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Ultra-high field 7 T MRI localizes regional brain volume recovery following corticotroph adenoma resection and hormonal remission in Cushing's disease: A case series

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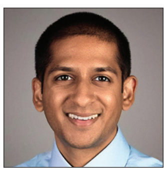

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ABSTRACT

Background: Cushing's disease (CD) is defined by glucocorticoid excess secondary to the increased section of corticotropin by a pituitary adenoma. Magnetic resonance imaging (MRI) studies performed at 1.5 or 3 Tesla (T) have demonstrated correlations between regional changes in brain structure and the progression of CD. In this report, we examine the changes in brain volume following corticotroph pituitary adenoma resection using ultra-high field 7 T MRI to increase the accuracy of our volumetric analyses.

Methods: Thirteen patients were referred to the endocrinology clinic at our institution from 2017 to 2020 with symptoms of cortisol excess and were diagnosed with ACTH-dependent endogenous Cushing syndrome. Five patients had follow-up 7 T imaging at varying time points after a transsphenoidal resection.

Results: Symmetrized percent change in regional volumes demonstrated a postoperative increase in cortical volume that was relatively larger than that of cerebral white matter or subcortical gray matter (percent changes = 0.0172%, 0.0052%, and 0.0120%, respectively). In the left cerebral hemisphere, the medial orbitofrontal, lateral orbitofrontal, and pars opercularis cortical regions experienced the most robust postoperative percent increases (percent changes = 0.0166%, 0.0122%, and 0.0068%, respectively). In the right cerebral hemisphere, the largest percent increases were observed in the pars triangularis, rostral portion of the middle frontal gyrus, and superior frontal gyrus (percent changes = 0.0156%, 0.0120%, and 0.0158%).

Conclusion: Cerebral volume recovery following pituitary adenoma resection is driven by changes in cortical thickness predominantly in the frontal lobe, while subcortical white and gray matter volumes increase more modestly.

Keywords: Brain volume, Cushing's disease, Pituitary adenoma, Ultra-high field MRI

INTRODUCTION

Cushing's disease (CD) is caused by a pituitary adenoma that secretes excess levels of adrenocorticotropic hormone (ACTH or corticotropin), which, in turn, stimulates the excess downstream release of cortisol. Supraphysiologic levels of cortisol from any cause result in a set of signs and symptoms that comprise the Cushing syndrome (CS), including characteristic fatty tissue deposits, purple striae, hirsutism, and fatigue, as well as reduced survival.[2,25,33] ACTHproducing adenomas are the cause of 65–70% of CS, which has an estimated incidence of 0.7–2.4 cases/million/year.[24,29] This state has also been associated with a number of cognitive and psychiatric disorders including memory impairment and depression.[9,32,35] While targeted resection of these adenomas is effective at resolving the direct symptoms of CD, significant cognitive decline and mood disorders have been reported to persist in children and adolescents after surgery.[8,14,15,22,27] Studies in adult patients have also found an increased incidence of depression and residual anxiety in the posttreatment period.[22,37]

Considering these associations, several investigators have analyzed cerebral morphometric parameters in relation to the progression and treatment of CD. One study of adult patients showed that there was an increase in white matter volume and a decrease in cortical thickness, mainly in the frontal and parietal lobes, of patients with persistent CS versus those who achieved endocrinological remission.[40] In a separate study, decreases in the third ventricle volume and bicaudate diameter were shown to correlate with CS resolution in adults.[4] Among pediatric patients with CS, certain brain compartments such as the cerebrum, hippocampus, and amygdala had lower volumes compared to controls.[22] Brain structural changes in relation to treatments are high interest areas in CD research, and with the increasing adoption of ultra-high field (UHF) magnetic resonance imaging (MRI) and automated analysis pipelines, future investigations have the potential to be more sensitive, precise, and reproducible.

To the best of our knowledge, all previous studies measuring cerebral atrophy in relation to CD have been conducted at conventional magnetic field strengths of 1.5 or 3 Tesla, which have poorer signal-to-noise and contrast-to-noise characteristics than UHF strength 7 T MRI. This difference is particularly important when examining fine structural features such as cortical thickness or pituitary microarchitecture. For example, it has been shown that up to 40% of patients with CD have adenomas that are not detectable by conventional MRI.[26] UHF MRI with sub-millimeter resolution, however, has been demonstrated to identify the site of adenoma reliably in several cases for which 1.5 or 3 T localization was inconclusive.[7,28] The ability to characterize pituitary adenomas accurately in patients with Cushing disease would not only decrease the morbidity associated with an invasive procedure such as inferior petrosal sinus sampling but would also decrease the morbidity associated with the pituitary surgery by allowing the surgeon to respect the pathologic component of the pituitary gland while sparing the healthy pituitary gland.

The improved spatial and contrast resolution of UHF MRI has yet to be applied to the volumetric analysis of brain regions in the setting of CD recovery. High-resolution structural detail is especially important for volumetric studies, as errors in linear measurements become geometrically magnified, and this can result in reduced sensitivity or spurious conclusions. In this report, we present the first such analysis of regional brain volumes in a cohort of patients with CD who underwent high-resolution UHF MRI before and following transsphenoidal surgery.

MATERIALS AND METHODS

Subjects

Thirteen patients were referred to the endocrinology clinic at our institution with symptoms of cortisol excess. Following clinical and laboratory workup, each patient was diagnosed with ACTH-dependent endogenous CS according to societal guidelines, with concern for CD.[19,28] Among the 13 patients who were referred for 7 T imaging between 2017 and 2020, five also had follow-up 7 T imaging after surgery. The exclusion criteria included overt signs of cognitive impairment, claustrophobia, and general contraindications for MRI which includes MR-incompatible medical devices, claustrophobia, pacemakers, contrast allergy, and weight limitations. Neuroimaging data measures include an MR structural imaging utilizing a sella protocol, which consists of sagittal and coronal T1- as well as coronal T2-weighted sequences, dynamic contrast-enhanced coronal T1-weighted sequence, as well as sagittal and coronal T1-weighted sequences all with attention to the sella after administration of IV gadolinium. Both 3 T and 7 T MRI data were obtained if the patient did not have prior imaging, with the 3 T imaging as part of the standard of care clinical imaging for patients with CD. This study was approved by the Institutional Review Board at our institution, and all patients in this work provided written informed consent.

MRI studies

The patients underwent 7 T MRI per previously published protocols, including whole-brain 0.7 mm isotropic resolution magnetization-prepared rapid gradient echo (MP-RAGE) sequences and postcontrast (0.2 mL/kg gadoterate meglumine) sellar sequences that identified focal hypoenhancing pituitary lesions in all cases.[32,33] Imaging was performed on a Siemens MAGNETOM Terra 7 T system with a Nova Medical 8Tx/32Rx head coil. All 13 patients subsequently underwent transsphenoidal resection with routine postoperative clinical imaging and processing. At various intervals after surgery, follow-up 7 T MRI was performed on five patients with the same scanning parameters as those used preoperatively. The patient 1 had a 3.9 mm lesion on 7 T MRI with histology identifying only Crooke hyaline change, but the patient experienced endocrinological remission following surgery, suggesting the presence of a true underlying adenoma. Patients 2–5 had

6.2, 6.5, 4.0, and 4.0 mm lesions on 7 T MRI, respectively. All of these were histologically confirmed to be corticotroph adenomas, and these patients also experienced postoperative endocrinological remission that was confirmed with serum cortisol measurements. No other macroscopic and microscopic abnormalities were detected in our study group. The patient characteristics are summarized in [Table 1]. MRI data were stripped of patient-specific information for the computational group analysis.

Volumetric and statistical analysis

To obtain quantitative measures for the differential recovery of different brain regions, we performed a volumetric analysis of the preoperative and postoperative 7 T MP-RAGE sequences using FreeSurfer's longitudinal workflow and a two-stage model.[32] This methodology takes advantage of the assumption that within-subject anatomical changes are significantly smaller than interindividual morphological changes to reduce imaging noise and subject variability. This longitudinal pipeline creates a temporally unbiased interpretation of any number of time points by first creating a within-subject template using a symmetric registration method. Cortical and subcortical segmentation and parcellation protocols use many nonlinear optimization techniques such as topology correction, which are traditionally calculated iteratively and are sensitive to the starting point of the solution. FreeSurfer addresses this variation by processing data in a longitudinal series with a common initialization and avoids the risk of temporal over-regularization.

The FreeSurfer workflow consists of three major steps.[32] First, a full image segmentation and surface reconstruction for each time point are independently constructed. Then, a within-subject template is created across all time points for each patient. Finally, each individual time point is processed longitudinally using algorithms such as intensity corrections, Talairach registration, brainmask creation, and surface generation. The cortical surface construction in FreeSurfer as seen with [Figure 1] starts with a tessellation of the gray-white matter boundary, automated topology correction, and surface deformations to optimally generate the gray/white and gray/CSF borders at locations where there is the greatest shift in intensity.[32] A general linear model (GLM) analysis was performed using the standard group analysis protocol in FreeSurfer. Various full-width/half-max values from 0 to 25 mm in 5 mm intervals were generated during this resampling, and the 15 mm value was used for FreeSurfer's built-in GLM module to create the significance maps, as shown in [Figure 2]. The method to correct for multiple comparisons is to run Monte Carlo simulations under the null hypothesis and to interpret how often the value of a statistic deviates from the true analysis.[32] The FreeSurfer simulator that is used for these multiple comparisons is roughly based on FSL's permutation simulator (randomize) and AFNI's null-z simulator (AlphaSim).[5,41] The frequency of the deviation is interpreted as the reported *P*-values for the thickness and volume changes for the group whole-brain analysis. An alpha-value such as 0.05 or 0.1 was not set since there were a limited number of patients in this investigation.

RESULTS

Both patients 2 and 3 underwent follow-up 7 T MRI at 81 days following surgery, while patients 1, 4, and 5 went through imaging at 882, 333, and 392 days following surgery, respectively. Direct visual comparison of the preoperative and postoperative scans revealed a clear reversal of cerebral atrophy, identifiable as increased cortical thickness and corresponding sulcal narrowing. A representative example of this phenomenon is provided in [Figure 1]. Symmetrized percent change in regional volumes as detected by automated segmentation demonstrated a postoperative increase in cortical volume that was 0.0172%, which was larger than the 0.0052% increase in cerebral white matter or the 0.0120% increase in subcortical gray matter. In the left cerebral hemisphere, the medial orbitofrontal, lateral orbitofrontal, and pars opercularis cortical regions experienced the largest postoperative percent increases (percent changes = 0.0166%, 0.0122%, and 0.0068%, respectively), while in the right cerebral hemisphere, the largest percent increases were observed in the pars triangularis, rostral portion of the middle frontal gyrus, and superior frontal gyrus (percent changes = 0.0156%, 0.0120%, and 0.0158%, respectively). [Figure 2] depicts a map of the average postoperative increase in cortical thickness over the cerebral hemispheres. We also noted marked postoperative decreases in volumes of the

Table 1: Size and histology of focal hypoenhancing pituitary lesions and postsurgical outcomes.

Patient	Longest dimension (mm)	Histology	Endocrinological remission	Time between surgery and postoperative MRI (days)
1	3.9	Crooke hyaline change	Y	882
2	6.2	Corticotroph adenoma	Y	81
3	6.5	Corticotroph adenoma	Y	81
4	4.0	Corticotroph adenoma	Y	333
5	4.0	Corticotroph adenoma	Y	392

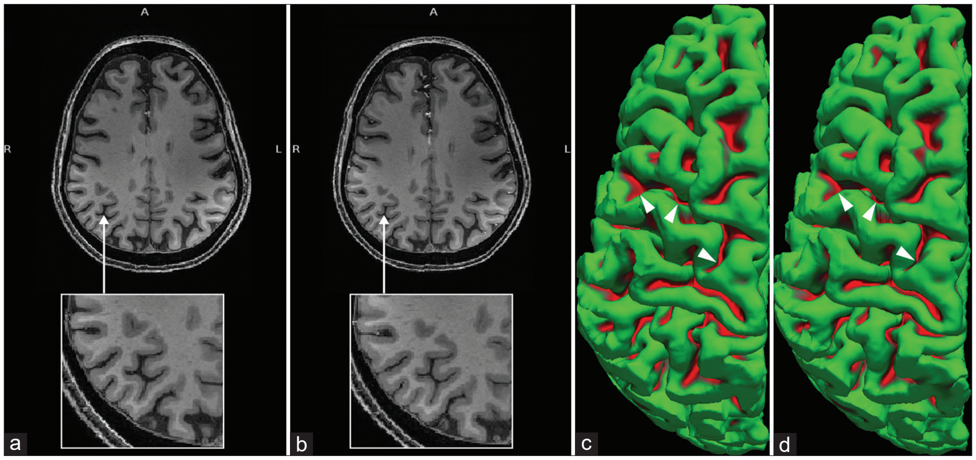

Figure 1: Postoperative cortical thickness recovery in patient 2. Matched T1-weighted axial slices from preoperative (a) and 81-day postoperative (b) 7 T MRI illustrates the expansion of the cortical gray matter with concordant narrowing of adjacent sulci, best seen on the magnified insets of the right parietal lobe (arrows). Superior views of 3D surface renderings of the right cerebral hemisphere generated from the same preoperative (c) and postoperative (d) 7 T MRIs also reveal narrowing of the frontoparietal sulci (red), best seen from this perspective along the precentral sulcus (arrowheads).

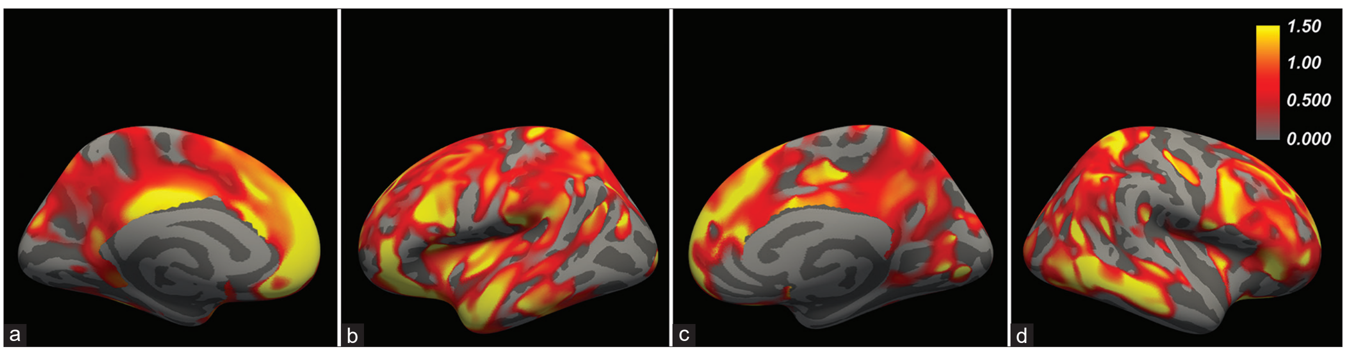

Figure 2: Regression results for postoperative increases in cortical thickness across all three subjects. Inflated cortical surface renderings are shown from the medial/lateral projections for the left (a and b) and right (c and d) hemispheres. In the overlaid color scale, golden hues indicate areas of greater postoperative cortical thickness increase, scaled as z-scores. The scale represents −log10 (p) values.

ventricular system (percent changes = −0.0816%, −0.0208%, −0.0628%, and −0.0630% for the 3rd, 4th, right lateral, and left lateral ventricles, respectively), which is consistent with our visual observations. These results are summarized in [Table 2].

DISCUSSION

Imaging analysis

Our findings demonstrate recovery of frontotemporal cortical volume in CD patients following surgical treatment with UHF 7 T MRI. We are able to better depict postoperative percentage increases with better spatial resolution. Two commonly used standards for gray matter analysis are cortical thickness and surface area. Thickness is a measure of neuron and glia size, number, and arrangement in specific brain regions, while surface area is associated with the number of columns in a region of interest. The data collected using 7 T MRI and analysis pipelines such as FreeSurfer in this work have shown that the frontotemporal areas of the brain may increase in cortical thickness and volume after CD surgical treatment and hormonal remission.[32] In this study, any changes in behavior or cognition in tandem with endocrinological remission posttreatment were not assessed. However, clinically, this work has a potential direction to help monitor cognitive changes in relation to brain structure volume and thickness restoration at high imaging resolutions following transsphenoidal surgery.

Literature review

CD is an important disease model for understanding the effect of cortisol on brain structures.[4,35] The reversal of symptoms following transsphenoidal resection is key to understanding the volumetric changes in the brain that happens due to the syndrome. Yet, the structural differences between active

Table 2: Relative changes in regional brain volumes following corticotroph adenoma resection.

Brain region	Postoperative percent change in volume
Cortical volume	+0.0172%
Cerebral white matter	+0.0052%
Subcortical gray matter	+0.0120%
Left medial orbitofrontal region	+0.0166%
Left lateral orbitofrontal region	+0.0122%
Left pars opercularis cortical region	+0.0068%
Right pars triangularis	+0.0156%
Right rostral portion of the middle frontal gyrus	+0.0120%
Right superior frontal gyrus	+0.0158%
3rd ventricle	−0.0816%
4th ventricle	−0.0208%
Left lateral ventricle	−0.0208%
Right lateral ventricle	−0.0630%

and remitted CD patients are still considered controversial due to the rare incidence of CD, varying criteria to define remission, and lack of longitudinal studies.[11,13] There is no consensus on the appropriate time for cortisol testing and the requirement of specific protocols to determine the true recurrence of the disease.[11] In fact, many previous studies in the field are cross-sectional, comparing images from preoperative and postoperative CD patients from different populations.[3,6,20,31,33] Imaging for these studies has mainly been at traditional field strengths such as 1.0 T and 1.5 T that may not have high enough resolution to detect the sensitive changes seen in CD.[4,12,17,22,34] Additional support for UHFs scans is shown by one recent meta-analysis which noted that patients undergoing primary TSS have the highest chance of remission when the adenoma is visible on preoperative imaging.[38] In general, the MRI scans in a handful of investigations also did not use whole-brain sequences and are limited to the pituitary region.[4,17] Finally, several key studies in the field have also mainly employed manual tracing of brain structures and have not been processed by objective neuroimaging processing workflows such as FreeSurfer.[35,36]

The volume changes in the brain after a transsphenoidal resection may reflect a reversal of damage in neuronal and nonneuronal glial cells in the affected areas, which may be sensitive to glucocorticoid (GC) excess. Animal models with GC excess have been shown to have a significant loss of synapses on pyramidal cells of hippocampal region CA3 and structural changes in afferent mossy fibers terminating on those neurons.[10] The loss of neurons associated with hypercortisolism is related to glutamate accumulation and elevated postsynaptic intracellular Ca^{2+} levels, which may explain the smaller preoperative cortical thickness in our group analysis.[21] A recent and similar investigation comparing brain structure volumes in active CD patients, remitted CD patients, and healthy controls using artificial intelligence (AI) and high-field 3 T MRI was reported by Hou *et al*.[12] Fifty patients were followed longitudinally during their CD surgical treatment, and the imaging was done at conventional field strengths. The frontoparietal changes recorded from monitoring this cohort are consistent with our observations in this longitudinal investigation. As a point of emphasis, average frontal lobe and parietal volumes were higher in remitted CD patients compared to active CD patients.[12] In addition, in reference to the study done by Tirosh *et al*., their team noted that patients with active disease had a general decrease in cortex thickness compared with patients who were in remission of CS.[40] This association is consistent with the cortical thickness increase posttreatment in our study.

Limitations

Due to the limited study sample of five patients, the observed volume changes are preliminary and will require follow-up studies to assess the time course of frontoparietal volumetric changes. Further follow-up with a larger-scale analysis is needed to make a more statistically significant call for the frontoparietal changes as seen in the data here. In this specific study, patients 2 and 3 had their follow-up MRI both at 81 days after surgery, which is an order of magnitude shorter than the other three patients' follow-up MRI. The changes in the brain for all five patients were still consistent with each other, so there may be a plateau in the parameter changes during the posttreatment period. Nonetheless, additional UHF scans at defined and consistent intervals after the patient's operations are an area of interest since some areas of the brain may recover more quickly than others. In addition, set intervals will show a more comprehensive timeline of the relief of CD symptoms in correlation with brain parameter changes.

Cognitive and psychiatric changes were not evaluated in our sample of five patients. Cognitive difficulties and depression can persist in patient's following pituitary resections, even when brain volumes have normalized.[1,16,30] In a recent literature review of 682 patients who had undergone transsphenoidal resections, the most commonly reported neurologic deficits included impairments in verbal and nonverbal memory.[1] Furthermore, patients who had undergone resections for CD compared with patients who had resections for nonfunctioning pituitary macroadenomas had lower scores on the Mini-Mental State Examination and the memory quotient of the Wechsler Memory Scale.[39] The authors theorized that the effects of excess GCs on the central nervous system, and the hippocampus, in particular, can have a long-term impact on memory and cognition. Significant psychiatric affective disorders were also reported in a case series of nine children who underwent surgery for treatment of CS, which may be attributed to the differential effects of GCs on the pediatric brain.[15] A 2005 study of nine children with surgically treated Cushing disease found that despite the reversal of cerebral atrophy in patients 1 year after surgery, these patients had statistically significant declines in Wechsler IQ scores and school performance.[22] UHF strength imaging of the postsurgical brain may reveal previously unseen anatomic changes. In future studies, a standardized cognitive examination may be added to further determine if anatomical changes correlate with patient improvement.

AI

The diagnosis and management of CD can be challenging since some patients may have an atypical presentation that overlaps with other metabolic syndromes. Thus, an AI platform could be useful to isolate features that are characteristic of preoperative and postoperative CD patients and to better determine when patients are in full remission of the disease.[18] AI-assisted segmentation and brain quantification software may outperform template-based segmentation and can provide even greater accuracy when applied to 7 T data. Reuter *et al*. built on the FreeSurfer template-based segmentation by introducing a new, patient-specific longitudinal template to help reduce variability.[32] Recent AI-assisted segmentation and brain quantification software such as AccuBrain have built on this framework and have introduced atlas-based segmentation software which has been validated by anatomic templates built by experienced radiologists. This atlas pool can be registered to an individual's MRI to calculate segmentation volumes of key metrics such as brain structure, lobe, and tissue within milliliters of accuracy.[12] Finally, since medical imaging datasets with UHF images are small since 7 T MRI is a relatively new technology, deep learning algorithms are limited compared to what has been demonstrated on large-scale datasets such as ImageNet.[23] As databases grow larger with increased implementation of UHF MRI in the clinical setting, significant improvements will be seen in the analysis of anatomic changes in neuropsychiatric conditions.

CONCLUSION

UHF MRI yields observable increases in cortical thickness and overall brain volume following corticotroph adenoma resection and achievement of hormonal remission in patients with Cushing disease. This cerebral volume recovery appears predominantly to involve the cortical gray matter compartment with a frontotemporal predominance. This proof-of-concept work highlights the sensitivity and accuracy of the 7 T technique, which may be applied in future, large-scale studies to elucidate the mechanisms underlying the cognitive and psychiatric symptoms associated with CD. In combination with AI tools, UHF imaging techniques have a high potential to analyze microlevel structural differences associated with certain neurological disorders consistently.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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