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Stressed-out stress systems: dysregulated stress-systems in the pathophysiology of stress-related disorders

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Chapter 4

Structural brain abnormalities in Cushing's syndrome

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Abstract

Purpose of review

Alongside various physical symptoms, patients with Cushing's disease and Cushing's syndrome display a wide variety of neuropsychiatric and cognitive symptoms, which are indicative of involvement of the central nervous system. The aim of this review is to provide an overview of the structural brain abnormalities that are associated with Cushing's disease and Cushing's syndrome and their relation to behavioral and cognitive symptomatology.

Recent findings

In this review, we discuss the gray matter structural abnormalities found in patients with active Cushing's disease and Cushing's syndrome, the reversibility and persistence of these changes and the white matter structural changes related to Cushing's syndrome. Recent findings are of particular interest because they provide more detailed information on localization of the structural changes as well as possible insights into the underlying biological processes.

Summary

Active Cushing's disease and Cushing's syndrome is related to volume reductions of the hippocampus and in a prefrontal region involving the anterior cingulate cortex (ACC) and medial frontal gyrus (MFG). Whilst there are indications that the reductions in hippocampal volume are partially reversible, the changes in the ACC and MFG appear to be more persistent. In contrast to the volumetric findings, changes in white matter connectivity are typically widespread involving multiple tracts.

Introduction

Cushing's disease is usually characterized by a tumor located on the pituitary that produces adrenocorticotropic hormone (ACTH), which in turn stimulates the release of glucocorticoids by the adrenal cortex. In individuals without Cushing's disease, an increase in glucocorticoids will trigger a negative feedback loop, inhibiting the release of ACTH. However, the ACTH-producing tumor in Cushing's disease is insensitive to this inhibition, therefore, the system is unable to regulate itself, resulting in increased levels of glucocorticoids or hypercortisolism. Physical manifestations of the hypercortisolism include: hypertension, abnormal fat distribution, thin skin sensitive to bruising, muscle weakness, osteoporosis, hirsutism, and gonadal dysfunction. Alongside these physical symptoms patients with Cushing's disease can also display a wide variety of psychiatric symptoms, including depression, emotional instability, cognitive impairments, apathy, anxiety and psychosis [1]. These symptoms are indicative of the effects of Cushing's disease on the central nervous system (CNS). In this review, we will summarize the existing literature available to date with regard to alterations of gray and white matter structure in the CNS related to hypercortisolism.

In 2015, Andela et al. [2] wrote a more elaborate review of the findings of studies on structural and functional abnormalities. Therefore, we will only shortly address these earlier findings to give more context to the recent findings, which we will discuss in detail. We will conclude by offering a number of suggestions for future research. As the number of studies investigating Cushing's disease is still rather limited, we expanded our review by including studies investigating excessive endogenous exposure to cortisol due to other causes (i.e. Cushing's syndrome).

Gray matter structural changes in active cushing's syndrome

The association between hypercortisolism and CNS damage was first described in 1952 by Trethowan and Cobb. Their findings were based on autopsy reports in which they found a decrease in weight of the brain and enlarged ventricles in patients with Cushing's syndrome [3]. These findings were later supported by the first in-vivo study conducted by Momose et al. [4], using a technique called pneumoencephalography. They found high incidences of atrophy in both cerebral and cerebellar regions in patients with Cushing's disease.

Starkman and colleagues in 2012 were the first to study changes related to Cushing's syndrome in a specific brain structure. Using MRI images, they manually estimated

the volume of the hippocampus in 12 patients with Cushing's syndrome. They found that 27% of the patients' hippocampal volume fell outside the 95% confidence intervals for normal individuals based on previous literature [5]. After these initial findings, several studies confirmed cerebral atrophy [6–8] and cerebellar atrophy in patients with active Cushing's disease [9]. Meanwhile, technological advancements have allowed for the acquisition of higher resolution imaging data, as well as more sophisticated automatic analysis tools. Using an automatic segmentation tool, Resmini et al. [8] were not able to replicate the finding of smaller hippocampal volumes in active Cushing's syndrome. However, they did find an impaired memory function in patients and also an association between impaired memory function and smaller hippocampal volumes [8]. In light of the high prevalence of the affective symptoms of depression and anxiety in Cushing's syndrome, a study from the same research group focused on the amygdala volumes and found smaller right amygdala volumes in Cushing's syndrome. They also found a negative correlation between the amygdala volumes and depression and anxiety scores in patients with Cushing's syndrome [10].

Manual and automatic segmentation procedures extract mean volume data from specific predetermined brain structures. These segmentation approaches are very robust measures to evaluate volumes of entire brain structures, however, they are less sensitive towards detecting smaller effects in subregions of the brain. The images derived from MRI acquisition are built up out of cubes called voxels. Voxelwise statistical tests compares the voxels of specific locations, thereby offering more information with regard to localization of effects in the brain. Burkhardt and colleagues used a voxelwise statistical approach to study structural brain changes in 19 Cushing's disease patients with a mean disease duration of 24 months compared with 40 healthy controls. They confirmed previous findings of reduced bilateral hippocampal and cerebellar volumes in Cushing's disease patients [11]. In partial agreement with these findings, Jiang et al. [12], also found reduced cerebellar volumes, although they did not find any differences in hippocampal volume in patients with Cushing's disease. In addition, they found decreased volumes in the parts of the medial frontal gyrus.

The high resolution T1-weighted MRI scans that are most commonly used to study gray matter tissue in the brain do not come without limitations. Although we can make increasingly more precise conclusions regarding localization of structural changes in the brain, we cannot draw conclusions concerning the underlying microstructural changes that are involved. Techniques that may provide more

information on this subject are Diffusion Kurtosis Imaging (DKI) and Diffusion Tensor Imaging (DTI). Both techniques rely on measuring the diffusion of water throughout the brain and its neurons. Increased diffusion has been found to be related to causes of structural changes such as the presence of an oedema and the demyelination of the white matter tracts. Jiang et al. [13&&] used DKI to investigate microstructural alterations in gray matter tissue in 15 patients with active Cushing's disease. They found increases of diffusivity parameters in the left hippocampus and parahippocampal gyrus and the left temporal lobe in Cushing's disease patients compared with healthy controls. Moreover, the diffusivity parameters in the parahippocampal gyrus correlated positively with the Cushing's syndrome severity index (CSI) scores, supporting the suggestion that hypercortisolism causes the microstructural changes [13].

Another way to obtain more information on microstructural changes associated with hypercortisolism is by measuring metabolites in the brain. Proton magnetic resonance spectroscopy (H-MRS) is a sensitive, noninvasive imaging technique that provides information on brain metabolites in vivo. Crespo et al. [14] used this technique to investigate the concentration of metabolites in the ventromedial prefrontal cortex (vmPFC) of 22 Cushing's syndrome patients, of which 15 were in remission. They found lower concentrations of glutamate and total N-acetyl-aspartate (NAA) in the vmPFC of Cushing's syndrome patients. Moreover, the duration of hypercortisolism and state anxiety were related to the decreases in NAA, suggesting a potential pathway through which hypercortisolism leads to anxiety symptoms [14]. Whilst this imaging technique sheds more light on the presence of metabolites in the brain, it does not provide information on active metabolism in the brain. Glucose metabolism in the brain can be measured using [(18)F]-fluorodeoxyglucose positron emission tomography (FDG PET), which has been used by Liu et al. [16] to acquire data regarding brain metabolism from 92 patients with Cushing's disease and 118 healthy controls. A voxelwise statistical approach revealed increased FDG uptake in the basal ganglia, anteromedial temporal lobe, thalamus, precentral cortex and cerebellum, as opposed to decreased FDG uptake within the medial and lateral frontal cortex, superior and inferior parietal lobule, medial occipital cortex and insular cortex. In most of these locations, FDG uptake was correlated with serum cortisol levels, indicating the involvement of hypercortisolism in changes of brain metabolism [15,16].

Most Cushing's disease patients are treated by means of transsphenoidal surgery, in some cases followed by postoperative radiotherapy and/or pharmacological

treatment, depending on the outcome of the surgery. Following the successful treatment of hypercortisolism, both the physical features and the psychiatric symptoms tend to improve substantially [17,18]. However, despite these improvements, a number of symptoms such as depression, anxiety, cognitive impairments and decreased quality of life persist, even in long-term remitted Cushing's disease patients [19–21]. The following two paragraphs will offer further insight into which structural changes seem to be reversible after curation, and which structural changes seem to be more persistent based on findings derived from longitudinal studies and studies conducted in remitted
Cushing's disease patients.

Reversible gray matter structural changes after remission of hypercortisolism
Reversibility of gray matter structural changes can only bemeasured using longitudinally designed studies. In 1999, Starkman et al. [22] found that the reduction of hippocampal volumes in patients with active Cushing's disease were partially reversible after curation. A follow-up study showed that these increases in hippocampal volume were associated with improvements in learning [23]. Increases in third ventricle diameter were also found to be partially reversible [7]. In children, the recovery phase after correction of hypercortisolism appears to progress at a more rapid pace. In a study conducted by Merke et al. [24], 14 patients with Cushing's syndrome, aged between 8 and 16 years, underwent an MRI scan before treatment and again 1 year after treatment. At baseline, smaller cerebral volumes, larger ventricles, and smaller amygdala were found. One year after treatment, cerebral volumes increased and ventricular size decreased to match those found in healthy age-matched controls. However, despite this reversibility, cognitive functioning remained impaired measured at follow-up [24]. In 2011, Toffaninet al. [25] manually divided the hippocampus into three subregions (i.e. the head, body and tail), and found that the reversibility of the effects of hypercortisolism were predominantly located in the head of the hippocampus. Of importance is that there are no recent studies, which have examined the reversibility of structural changes using a longitudinal design, higher resolution imaging data, and technically more advanced analyses methods such as voxelwise statistics or automatic segmentationprotocols.

Persistent changes in gray matter structure after remission of hypercortisolism
Studying patients with remitted Cushing's disease provides further insight into the persistence of the detrimental effects of hypercortisolism on the brain. Resmini et al. [8] were the first to show reduced cortical gray matter in a group constituted of both active Cushing's syndrome patients (N=11), and remitted Cushing's

syndromepatients (N=22; mean remission time: 7.3 ±2.4 years). Using voxelwise statistics, Andela et al. [26] found reduced anterior cingulate cortex (ACC) volumes in 25 patients with a mean remission duration of 11.2 years. This involvement of (areas within) the ACC was also recently demonstrated in patients with active Cushing's disease [12]. The ACC is a moderately large structure in the brain, and the reductions found in patients in comparison with healthy controls have been found to be situated almost ubiquitously throughout the entire ACC. These findings seem to explain the consistent findings with regard to reductions of cortical gray matter and provide more information on localization of the detrimental effects. Studies focusing on cerebellar volumes in remitted patients are less unidirectional. Studies have shown both increases [26] and decreases [9] in cerebellar volume in patients with Cushing's syndrome in remission. Finally, only one study using H-MRS examined metabolite levels in remitted Cushing's syndrome patients. In accordance with the results of a study conducted by the same research group in patients with active Cushing's syndrome [14], lower levels of NAA, a putative marker of neuronal vitality, were found in the left and right hippocampus and in the right hemisphere. The authors interpreted this as a sign of neuronal loss or dysfunction in these areas. They also found increased concentrations of glutamate and glutamine in both the left and right hippocampus, which could indicate glial proliferation [27].

White matter structural changes

The majority of the more recent studies conducted with (remitted) Cushing's disease and Cushing's syndrome patients have focused on examining white matter structural changes in relation to Cushing's disease. In 2014, our group investigated local white matter integrity in patients with long-term remission of Cushing's disease using DTI. We found widespread reductions of white matter integrity throughout the brain. White matter integrity in the left uncinate fasciculus (a white matter tract connecting the limbic structures with the prefrontal cortex) correlated negatively with depressive symptoms [28]. The widespread reductions in integrity were replicated by Pires et al. [29,30] in a sample of patients with both active and remitted Cushing's syndrome, providing further support for a relationship between decreased white matter integrity and depressive symptoms. The specific pattern of diffusion parameters in these studies suggest that the reductions in white matter integrity are caused by demyelination of the white matter tracts. The results of the most recent study investigating white matter tissue using DKI are in line with the previous results, showing decreases of white matter integrity throughout the brain, and the pattern of diffusion parameters indicating demyelination of the white matter tracts [13]. Finally, a study using a more conventional structural MRI

technique showed a higher degree of white matter lesions in remitted Cushing's syndrome patients, which correlated positively with DBP and hypertension, but not with cognitive performance [31].

Conclusion

Data on structural brain changes in Cushing's disease and Cushing's syndrome generally point in the same direction. The detrimental effects that have been found most consistently constitute of hippocampal volume reductions, which can partially be reversed after cure, and reduced cortical volume, which seems to be specifically driven by reduced anterior cingulate cortex volumes. Studies examining white matter tissue appear to agree that hypercortisolism affects the entire brain, and not specific locations, with indications for demyelination underlying the reductions in white matter integrity. Over recent years, advances in neuroimaging techniques and analysis methods have resulted in more specific information regarding the location of the detrimental effects of hypercortisolism on the brain. However, there is no published well-designed longitudinal study that used these state-of-the art techniques and approaches to investigate reversibility and persistence of these effects. Importantly, conclusions regarding the underlying microbiological processes cannot be drawn from MRI studies. For example, on a macroscopic level, the volume of the hippocampus appears to decrease under influence of hypercortisolism, and the reduction is at least partially reversed after correction of hypercortisolism. However, it remains unclear what microbiological processes are causing these reductions and reversibility. To develop an effective medical treatment for the detrimental effects of hypercortisolism, it is imperative that the underlying microbiological processes are uncovered. One way to get more insight into these processes is to combine the information from high resolution imaging scans with high resolution information from other sources such as the Allen Brain Atlas, which hosts information about gene expression across the human brain [32]. Combining this information could give us an indication of which genes interact with hypercortisolism to induce structural changes in the brain. Another way that we may gain more insight into the into the pathway through which hypercortisolism leads to brain structural changes are animal models. Recently, by inactivating specific gene mutations, researchers have been able to induce Cushing's syndrome resembling phenotypes in mice [33–35].

In summary, structural brain changes related to Cushing's disease have been repeatedly found and findings are generally unidirectional. With the advent of

newer imaging approaches, localization and characterization of the changes in the brain has become increasingly specific. However, state-of-the art longitudinal neuroimaging studies, which could provide on course and reversibility of the effects and their associations with symptomatology are currently lacking. In addition, more research should be conducted to uncover the underlying pathways through which hypercortisolism leads to structural changes.

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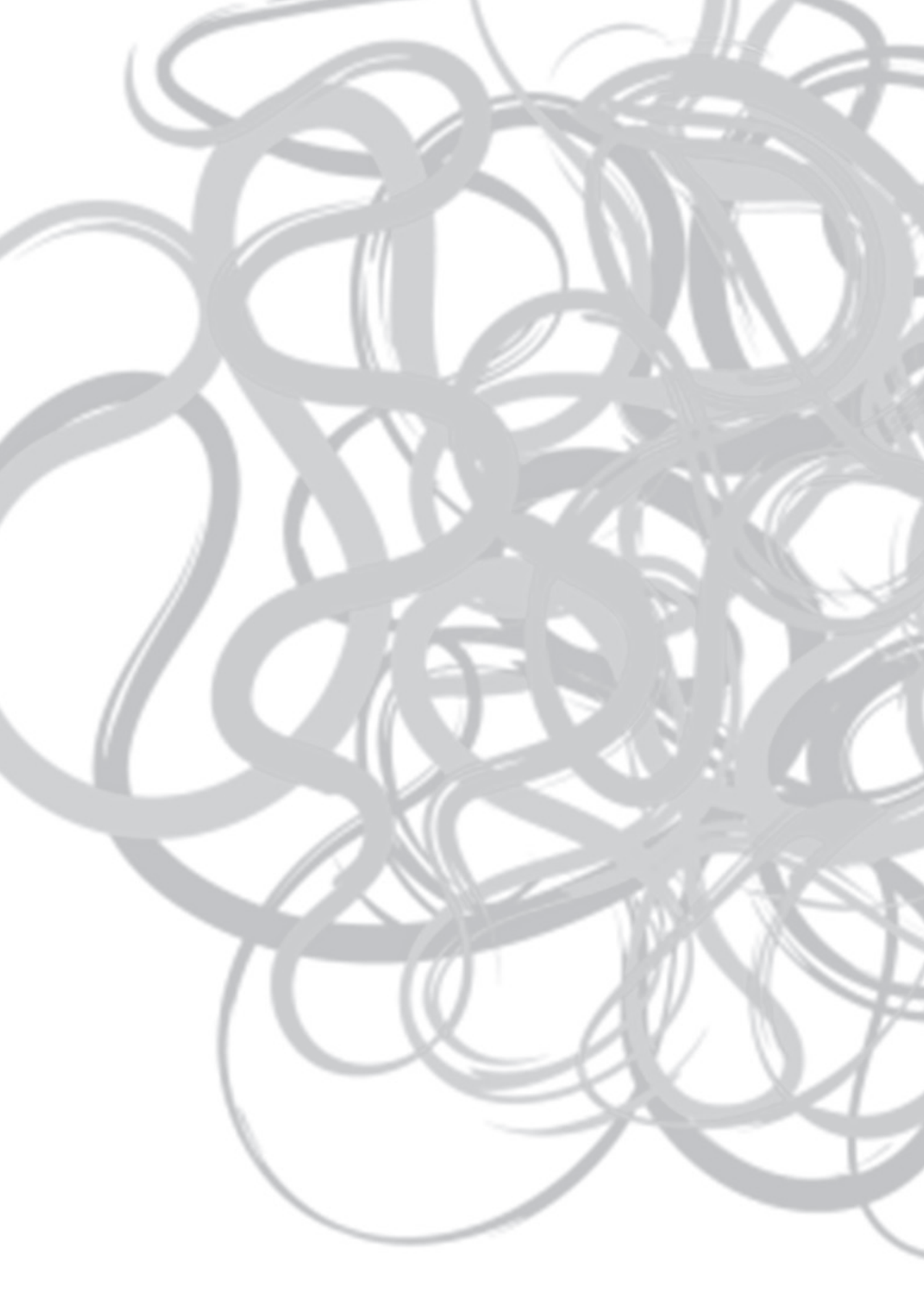
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