MECHANISMS IN ENDOCRINOLOGY

Cushing’s syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies

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Abstract

Background: Cushing’s syndrome (CS) is characterized by excessive exposure to cortisol, and is associated with both metabolic and behavioral abnormalities. Symptoms improve substantially after biochemical cure, but may persist during long-term remission. The causes for persistent morbidity are probably multi-factorial, including a profound effect of cortisol excess on the brain, a major target area for glucocorticoids.

Objective: To review publications evaluating brain characteristics in patients with CS using magnetic resonance imaging (MRI).


Results: Nineteen studies using MRI in patients with CS were selected, including studies in patients with active disease, patients in long-term remission, and longitudinal studies, covering a total of 339 unique patients. Patients with active disease showed smaller hippocampal volumes, enlarged ventricles, and cerebral atrophy as well as alterations in neurochemical concentrations and functional activity. After abrogation of cortisol excess, the reversibility of structural and neurochemical alterations was incomplete after long-term remission. MRI findings were related to clinical characteristics (i.e., cortisol levels, duration of exposure to hypercortisolism, current age, age at diagnosis, and triglyceride levels) and behavioral outcome (i.e., cognitive and emotional functioning, mood, and quality of life).

Conclusion: Patients with active CS demonstrate brain abnormalities, which only partly recover after biochemical cure, because these still occur even after long-term remission. CS might be considered as a human model of nature that provides a keyhole perspective of the neurotoxic effects of exogenous glucocorticoids on the brain.

European Journal of Endocrinology
(2015) 173, R1–R14
Introduction

Cushing’s syndrome (CS) is a rare clinical syndrome characterized by excessive endogenous exposure to cortisol due to various etiologies. The majority of patients have adrenocorticotropic hormone (ACTH)-producing pituitary tumors (i.e., Cushing’s disease (CD)); other causes include adrenal tumors or ectopic ACTH-secreting tumors. CS manifests all characteristic features of excess stress hormone exposure, i.e. psychopathology, gonadal dysfunction, hirsutism, abnormal (central) fat distribution, thin skin with easy bruising, hypertension, muscle weakness, and osteoporosis (1). Patients are treated with surgery, and in case surgical remission is not obtained, radiotherapy and/or with medical treatment (2). Although symptoms improve substantially after biochemical cure, cardiovascular morbidity and mortality remained elevated (3, 4, 5). Furthermore, despite long-term remission, patients with CS report impaired quality of life (6), higher prevalence of psychopathology, and demonstrated impairments in cognitive functioning (7, 8). It is likely that the causes for persistent morbidity are multi-factorial, including intrinsic imperfections of surgical or endocrine replacement therapy; the impact of living with a chronic disease in addition to the irreversible effects of cortisol excess on the CNS during remission may affect personality, behavior, and metabolism, which cannot be neglected. Although the attention for the presence of psychopathology and impairments in cognitive functioning in patients with active, as well as remitted CS is self-evident, the number of studies evaluating brain structures and activity in patients with CS has been rather limited.

The detrimental effects of hypercortisolism, such as in CS, on the human brain were first highlighted in autopsy reports, describing a lighter brain and enlarged ventricles in deceased CS patients (9). The first in vivo studies in the human evaluating these brain characteristics were performed in patients with CS using pneumoencephalography. Momose et al. (10) used pneumoencephalography in 31 patients with CD, and demonstrated cerebral cortical atrophy in 90% of the patients and cerebellar cortical atrophy in 74% of the patients compared with normal references derived from the literature. The introduction of the magnetic resonance imaging (MRI) scanner in 1977 enabled the assessment of brain volumes and brain structures more accurately and in more detail. Starkman et al. (11) were the first to report on hippocampal volumes obtained from routine pituitary MRI diagnostics of patients with active CS, and compared these with healthy control data derived from the literature. Hippocampal volume was decreased during active CS, but a partial recovery could be observed after successful treatment (12, 13). However, new imaging techniques are emerging that enable to better evaluate brain structures and functioning.

The aim of this study was to systematically review the literature on structural and functional changes in the brain identified with (MRI) in patients with CS. The secondary aim was to review potential associations between brain characteristics and disease status, cognitive functioning, psychopathology, and general well-being.

Methods

Search strategy and data extraction

The following electronic databases were searched: PubMed, Embase, Web of Knowledge, and Cochrane. The search was performed on August 5, 2014. We composed a search strategy focusing on MRI studies in patients with CD and CS (see Supplement 1 for the complete search strategy, see section on supplementary data given at the end of this article). Studies on patients with CS due to the use of exogenous corticosteroids were excluded. Data extraction and eligibility were assessed by two independent investigators (C D Andela and A M Pereira). Inconsistencies were resolved by consensus. All references were checked for additional papers. The following data were extracted: i) sample size, ii) gender distribution, iii) mean age of included patients, iv) disease status (active/remission), v) estimated duration of exposure to hypercortisolism, vi) methods used, and vii) results.

Quality assessment

Due to different designs and methods in the studies that were identified, it was not possible to use a pre-existing quality assessment tool. Therefore, we formulated a quality assessment list adapted from the list used in a systematic review on neuroimaging studies in patients with multiple sclerosis (14). Sixteen items were defined: clear study objective, inclusion/exclusion criteria, population demographics, diagnostic criteria and/or remission criteria, estimation of disease duration, composition of patient group (i.e., heterogeneous or homogenous regarding to origin of CS (pituitary–adrenal) and disease status (active-remission)), sample size, design (retrospective assessment based on scans obtained from routine pituitary evaluation, or prospective or cross-sectional), inclusion of a control group assessed in the same...
manner as the patient group, assessment of cognitive and psychological functioning, imaging protocol, scanner type (1T, 1.5T or 3T), strength of effect reported, multivariate analysis, and discussion of limitations. Total individual quality scores ranged from 0 to 20 points (see Table 1).

The quality of each study was assessed by two independent reviewers (C D Andela and A M Pereira) and discrepancies were discussed and resolved by consensus. Total scores were calculated as percentages (‘individual total score’/20×100%). The median of the quality scores was 75% and was used as cut-off point, with papers with quality scores ≥75% being considered as high quality papers. Given the low number of studies, studies were not excluded based on the quality assessment (Table 2).

Results

Literature overview

The literature search identified 142 publications, of which 16 were eligible for inclusion. By scanning references of included articles, three articles were added to the selection. Therefore, the final selection consisted of 19 articles including a total number of 339 unique patients (Table 3 and Fig. 1). This selection consisted of six longitudinal studies, 11 cross-sectional studies, and two studies using both designs. The majority of the studies used structural MRI (n = 14), three studies used proton magnetic resonance spectroscopy (H-MRS), and two studies used functional MRI (fMRI). Nine studies combined MRI outcome with the assessment of cognitive functioning. Further information on the MRI techniques, neuropsychological tests, and behavioral measures are provided in the Supplementary file 2, see section on supplementary data given at the end of this article.

Quality assessment

The individual quality scores of the studies ranged from 30 to 100%, with a median of 75%. Overall, the more recent articles had higher quality scores, which can partly be explained by the transition from using 1.5T scanners to 3T scanners, and the absence of applying multivariate analysis in the earlier studies. Furthermore, 53% of the studies (n = 10) included patients with CS of both pituitary and adrenal origin, and approximately half of the studies did not include psychological (n = 11) and/or cognitive measures (n = 9).

Endocrine evaluation

Diagnostic criteria for CS were clearly defined in 13 studies (68%). Five studies (26%) did not describe diagnostic
criteria, but mentioned criteria of remission (15, 16, 17, 18, 19). One study did neither describe diagnostic nor remission criteria (20).

Described diagnostic criteria were clinical features (truncal obesity, skin and muscle arthophy, moon facies) (11, 12, 13, 21), elevated urinary free cortisol (UFC) (11, 12, 13, 21, 22, 23, 24, 25, 26, 27, 28, 29), elevated cortisol secretion rates (11, 12, 13, 21, 23, 24, 25, 30), elevated midnight salivary cortisol (29, 31), absence of blunted circadian rhythm of cortisol secretion (11, 12, 13, 21, 26, 27, 30, 32, 33), elevated ACTH levels (in CD only) (12, 13, 21, 23, 24), lack of suppression after low dose dexamethasone ((1 mg) (22, 25, 29, 33), (2 mg) (12, 13, 21), dose not mentioned (23, 24)) or 50% suppression after high dose (8 mg) (12, 13, 21), and abnormal response to corticotropin releasing hormone (CRH) (30).

Described remission criteria were normal UFC (15, 16, 17, 18, 19), adrenal insufficiency, morning cortisol suppression after low dose dexamethasone overnight (1 mg) (17, 18, 19), or <30 mg hydrocortisone/day (15).

All studies (except four (15, 20, 23, 24)) reported on the estimated duration of hypercortisolism, which was based on patient’s history and old photographs. In studies that included pediatric patients with CS, the onset of decreased growth velocity was used (26, 27). The mean estimated duration of hypercortisolism ranged from 2.6 to 7.9 years.

MRI outcome in patients with active CS

The first studies evaluating brain volume with MRI in patients with active CS used MRI scans obtained from routine pituitary evaluation. In 1992, Starkman et al. (11) reported hippocampal volume to be outside the 95% CI of healthy control data derived from the literature in 27% of the patients (total sample size n = 12). In a larger cohort (n = 63), patients with CS were reported to have more brain atrophy compared with controls (Fig. 2) (20). In agreement, Bourdeau et al. (15) demonstrated that patients with active CS had increased third ventricle diameter, bicaudate diameter, and cerebral atrophy, compared with control patients with no sellar tumors. A recent study has found smaller grey matter volumes of the bilateral cerebellum in patients with active CS compared with controls (19).

When investigating the effect of CS on the developing brain, children with CS were found to have smaller cerebral volumes, larger ventricles and smaller amygdala than controls (27).

Khiat et al. (23) used H-MRS, a non-invasive tool that can be used to evaluate changes in cerebral metabolites. The patients with active CS had decreased ratios of creatine and phosphocreatine ratios (markers of energy metabolism) and decreased choline-containing compounds (a membrane marker) in fronto and thalamic areas, indicating persistent alterations in the cholinergic system (23).
### Table 3  Study characteristics of MRI studies in patients with CS.

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Gender (m/f)</th>
<th>Age (mean ± s.d.)</th>
<th>Active/ treated</th>
<th>Procedure and method</th>
<th>Evaluated brain areas</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional (11)</td>
<td>12</td>
<td>2/10</td>
<td>37.3 ± 13.95</td>
<td>9 active CD, 3 active CS, 1 healthy control</td>
<td>Range 1–4 years</td>
<td>1.5T MRI scans obtained from routine pituitary MRI, Volumes were manually traced and digitally calculated</td>
<td>Dentate gyrus, Hippocampus proper, subiculum</td>
</tr>
<tr>
<td>(23)</td>
<td>13</td>
<td>0/13</td>
<td>Mean: 42.0 (range 21–64)</td>
<td>6 active CD, 7 active CS, 40 healthy controls</td>
<td>NA</td>
<td>1.5T MRI, H-MRS, Metabolites were quantified</td>
<td>2 cm³ localized in the thalamic, frontal and temporal area of the left hemisphere</td>
</tr>
<tr>
<td>(20)</td>
<td>63</td>
<td>48/15</td>
<td>NA</td>
<td>63 active CD, 63 controls with non-ACTH producing sellar pathology, age and gender matched</td>
<td>NA</td>
<td>CT/MRI obtained during treatment period, Atrophy was rated</td>
<td>Whole brain</td>
</tr>
<tr>
<td>(15)*</td>
<td>36/2b</td>
<td>9/29</td>
<td>41.3 ± 12.0</td>
<td>21 active CD, 17 active CS, 18 controls with non-ACTH producing sellar tumors, 20 controls with no sellar tumors</td>
<td>NA</td>
<td>CT and/or MRI obtained from routine pituitary evaluation, Measurement of diameters and subjective estimation of degree of cerebral atrophy</td>
<td>Third ventricle, Bicaudate, Whole brain</td>
</tr>
<tr>
<td>(27)*</td>
<td>11</td>
<td>5/6</td>
<td>12.1 ± 3.4</td>
<td>10 active CD, 1 active CS, 10 healthy age- and gender-matched controls</td>
<td>4.4 ± 1.2</td>
<td>1.5T MRI, Volumes were manually traced and quantified</td>
<td>Cerebrum, ventricles, temporal lobe, hippocampus amygdala</td>
</tr>
<tr>
<td>(26)</td>
<td>12</td>
<td>4/8</td>
<td>13.5 ± 2.9</td>
<td>10 active CD, 2 active CS, 22 healthy controls</td>
<td>Mean 2.6 years (range 1–4.5)</td>
<td>3T fMRI, Face Memory Task, BOLD signal</td>
<td>Amygdala, Anterior hippocampus</td>
</tr>
<tr>
<td>References</td>
<td>n</td>
<td>Gender (m/f)</td>
<td>Age (mean ± s.d.)</td>
<td>Active/ treated</td>
<td>Estimated duration of hypercortisolism</td>
<td>Procedure and method</td>
<td>Evaluated brain areas</td>
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<tr>
<td>(25)</td>
<td>21</td>
<td>4/17</td>
<td>34.4 ± 14.9</td>
<td>20 active CD</td>
<td>32.4 ± 2.3.7 months</td>
<td>3T fMRI Facial emotion perception test BOLD signal</td>
<td>Hippocampus Amygdala Whole brain</td>
</tr>
<tr>
<td>(17)</td>
<td>33</td>
<td>6/27</td>
<td>44.8 ± 11.8</td>
<td>7 active CD</td>
<td>5.5 ± 3.7 years</td>
<td>3T MRI Volumes were automatically segmented and measured</td>
<td>Hippocampus Cortical GM Subcortical GM</td>
</tr>
<tr>
<td>(22)</td>
<td>25</td>
<td>4/21</td>
<td>45 ± 8</td>
<td>25 CD remission</td>
<td>7.9 ± 7.9 years</td>
<td>3T MRI Harvard-oxford cortical and subcortical structural atlases were used to create a mask</td>
<td>Hippocampus, amygdala, ACC Whole brain</td>
</tr>
<tr>
<td>(18)</td>
<td>18</td>
<td>3/15</td>
<td>44.8 ± 12.5</td>
<td>15 remission CD</td>
<td>4.7 ± 2.6 years</td>
<td>3T MRI H-MRS Measurement of metabolic peaks</td>
<td>Hippocampus head</td>
</tr>
<tr>
<td>(29)</td>
<td>22</td>
<td>4/18</td>
<td>42.42 ± 7.33</td>
<td>22 remission CD</td>
<td>6.73 ± 5.39 years</td>
<td>3T MRI Johns Hopkins University WM atlas was used to create a mask</td>
<td>Bilateral cingulate cingulum Bilateral hippocampal cingulum Bilateral uncinated fasciculus Corpus callosum Whole brain</td>
</tr>
<tr>
<td>References</td>
<td>n</td>
<td>Gender (m/f)</td>
<td>Age (mean ± s.d.)</td>
<td>Activity/ treated</td>
<td>Estimated duration of hypercortisolism</td>
<td>Procedure and method</td>
<td>Evaluated brain areas</td>
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<tr>
<td>(19)</td>
<td>36</td>
<td>6/30</td>
<td>Active: 44.2 ± 9.3</td>
<td>10 active CD 5 active CS 3 remission CS</td>
<td>10 active CD 5 active CS 3 remission CS</td>
<td>3T MRI</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>(16)</td>
<td>35</td>
<td>5/30</td>
<td>Medically treated: 41.4 ± 12.3</td>
<td>4 medically treated CD 4 medically treated CS 24 remission CD 3 remission CS</td>
<td>Medically treated: 46.5 ± 32.5 months</td>
<td>3T MRI</td>
<td>Whole brain</td>
</tr>
<tr>
<td>Longitudinal (24)</td>
<td>10</td>
<td>0/10</td>
<td>Mean: 41.3 (range 21–64)</td>
<td>5 active CD 5 active CS</td>
<td>NA</td>
<td>1.5T MRI</td>
<td>NA</td>
</tr>
<tr>
<td>(12)</td>
<td>18/4</td>
<td>5/17</td>
<td>38.7 ± 14.8</td>
<td>22 active CD</td>
<td>2.6 ± 2.3 years</td>
<td>1.5T MRI</td>
<td>Hippocampus, Caudate head</td>
</tr>
<tr>
<td>(15)*</td>
<td>22</td>
<td>NA</td>
<td>40.9 ± 10.7</td>
<td>14 active CD 8 active CS</td>
<td>NA</td>
<td>CT and/or MRI obtained from routine pituitary evaluation</td>
<td>Third ventricle, Bicaudate</td>
</tr>
<tr>
<td>(13)</td>
<td>5/19</td>
<td>4/20</td>
<td>33.7 ± 13.1</td>
<td>24 active CD</td>
<td>2.7 ± 2.1 years</td>
<td>1.5T MRI</td>
<td>Hippocampus, Caudate head</td>
</tr>
<tr>
<td>References</td>
<td>n</td>
<td>Gender (m/f)</td>
<td>Age (mean ± s.d.)</td>
<td>Active/treated</td>
<td>Estimated duration of hypercortisolism</td>
<td>Procedure and method</td>
<td>Evaluated brain areas</td>
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<tr>
<td>(30)</td>
<td>5/22</td>
<td>4/23</td>
<td>38.74 ± 13.24</td>
<td>27 active CD</td>
<td>3.64 ± 3.09 years</td>
<td>1.5T MRI</td>
<td>Hippocampus, caudate head</td>
</tr>
<tr>
<td>(27)</td>
<td>11</td>
<td>5/6</td>
<td>12.1 ± 3.4</td>
<td>10 active CD</td>
<td>4.4 ± 1.2 years</td>
<td>1.5T MRI</td>
<td>Cerebrum, ventricles, temporal lobe, hippocampus, amygdala</td>
</tr>
<tr>
<td>(21)</td>
<td>4/19</td>
<td>4/19</td>
<td>34.0 ± 13.2</td>
<td>23 active CD</td>
<td>2.7 ± 2.1 years</td>
<td>1.5T MRI</td>
<td>Hippocampus, caudate head</td>
</tr>
<tr>
<td>(33)</td>
<td>10</td>
<td>2/8</td>
<td>38.2 ± 13.1</td>
<td>Ten active CD</td>
<td>3.5 ± 1.1 years</td>
<td>1T MRI</td>
<td>Hippocampus, whole brain</td>
</tr>
</tbody>
</table>

HV, hippocampal volume; HFV, hippocampal formation volume; CHV, caudate head volume; ICV, intracranial volume; GM, grey matter; WM, white matter; VBM, Voxel-based morphometry; ACC, anterior cingulate cortex; H-MRS, Proton magnetic resonance spectroscopy; Cr, creatine and phosphocreatine; Cho, choline-containing compounds; NAA, N-Acetyl-Aspartate; Glx, Glutamate + Glutamine; QoL, quality of life.

*Cross-sectional and longitudinal design.

aPatients from study of (11).
bPatients from study of (17).
cPatients from study of (22).
dPatients from study of (23).
ePatients from study of (12).
Only two studies have investigated patients with active CS with fMRI. Using an emotional faces task, adult patients demonstrated less activation in the left anterior superior temporal gyrus, and higher activation in the frontal, medial, and subcortical regions during the identification of emotional faces. These findings indicated alterations in brain activity in regions used for emotion processing (25). Furthermore, adolescents with active CS demonstrated increased activation in the left amygdala and right anterior hippocampus in response to successful encoding during the performance of a facial memory task. These results point toward alterations in brain activity in substrates related to depressive symptoms and emotional memory. Interestingly, none of the adolescents suffered from psychiatric disease, therefore the authors postulated that the exaggerated amygdala activity and exposure to elevated cortisol levels are not sufficient for initiating depression in adolescents (26).

Longitudinal studies assessing the potential reversibility of brain abnormalities

Eight studies evaluated the potential reversibility of alterations in the brain after correction of hypercortisolism (mean duration of follow-up between 6 and 40 months).

Correction of hypercortisolism increased hippocampal volume (12), and decreased third ventricle- and bicaudate diameter, and regressed brain atrophy (15). Toffanin et al. (33) reported a significant increase in right and left hippocampus head volumes in CD patients after transsphenoidal surgery, with no significant increase in the body and tail of the hippocampus, suggesting that the head of the hippocampus is more sensitive to excessive cortisol exposure. Recovery in metabolite concentrations was also accompanied by an increase in thalamic and frontal choline levels up to 6 months after correction of hypercortisolism, indicating improvement in cholinergic system function (23). Children with CS demonstrated an increase in cerebral volumes and a decrease in ventricular volumes after surgery, and total cerebral volume and ventricular size after 1-year follow-up were comparable with age-matched controls (27).

MRI outcome in patients in long-term remission of CS

Six studies evaluated patients in remission of CS using a cross-sectional design and identified structural, functional, and biochemical abnormalities. The average duration of remission ranged from 3.4 to 11.9 years.

Resmini et al. (17) found no differences between patients with active disease and patients in remission, and therefore analyzed these patients as one group. They found no differences in hippocampal volume between patients and healthy-matched controls, but total grey matter (cortical and subcortical) and cortical grey matter were smaller in patients compared with controls. Andela et al. (22) found smaller grey matter volumes of the anterior cingulate cortex (ACC) and larger grey matter volumes of the left posterior lobe of the cerebellum in CD patients in long-term remission compared with healthy-matched controls (Fig. 3), whereas Santos et al. (19) found no differences in cerebellar volumes between patients in remission and controls. Recently, Crespo et al. (16) have evaluated cortical thickness in medically treated eucortisolemic patients and patients in remission and demonstrated that patients with CS had decreased cortical thickness when compared with controls.
At present, only one study has evaluated white matter integrity in patients with long-term remission of CD and demonstrated widespread reductions of integrity in white matter tracts throughout the brain (29).

Finally, using H-MRS, Resmini et al. demonstrated lower N-acetyl-aspartate (NAA) ratios (marker of neuronal density, integrity, and variability) in the bilateral hippocampus in patients in remission of CS compared with controls, reflecting neuronal damage. Furthermore, patients demonstrated higher glutamate (excitatory neurotransmitter) and glutamine (glial marker) levels in both hippocampi, indicating proliferation as a repair mechanism. The authors postulated that these persisted alteration in biochemical markers in the brain could be related to glucocorticoid neurotoxicity (18).

**Figure 3**

Grey matter volumes in patients after long-term remission of CD. (A) Results of regions of interest analysis, with lesser grey matter volumes in patients than that in controls ($P < 0.05$; 617 voxels, 2-mm isotropic). (B) Results of whole brain analysis with lesser grey matter volumes in patients than that in controls ($P < 0.05$; 37 voxels, 2-mm isotropic). (C) Results of whole brain analysis with greater grey matter volumes in patients than that in controls ($P < 0.05$; 323 voxels, 2-mm isotropic). The left hemisphere corresponds with the right side of the image (22).

**Associations between brain abnormalities and clinical characteristics**

Several studies found associations between structural and functional brain abnormalities and clinical and laboratory characteristics in patients with CS.

In patients with active disease, hippocampal volumes were negatively correlated with plasma cortisol levels, but not with UFC, current age, and cortisol levels multiplied by the estimated duration of disease (11). In fMRI studies in active disease, dorsal anterior cingulate activation during emotional task was positively associated with percent decline in ACTH from morning peak to afternoon nadir, but not with percent cortisol decline from morning peak to afternoon nadir (25). On the other hand, in adolescents with active disease left amygdala activation and right anterior hippocampal activation during a facial memory task was not correlated with 24-h UFC levels (26). Bicaudate diameter was correlated with UFC in patients with active CD, whereas no associations were found with degree of cerebral atrophy. In patients with adrenal CS, UFC did correlate with the degree of cerebral atrophy (15). Duration of hypercortisolism was negatively associated with subcortical grey matter volume (17), and significant differences in brain atrophy were found between subsets of patients with a long disease duration compared with patients with shorter disease duration (20). Furthermore, grey matter volume of the bilateral cerebellum was negatively associated with age at diagnosis and triglyceride levels, but not with current age, level of cholesterol, glucose, UFC, duration of exposure to hypercortisolism (19). Furthermore, cortical thickness was not associated with duration of eucortisolism, duration of prior hypercortisolism, and UFC (16).

Increase in hippocampal volume after correction of hypercortisolism was negatively associated with current age (12), and significant differences in the degree of brain atrophy were found between subsets of patients of different age (20). In contrast, Bourdeau et al. (15) found no correlation between brain volume and current age, although this could be related to the relatively young sample of patients included. An increase in hippocampal volume was associated with a decrease in UFC after treatment (12, 13, 21), but not with reduction in plasma cortisol, duration of disease, or the number of months relapsed since treatment (21, 30). Increase in right caudate head volume (CHV) was also associated with decrease in UFC, while increase in left CHV and right and left CHV together were not associated with change in UFC (13, 21).
In patients with long-term remission, no correlations were found between grey matter volumes of the ACC and cerebellum and white matter integrity, and estimated duration of hypercortisolism, duration of remission and clinical severity (22, 29), nor between NAA and GLX ratios and duration of hypercortisolism and duration of remission (18).

**Associations between brain abnormalities and behavioral outcome/measures**

In several studies, associations between structural and functional brain abnormalities and behavioral measures, especially in memory and mood domains, were found.

In patients with active disease, hippocampal volumes were positively associated with verbal learning and verbal recall (11). Increased activation of the left lateral posterior/pulvinar nuclei of the thalamus and the left middle frontal gyrus was positively correlated with accuracy of emotion identification in patients with active disease, whereas activation in the left superior parietal lobule was not significantly correlated with accuracy of emotion identification (25). In adolescents with active CS, left amygdala activation and right anterior hippocampal activation did not correlate with the performance of a facial memory task (26). Increase in hippocampal volume after correction of hypercortisolism was positively associated with improvement in learning (13, 30), but change in CHV was not (13, 30). An increase in right caudate volume was associated with improvement in mood (depression and anxiety) and related ideation (obsessive–compulsive and paranoid ideation), whereas change in left CHV and hippocampal volume were not correlated with mood or ideation (21).

Recently, Crespo et al. have demonstrated that cortical thickness was not associated with decision-making in medically treated eucortisolemic patients and patients in remission (16). Furthermore, in a group of patients with active disease, as well as patients in remission, patients with severe memory impairment showed smaller hippocampal volumes than controls (17), and grey matter volumes of the left lobe of the cerebellum were positively associated with visual memory and grey matter volumes of the right lobe of the cerebellum were positively associated with reported disease-specific quality of life (19).

In patients with long-term remission, reductions in white matter integrity in the left uncinate fasciculus were associated with severity of depressive symptoms, whereas no correlations were found between white matter integrity in other brain regions, grey matter volumes in the ACC and cerebellum, and behavioral outcome (i.e., depressive symptoms, anxiety, apathy, irritability, and cognitive failure) (22, 29).

**Discussion**

This systematic review shows that endogenous glucocorticoid excess in CS has profound effects on the human brain. This includes structural grey matter, possibly white matter abnormalities and neurochemical and functional alterations. After correction of hypercortisolism, the structural and neurochemical alterations improve substantially and correlate with improvements in clinical and behavioral outcomes. Nevertheless, abnormalities in both grey- and white matter are not completely reversible at long-term remission and are accompanied by psychological symptoms and impairments in cognitive functioning (7, 22, 29, 34).

The brain, and in particular the limbic system, is a major target area for cortisol, considering the high density of both the mineralocorticoid and glucocorticoid receptors (35). The neurotoxic effects of corticosteroid excess on the CNS are well-recognized in experimental animal studies: i.e. reduction in apical dendrites of hippocampal pyramidal neurons (36), hippocampal volume reduction (37), and reduction volume of the left anterior cingulate gyrus (38). Furthermore, experimental models of chronic stress have clearly shown neurotoxic effects that appeared to be reversible by anti-glucocorticoid treatment (39). However, long-term experimental histopathological data after abrogation of corticosteroid overexposure are not available to our knowledge. It is tempting to speculate that the observed psychological morbidity and cognitive impairment in patients with active CS (40, 41) could be explained, at least in part, by the findings of MRI studies. In support of this, brain abnormalities and behavioral outcomes are clearly correlated. The ACC, hippocampus, and amygdala together constitute the neurocircuitry of stress (42). Therefore, psychopathology and cognitive impairment in patients with active CS might be related to structural alterations within this circuitry, in addition to alterations in functional activity and connectivity within it. In accordance, changes in functional activity were reported during a facial emotion task in adult patients (25) and a facial memory task in adolescents (26). FMRI studies on other emotional and cognitive tasks (e.g., executive function, and memory) in adult patients with CS, or studies assessing functional connectivity during rest have not been reported. Also, there were no fMRI studies in patients...
in remission of CS published in the time window of our literature search.

At present, brain characteristics in CS patients who are in long-term remission have been reported in only six cross-sectional MRI studies, with an average duration of remission ranging from 3.4 to 11.9 years. These studies showed smaller grey matter volumes in the ACC, larger grey matter volumes in the cerebellum, widespread reductions in white matter integrity (22, 29), and alterations in specific neuronal metabolites in the hippocampus (18). The behavioral phenotype of patients in remission of CS (7, 34) might also be, at least in part, explained by these findings. This is supported by the observed correlations between reductions in white matter integrity in the left uncinate fasciculus and severity of depressive symptoms in one diffusion tensor imaging (DTI) study. However, no other correlations were identified between the structural brain abnormalities and behavioral outcomes in patients in remission of CS, which might be due to a limited power or to the fact that behavioral outcomes may show stronger associations with functional brain abnormalities (22, 29).

The actual course of the residual alterations in patients in long-term remission is hard to capture, because longitudinal studies with long-term follow-up are lacking (i.e., mean duration of follow-up in available studies ranging from 6 to 40 months). Furthermore, previous studies in patients with active CS mainly evaluated the hippocampus, and the first MRI studies in patients with CS did not have access to modern and more sophisticated analytical tools. Therefore, it is plausible to assume that previous studies have been unable to document abnormalities at least in active patients. For instance, white matter integrity as assessed with diffusion tensor imaging (29) has not been evaluated in patients with active disease, which retains us from drawing conclusions about the development of these reductions in white matter integrity.

It is tempting to speculate that the brain abnormalities found in patients with CS during active disease, as well as during remission, also apply for patients with iatrogenic CS due to glucocorticoid treatment. This is supported by findings of similar brain abnormalities in patients while on long-term corticosteroid therapy as in patients with CS (smaller hippocampal, amygdala volumes, cerebral atrophy, and alterations in neurochemical concentrations) (43, 44, 45, 46).

A considerable amount of between-study heterogeneity was observed. First of all, heterogeneity was present regarding sample composition, with some studies analyzing homogenous groups of patients with pituitary CD or patients with adrenal CS, whereas other studies analyzed a more heterogeneous group of patients with pituitary as well adrenal CS. In addition, some studies analyzed homogenous groups of patients with active disease or patients in remission, whereas other studies analyzed patients with active, as well as with remitted disease. Secondly, studies demonstrated a great variety in analyzed brain regions of interest and in the methodology used. Consequently, no meta-analysis could be performed. Furthermore, it should be acknowledged that CS is associated with multisystem morbidity (5) and pituitary hormone deficiencies, which all can affect the brain (47, 48, 49, 50, 51).

In conclusion, patients with CS demonstrate structural brain abnormalities, as well as neurochemical and functional abnormalities, which only partly recover during long-term remission, because these still occur even after long-term remission. CS might be considered as a human model of nature that provides a keyhole perspective of the neurotoxic effects of exogenous glucocorticoids on the brain.

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**Supplementary data**

This is linked to the online version of the paper at [http://dx.doi.org/10.1530/EJE-14-1101](http://dx.doi.org/10.1530/EJE-14-1101).

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

**Funding**

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**References**


Received 11 December 2014
Revised version received 27 January 2015
Accepted 3 February 2015