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The relationship between cumulative exogenous corticosteroid exposure and volumes of hippocampal subfields and surrounding structures

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Abstract

Purpose/Background: Glucocorticoids are a class of hormones that include naturally occurring cortisol and corticosterone, as well as prescription drugs commonly used to manage inflammatory, autoimmune, and allergic conditions. Adverse effects, including neuropsychiatric symptoms, are common. The hippocampus appears to be especially sensitive to the effects of glucocorticoids. However, to our knowledge, no studies to date have examined hippocampal subfields in humans receiving glucocorticoids. We examined patients on chronic glucocorticoid regimens to determine relationships between dose and duration of treatment, and hippocampal subfields, and related regions volumes.

Methods/Procedures: The study included adult men and women receiving at least 5 mg daily of prednisone equivalents for at least 6 months. Volumes of brain regions were measured via magnetic resonance imaging (MRI). A multivariate general linear model was used for analysis, with brain volumes as dependent variables and age, gender, and cumulative corticosteroid exposure, as predictors.

Findings/Results: The study population consisted of 81 adult outpatients (43 male) on corticosteroids (mean dose = 7.88 mg, mean duration = 76.75 months). Cumulative glucocorticoid exposure was negatively associated with left and right hippocampal dentate gyrus/CA3 (DG/CA3) volume. In subsequent subgroup analysis, this association held true for the age group older than the median age of 46 years but not for the younger age group.

Implications/Conclusions: This finding is consistent with previous studies showing detrimental effects of elevated glucocorticoids on the hippocampus but further suggest that the dentate gyrus and CA3 regions are particularly vulnerable to those effects, which is consistent with animal models of chronic stress but has not been previously demonstrated in humans.

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Keywords

Hippocampus; corticosteroids; neuroimaging

Introduction

Glucocorticoids are a class of steroid hormones involved in metabolism, modulation of the immune system, and mediation of the stress response.[1,2] In humans, the major endogenous glucocorticoid is cortisol. Glucocorticoids are also widely prescribed to manage a variety of inflammatory, allergic, and autoimmune conditions.[3] High levels of both endogenous and exogenous glucocorticoids have been associated with systemic effects, including neuropsychiatric symptoms such as memory impairment and mood disorders.[4,5] In extensive animal studies, the hippocampus appears to be especially sensitive to the deleterious effects of elevated glucocorticoids, including dendritic shortening, impaired neurogenesis, and neuronal death.[6] Among the hippocampal subfields, some animal studies have shown that the CA3 region is exquisitely sensitive to the effects of exogenously administered glucocorticoids or conditions associated with elevated glucocorticoids, such as chronic stress.[7–9] However, other studies suggest that the CA1 region may also be affected.[10–12]

To date, no studies have delineated the effects of chronic glucocorticoid administration on separate subfields of the hippocampus in humans although the limited existing data suggest overall detrimental effects of elevated glucocorticoid levels on brain structure and function. In patients with Cushing's syndrome, characterized by hypercortisolemia, lower hippocampal volume was associated with higher plasma cortisol levels and lower performance on verbal learning and recall tasks.[13] We previously reported that patients on chronic corticosteroid regimens had smaller hippocampal volumes, lower N-acetylaspartate (NAA; a marker of neuronal viability), and performed worse on declarative memory assessments compared to controls.[14] Structures surrounding the hippocampus may also be affected by glucocorticoid exposure. Acute administration of cortisone decreased blood flow to the parahippocampal gyrus, visual cortex, and cerebellum in humans.[15] Chronic glucocorticoid exposure could thus conceivably result in prolonged blood flow reduction and atrophy within these regions. In this study, we examine the relationship between cumulative corticosteroid use and volumes of hippocampal subfields (dentate gyrus (DG)/CA3, CA1, and subiculum) and surrounding structures of the medial temporal lobe (MTL) (entorhinal, perirhinal, parahippocampal cortices).

Materials and Methods

We analyzed baseline data from two studies (and) involving outpatients receiving chronic corticosteroid therapy. Inclusion criteria were: age 18–70 years old and prescription of ≥ 5 mg oral corticosteroids for ≥ 6 months. Exclusion criteria included: individuals with conditions that involve the central nervous system (CNS), cognitive impairments unrelated to corticosteroid use, members of vulnerable populations, individuals unlikely to follow up with future visits, those with severe illnesses, those judged to be at elevated risk of harming themselves or others, and contraindications to MRI (e.g., metal implants, claustrophobia).

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Structural MRI data were collected at baseline before initiating study drug or placebo. All participants provided UT Southwestern IRB-approved written informed consent and were largely recruited from Parkland Memorial Hospital and UT Southwestern clinics.

1.1. MR Methods

Neuroimaging data were attained with a whole-body horizontal bore Philips 3T scanner (Philips Medical Systems; Best, The Netherlands) at the Advanced Imaging Research Center, UT Southwestern Medical Center. A survey scan was performed followed by sagittal T1–weighted images of the brain (MP-RAGE: TE/TI/TR=3.8/875/1360 ms, 256 × 256 × 160 mm^3 field of view, 160 slices, voxel size 1 × 1 × 1 mm^3) for measurement of hippocampal subfield volumes. A variable-flip angle water suppression scheme provided by Philips was used. Shimming was performed using fast automatic shimming technique by mapping along projections (FASTMAP).

1.1.1. Structural MRI volumetric analysis—For hippocampal subfield segmentation, consensus labeling was performed using an in-house set of 19 labeled T2-weighted atlases acquired from cognitively normal subjects via an optimized hippocampus-specific acquisition protocol (image resolution: 0.47 × 0.47 mm^2 in-plane, 2.0 mm slice thickness). Separate labels were assigned for right and left dentate gyrus (DG)/CA3, CA1, and subiculum. Scans were paired with T1-weighted images (image resolution: 0.75 × 0.75 × 0.75 mm^3) acquired for multi-spectral atlas-based registration. Intra-subject atlas T1/T2 rigid transforms were calculated using the Advanced Normalization Tools (ANTs) package. ANTs software was also used for spatial normalization of the atlas set to the unlabeled T1-weighted images of the study subjects and subsequent joint label fusion.[16,17] An optimal shape and intensity T1-weighted template representing the atlas set was created with byproduct being the set of optimal transforms between the T1-weighted images of the atlas set and the T1 template.[18] The T2-weighted atlas image with corresponding labels were warped to each unlabeled T1-weighted image for joint label fusion by concatenating the T1 atlas /T2 atlas rigid transformation, the T1 atlas/T1 template deformable transformation, and the T1 template/and T1 subject deformable transformation. Volumes for the segmented regions were determined by counting voxels within the regions and multiplying by voxel resolution. The above methods and templates are based on recently published studies.[19]

1.2. Statistical analysis

Statistical analysis was performed using IBM SPSS version 24 (IBM; Armonk, New York). We used a multivariate general linear model to analyze the relationship of scale predictors (“covariates”) and categorical predictors (“fixed factors”) to multiple dependent variables. Age and cumulative corticosteroid exposure, defined as the current dose in milligrams multiplied by the duration in months, were set as covariates with gender as a fixed factor. Dependent variables were brain volumes (14 in total). An alpha of 0.05 was used to determine significance. By including all regions (DG/CA3, CA1, and subiculum regions of the hippocampus and entorhinal, perirhinal, parahippocampal cortices) in a single model, we controlled for experiment-wise error and did not make corrections for multiple comparisons.

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Results

Demographic data are shown in Table 1. The analyzed sample consisted of approximately equal numbers of men and women. Mean age was 43.75 years (median age 46 years) with a range of 20–66 years. Most patients (77.8%) were prescribed corticosteroids for immunosuppression post-renal transplant, with 70% receiving prednisone and 30% receiving prednisolone. Other diagnoses include systemic lupus erythematosus (8.6%), glomerulonephritis (6.2%), asthma (3.7%), rheumatoid arthritis (2.5%), and hypereosinophilia (1.2%). The mean daily dose of corticosteroids was 7.88 mg of prednisone equivalents with a range of 5–35 mg. Mean duration of corticosteroid use was 76.75 months with a range of 6–312 months.

As we were interested in the cumulative exposure to corticosteroids, we calculated a new variable by multiplying dose and duration. The computed cumulative corticosteroid exposure term was included in the model for subsequent analysis of brain volumes (Table 2). There was a significant negative association of cumulative exposure with both the left (B = −.027; $t(77)$ = −2.234; p = .028) and right (B = −.029; $t(77)$ = −2.255; p = .027) DG/CA3 regions of the hippocampus; that is, a higher cumulative exposure predicted smaller DG/CA3 volume. No other subfields demonstrated a significant association with cumulative corticosteroid exposure; however, there was a trend towards a significance negative association with left CA1 region (B = −.050; $t(77)$ = −1.849; p = .068).

As the age of study participants ranged from 20–66 years, effects of age on this negative association between cumulative dose and hippocampal subfield volume was explored. Inserting an interaction term of age*cumulative exposure into the model resulted in significance for the R DG/CA3 volume (p=.044), implying that response to exposure differed with age. Interestingly, this interaction term was not significant for the L DG/CA3 volume (p=.362). The analysis was repeated after dichotomizing individuals into younger and older groups using a cutoff of the median age of 46 years. The association between cumulative corticosteroid exposure and DG/CA3 volume remained significant for the older individuals in both the left (B = −.036; p = .006) and right hemispheres (B = −.048; p = .001). This association however did not hold true for individuals that were less than 46 years old in either left (B = −.008; p = .710) or right hemispheres (B = .006; p = .794).

Discussion

This study examined the effects of chronic glucocorticoid exposure on volumes of hippocampal subfield and related brain regions. We found that cumulative exposure, as represented by dose*duration, was negatively associated with left and right DG/CA3 volumes. Animal models have also shown that, among the hippocampal regions, CA3 is especially sensitive to glucocorticoids or stress.[7–9] Furthermore, chronic stress induced spatial memory impairment and CA3 dendritic atrophy, which was dependent on the corticotropin-releasing hormone receptor.[20] Human imaging studies have shown decreased hippocampal volume or other hippocampal formation changes in conditions with elevated glucocorticoid levels, such as Cushing's disease[21], depression[22,23], and exogenous glucocorticoid administration.[14] However, to our knowledge, this is the first study to

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specifically show detrimental effects on CA3 volume in humans receiving chronic corticosteroids. Our finding that the negative association between cumulative glucocorticoid exposure and hippocampal volume is more prominent in older individuals warrants further investigation. Human and animal studies have shown that plasma glucocorticoid levels tend to increase with age and that age is associated with hippocampal volume loss.[24] Additional exposure in the form of exogenous corticosteroids may thus exacerbate the volume loss in this sensitive population.

Various studies have shown that the CA1 region may also be affected by chronic stress. Neurons from rats exposed to activity-stress, consisting of housing in activity wheels and food restriction, were shorter and had decreased branch points in both CA1 and CA3 regions.[10] This paradigm may more accurately represent chronic stress as animals were housed in the wheels for the entire day instead of being exposed to the stressor for only part of the day as in many other studies. In another study, rats exposed to varied chronic stressors and those injected with corticosterone showed dendritic atrophy in both CA1 and CA3.[11] A different study showed that chronic stress alone did not induce changes in the CA1 regions of rats; however, reduced dendritic lengths were observed in CA1 when slices from stressed rats were briefly exposed to corticosteroids.[12] This suggests that chronic stress sensitizes CA1 neurons to acute stressors but does not induce observable changes by itself. Our results show a negative association between cumulative corticosteroid exposure and the left CA1 region although this did not reach significance. These results are significant because of the role of the hippocampus in spatial processing and memory formation. The CA3 region forms connections with areas both within the hippocampus, including the dentate gyrus and CA1, and external to it.[25] Accordingly, glucocorticoids affect different forms of cognition, including spatial working memory and declarative memory.[5] The dentate gyrus is the only site of neurogenesis in the adult human hippocampus[26] and stress has been variably shown to inhibit cell proliferation in that region in various animal models.[27–29] The decreased volume we see in DG/CA3 may thus reflect decreased neurogenesis along with dendritic atrophy.

Several mechanisms could contribute to the detrimental neurological effects of elevated glucocorticoids. High glucocorticoid levels have been proposed to exacerbate damage during times of stress, such as that related to ischemia or excitatory excess.[30] In rats, both acute[31] and repeated[32] restraint stress induced release of the excitatory neurotransmitter glutamate in the hippocampus. At the same time, glucocorticoids downregulate glucose metabolism; this may render neurons more vulnerable to excitotoxicity as the increased metabolic demand from glutamate transmission outpace energy supplies.[33] The increase in vulnerability to stressors may result in the changes seen with elevated glucocorticoids in animal studies, including reductions in dendritic length and branch points.[7,34,35] Further support for the excitotoxicity theory comes from a study where phenytoin, a glutamate release inhibitor, attenuated the dendritic retraction induced by both chronic stress and glucocorticoids in the CA3 region of rats.[36] We have shown that in patients on chronic corticosteroids, administration of lamotrigine, another glutamate release inhibitor, improved declarative memory, a function in which the hippocampus plays an important role.[37] In addition to glutamate excitotoxicity, glucocorticoids may also exert damage via generation of reactive oxygen species (ROS). In hippocampal cultures, glucocorticoids increased toxicity induced

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by Adriamycin, a ROS generator, and also increased ROS production in the absence of Adriamycin.[38] Future studies could explore the relationship of chronic corticosteroid treatment with neurotransmitter and ROS levels. Brain-derived neurotrophic factor (BDNF), a protein involved in neuronal survival and neurogenesis, is reduced in depressed patients and correlated with hippocampal volume.[39] Interestingly, this association was not seen in normal controls, suggesting existence of a threshold BDNF level below which there is hippocampal volume loss. A study showing decreased expression of BDNF in mouse hippocampal cells exposed to dexamethasone supports this finding.[40] The specific BDNF protein that is expressed may play an important role, as depressed patients with certain genotypes show greater reductions in hippocampal volume.[41]

The study has several limitations. First, it did not have a control group not receiving corticosteroids. Therefore, the analysis is limited to examining relationships between the effects of dose and duration of prednisone exposure on the hippocampus. The mean prednisone dose was relatively modest. Stronger relationships, that might include regions beyond CA3, might be observed at higher doses. However, while the mean dose was modest, participants were receiving a wide range of prednisone doses. Finally, the use of current dose*duration as a measure of cumulative corticosteroid exposure is imprecise because the dose could have changed over time. Strengths of our study include the relatively large sample size and the analysis of the hippocampus according to subfields.

In summary, we detected a negative association between cumulative corticosteroid exposure and volumes of the left and right DG/CA3 regions in patients on chronic corticosteroid therapy. These results are consistent with animal studies showing detrimental effects of elevated corticosteroids on this subfield of the hippocampus.

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Table 1.

Demographic data of study participants

Mean age, in years (SD) (range)	43.75 (11.42) (20–66)
Gender, *n* (%)	
Male	43 (53.1%)
Female	38 (46.9%)
Race, *n* (%)	
Caucasian	12 (14.8%)
African American	38 (46.9%)
Hispanic	28 (34.6%)
Asian/Pacific Islander	2 (2.5%)
Other	1 (1.2%)
Diagnosis requiring corticosteroids, *n* (%)	
Renal transplant	63 (77.8%)
Systemic lupus erythematosus	7 (8.6%)
Glomerulonephritis	5 (6.2%)
Asthma	3 (3.7%)
Rheumatoid arthritis	2 (2.5%)
Hypereosinophilia	1 (1.2%)
Mean prednisone or prednisolone dose, in mg/day (SD) (range)	7.88 (6.50) (5–35)
Mean prednisone or prednisolone duration, in months (SD) (range)	76.75 (76.38) (6–312)

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Table 2.

T values and *P* values of multivariate analysis of covariance model analyzing the effects of age, dose*duration of corticosteroids, and gender on volumes of medial temporal lobe structures

Model 1: MANCOVA Results			
Structure	**Parameter**	***t*-value**	***p*-value**
L anterolateral entorhinal	Age Dose*duration Gender	.459 .410 −2.472	.648 .683 .016
R anterolateral entorhinal	Age Dose*duration Gender	.030 −1.182 −.875	.976 .241 .384
L posteromedial entorhinal	Age Dose*duration Gender	.152 .614 −1.127	.879 .541 .263
R posteromedial entorhinal	Age Dose*duration Gender	.079 −.015 .585	.937 .988 .560
L perirhinal	Age Dose*duration Gender	1.124 −.416 −3.522	.265 .679 .001
R perirhinal	Age Dose*duration Gender	.591 −.521 −2.524	.556 .604 .014
L parahippocampal	Age Dose*duration Gender	−.188 −.258 −1.450	.851 .797 .151
R parahippocampal	Age Dose*duration Gender	−.504 −.710 −1.514	.616 .480 .134
L DG/CA3	Age Dose*duration Gender	−1.816 −2.234 −.976	.073 .028 .332
R DG/CA3	Age Dose*duration Gender	−.119 −2.255 −.491	.906 .027 .625
L CA1	Age Dose*duration Gender	−.075 −1.849 −3.040	.941 .068 .003
R CA1	Age Dose*duration Gender	.912 −1.550 −2.292	.365 .125 .025
L subiculum	Age Dose*duration Gender	−1.539 .715 −3.179	.128 .477 .002
R subiculum	Age Dose*duration Gender	−.090 −.751 −2.259	.928 .455 .027