain damage, are apt to re-

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peat correctly the digits but mix up the order (Lezak, 1995). Ruff et al. (1986) have also suggested that a reduction in the number of digits may mean severe brain injury in CS.

Scale VI of the Wechsler Memory Scale: Copy Administration and the Benton Visual Retention Test were used in tasks of visual recall. The present results showed that, relative to controls, the performance of CS patients was significantly lower in the visual reproduction task only. It is possible that the constructive or visuomotor component involved in copying tests may explain this dissociation between visual reproduction and visual retention. This is consistent with the performance of CS patients in other tests exploring construction abilities and visuomotor functions.

In the present study, performance in both the Similarities and Raven's Progressive Matrices Tests, as well as in Comprehension, was significantly poorer in CS participants (but see Mauri et al., 1993). Although, not statistically significant, the large difference between the two groups in the Picture Arrangement Test adds to the suggestion that conceptual problems and impaired reasoning may also be characteristics of a cognitive decline in CS (see also Whelan et al., 1980).

Finally, vocabulary level and language performance were also significantly depressed in CS. The quality of responses given by CS patients is poorer than that of controls: Responses are vague and not as detailed. Houlihan et al. (1985) showed similar results in patients with Alzheimer's disease. Again, the lower performance of CS patients in verbal fluency may be indicative of frontal lobe damage (e.g., Janowsky et al., 1989).

It is tempting to speculate that overall differences in IQ may explain the differences observed between CS and controls. However, not all aspects of performance were equally impaired in CS. As mentioned previously, problems were primarily evident in tasks of visuospatial processing or with visuospatial components (e.g., Raven's matrices, letter cancellation). Moreover, there was no difference between Verbal IQ and Performance IQ scores, for both groups. We suggest, for reasons presented below, that excess of glucocorticoid secretion may, at least partly, explain the results observed here.

The presumed effects of glucocorticoid hormones on all but aspects of cognition have been infrequently reported. Usually, most descriptions of glucocorticoid effects are largely limited to cognitive functions or mechanisms mediated by cerebral structures that present an interaction between these adrenal hormones and specific receptors. Until now, the majority of investigations on this interaction were directed at so-called hippocampus-associated functions—the hippocampus being particularly rich in adrenal steroid receptors (McEwen, 1988). Furthermore, evidence also suggested that prolonged exposure to elevated levels of glucocorticoid hormones leads to loss of hippocampal neurons (Sapolsky et al., 1985).

Thus, most studies of the effect of GC and cognitive function have focused on the interaction between GC, hippocampal integrity, and memory deficits. For example, administration of synthetic GC to healthy participants results in impaired attention and verbal memory (Kopell et al., 1970; Newcomer et al., 1994; Wolkowitz et al., 1990). In depressed patients, excess production of ACTH and cortisol was correlated with poor visual and verbal learning performance (Aperia et al., 1985) and, in Alzheimer's disease, associations between plasma cortisol concentrations and memory impairments have been reported (Leon, 1988). This has also been the case in schizophrenia (Keshevan et al., 1989; Newcomer et al., 1991) and in aged healthy volunteers with high cortisol secretion (Lupien et al., 1994). In studies with CS patients, investigators had also directed their attention to memory impairment (Mauri et al., 1993; Starkman et al., 1992). Finally, Starkman et al. (1992) reported an association between reduced hippocampal formation volume, memory dysfunction, and elevated cortisol levels in patients with CS.

Nevertheless, the site-preferential effects of GC on hippocampal neurons does not provide an adequate account of the observed impairments in visuospatial, language, and attention information processing in CS. An alternative account relies on the implication of type II receptors distributed more or less uniformly throughout other brain regions such as frontal, frontoparietal, and occipital cortex and in the brainstem (Aronsson et al., 1988). Type II adrenal steroid receptors have a low affinity for adrenal hormones and are especially targeted when glucocorticoid hormone levels are elevated, as is the case at diurnal secretory peaks of cortisol, repeated or prolonged physical and psychological stress, and in CS (McEwen, 1988). In the rat neocortex, which has moderate numbers of adrenal steroid receptors, hypoxia–ischemia damage was modulated by glucocorticoid manipulation (Koide et al., 1986; Sapolsky & Pulsinelli, 1985). In the striatum, which contains adrenal steroid receptors, a moderate degree of hypoxia–ischemia damage by GC was noted (Sapolsky & Pulsinelli, 1985), while another study saw a protection effect (Koide et al., 1986). Finally, as suggested by Newcomer et al. (1994), the notion that GC may preferentially affect the functioning of hippocampus remains to be tested by direct measures of neuronal function. We are currently investigating this aspect with spectroscopic and magnetic resonance techniques.

It is thus plausible that extrahippocampal effects of GC can lead to cognitive impairments other than the commonly reported effects on memory and learning, especially in chronic hypercortisolemia conditions. Recent observations in Alzheimer's disease—a well-documented example of disorder with hypercortisolemia—add support to this alternative account. Until now, memory impairment had been regarded as the primary symptom of cognitive impairment in the early stages of the disease. Recently, Kaskie and Storandt (1995) have shown that visual processing abnormalities were also present in the early stages of Alzheimer's disease. Finally, it should be recalled that Whelan et al. (1980) had already suggested that the pattern of neuropsychological deficits of CS patients were comparable to those seen in patients with other types of diffuse bilateral neuropathological processes.

To the extent that we can attribute differences in cognitive performance to differential effects of cortisol secretion, this study illustrates that several cognitive domains may be susceptible to hormonal dysregulation. Research directed at determining the influence of GC on cognitive function may be oriented toward specific cognitive areas, as suggested by the data presented here.

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