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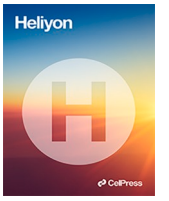

Research article

Impact of growth hormone-secreting pituitary adenoma on limbic system and its correlation with cognitive impairment

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A B S T R A C T

Purpose: To assess the quantitative gray matter volume of the limbic system in growth hormone-secreting pituitary adenoma (GHPAs) patients and its correlation to cognitive function.
Method: 91 right-handed patients with pituitary adenomas were retrospectively included from the First Affiliated Hospital of Sun Yat-sen University −48 with GHPAs and 43 with non-functioning pituitary adenomas (NFPAs). Participants underwent serum hormone assessment, regular sellar MRI scanning with T1WI-MPRAGE. Cognitive function was gauged using MoCA and MMSE. Brain region auto-segmentation and gray matter volume calculation were conducted on the Brainsite platform.
Results: Compared to NFPAs patients, GHPAs patients had higher gray matter volume (758,285 vs 674,610 mm^3, $p < 0.001$). No significant volumetric differences in both sides of limbic system gray matter while there were evident differences in the relative volumes of limbic system gray matter between groups. GHPAs patients scored lower on MOCA (24.0 (2.18) vs 25.1 (2.28), $p < 0.031$), with no difference in MMSE. We observed a significant correlation between the relative limbic volume and MOCA scales, while no evident correlation was found between relative limbic volume and serum hormone or tumor aggressiveness. Univariate and multivariate Logistic regression showed that hippocampus and limbic cortex (parahippocampal gyrus and internal olfactory area) of advantageous hemisphere correlated significantly with occurrence of mild cognitive impairment with the C-statistic reaching 0.90.
Conclusion: Patients with GHPAs show a relative decrease in limbic gray matter volume, especially in the hippocampus and limbic cortex of the dominant hemisphere, which is associated with mild cognitive impairment.

1. Introduction

Pituitary adenoma is one of the most common tumors of the central nervous system, of which the growth-hormone pituitary adenoma (GHPAs) can lead to high GH/IGF-1 exposure in adults, resulting in acromegaly [1–5]. Over secretion of growth hormone (GH) can lead to high level of insulin-like growth factor 1 (IGF-1), consecutively leading to tissue hypertrophy, osteoarthritis, facial and limbal deformities, obstructive apnea and many other visceral complications [5–7]. In recent years, in addition to somatic symptoms

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caused by high GH/IGF-1 exposure, researchers have increasingly focused on the cognitive impairments (CI) in patients with GHPAs [8–12].

Recent studies suggest that brain tumors, including pituitary adenoma, might disrupt neural connections not only through mass effects but also due to endocrine abnormalities from abnormal hormone secretion, potentially impacting cognitive functions [14–18]. Notably, pituitary adenoma, primarily confined to the sellar region, are less likely to induce mass effects. However, emerging research indicates that pituitary adenoma predominantly cause mild cognitive impairments (MCI) through endocrine dysregulation [17,18]. In patients with GHPAs, the primary cognitive impairments observed are executive dysfunction and memory loss, closely linked to the limbic system [11–13]. Although several studies report hippocampus or amygdala atrophy in response to elevated GH/IGF-1 levels, others present contrasting findings [12,19,20]. These studies usually studied the absolute volume of the corresponding brain region, but less often analyzed its relative volume, i.e., the ratio of specific region's absolute gray matter volume to the overall gray matter volume.

Previous studies usually performed manual or semi-automatic brain region segmentation, whereas some other studies have investigated brain region segmentation algorithms in detail, with the rapid advancement of deep learning algorithms in recent years [21–25]. The segmentation algorithms are commonly performed in widely acceptable standard spaces/atlases; however, when using these standard spaces for segmentation, it could be challenging to account for the bias due to the patient's age, gender, and other biological variations. By jointly using multiple widely used atlases, Tang et al. developed a more generalized automatic segmentation algorithm based on the likelihood fusion algorithm and pre-selection strategy, achieving a maximum Dice overlap of 0.937 (0.0259), which improves the segmentation accuracy obtained from single-atlas LDDMM (Large Deformation Diffeomorphic Metric Mapping), and further transplanted the segmentation pipeline to a cloud platform [21]. By inputting the structural sequences of T1WI MRI of patients, the segmentation results and volumetric statistics of up to 283 brain regions can be obtained, greatly reducing the labeling time and human errors of manual segmentation. The images can be uploaded to the cloud platform and the results can be simultaneously reviewed by multiple investigators, thus enabling more efficient coordination of work for clinical and preclinical use [26].

By using the automatic segmentation algorithm on Brainsite platform (http://brainsite.cn), we segmented the brain regions and sub-regions of limbic system of GHPAs patients and NFPAs patients. To exclude the influence of mild hyperprolactinemia, which often occurs in patients with pituitary tumors, we chose NFPAs as the control group. We compared the relative volumes of brain regions and sub-regions of the limbic system between patients with GHPAs and NFPAs and their correlations with cognitive scales to explore the impact of high GH/IGF-1 exposure on these areas.

2. Methods

2.1. Populations

91 inpatients of the department of neurosurgery in the First Affiliated Hospital of Sun Yat-sen University were retrospectively included from January 2019 to December 2021. Among them there were 48 with GHPAs and 43 with NFPAs.

The inclusion criteria were as follows [1]: pre-operative MRI scanning was performed 1 week before surgery, including regular sellar scanning and 3D T1WI-MPRAGE sequence of whole brain [2]; pre-operative serum hormone level accords with the diagnostic criteria of GHPA (nadir GH $>$ 1 ng/ml after OGTT and over-secretion of IGF-1 compared to normal range of corresponding age) or NFPA (normal serum hormone level or prolactin less than 120 ng/ml) [3]; pathologic type was verified by regular HE staining and histochemical analysis (GHPA: reticulin framework is disrupted, with eosinophilia, and strong positivity for GH; NFPA: reticulin framework is disrupted, with basophilia or amphophilicity, and GH, PRL, TSH, ACTH are negative or weakly positive) [4]; cognitive function was evaluated 1 days before surgery [5]; all participants had received education at high school level or above (more than 12 years of education).

Exclusion criteria were [1]: left-handed patients [2]; illiteracy [3]; accompanied by decreased or increased levels of other hormones (thyroid hormones, cortisol, adrenocorticotropic hormone, etc.) [4]; microadenomas [5]; pituitary adenomas with suprasellar extension [5]; previous diseases, such as stroke, dementia or other diseases affecting cognitive function. Sociological characteristic data, laboratory tests results, imaging data, pathological examination results, and results of cognitive function evaluation of all patients were collected.

2.2. Test of serum hormone level

All the serum hormone related with pituitary axis were measured 1 day before surgery, including prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and insulin-like growth factor-1 (IGF-1), etc. The blood sample were collected from patients' vein between 6 a.m. and 10 a.m. after 10–12 h of fasting. The standard IGF-1 (st IGF-1) were calculated as follows: serum IGF-1/upper limits of normal age and sex-adjusted range.

2.3. Evaluation of the extent of invasion of pituitary adenomas

The Knosp grading system is used to describe the extent of invasion of pituitary adenomas. This system is based on the position of the pituitary tumor relative to the cavernous sinus, particularly the extent of the tumor's extension relative to the lateral wall of the cavernous sinus [27]. All cases were graded in the Knosp grading system individually by two experienced neurosurgeons, each with over five years of practice, based on MRI images. They were then categorized according to grades 0–2 (non-invasive group) and 3–4

(invasive group) for statistical analysis. In the event of a discrepancy in the evaluation results between the two neurosurgeons, a final judgment is made by a professor specializing in pituitary adenoma, with over ten years of experience in the sub-specialty.

2.4. Evaluation of cognitive function

Cognitive function was evaluated using standard MoCA and MMSE scales 1 day before surgery [28,29]. The evaluation was performed by an experienced doctor under quiet and restful condition. Patients with accents were allowed to be companied by a family member but no interpretation except translation was allowed. The MMSE has a maximum score of 30 points, with 27–30 points considered the normal range, and scores less than 27 points are considered to indicate cognitive dysfunction and the total MoCA score is also 30 points, with a score $\geq$26 considered normal, 18–26 points indicate mild cognitive impairment, 10–17 points indicate moderate dementia, and $<$10 points indicate severe dementia.

2.5. MRI scanning

All patients undergo a 3.0T MRI scanning using a 64-channel head coil (*Magnetom Verio, Siemens*, Erlangen, Germany). Regular sellar scanning and enhanced scanning were performed with parameters as follows: T1WI: slice thickness: 3 mm, echo time: 8 ms, repetition time: 550 ms, field of view: 256 $\times$ 240 mm^2; T2WI: slice thickness: 3 mm, echo time: 116 ms, repetition time: 4000 ms, field of view: 256 $\times$ 240 mm^2, flip angle: 8°. A 3D T1WI MPRAGE sequence of whole brain without enhance was also collected with parameters as follows: sagittal view, slice thickness: 0.65 mm, inversion time: 1000 ms, echo time: 2.22 ms, repetition time: 2400 ms, field of view: 256 $\times$ 240 mm^2, flip angle: 8°. As there were no patients with microadenomas, the dynamic enhanced scanning was not performed.

2.6. Image processing and segmentation

The raw data in DICOM format were collected from the Radiology Department of the First Affiliated Hospital of Sun Yat-sen University. The data were then converted to NIFTI format using MRIcron software (v2.1.61-0), which provides *dcm2nii* programs for converting DICOM images to NIfTI format. The 3D T1WI MPRAGE sequences were uploaded to the *Brainlabel* platform(http://brainsite.cn), a cloud service for brain segmentation of T1 image based on multiple atlas likelihood fusion algorithm and pre-selection strategy [21,24], for auto-segmentation of brain regions. The summary of volumetric data was downloaded from the same website. The relative volume of all parts of limbic cortex were calculated as the ratio of specific part's absolute gray matter volume to the volume of whole brain gray matter.

2.7. Statistical analysis

The baseline information of patients in the GHPAs group and the NFPAs group was compared using the *t*-test, Wilcoxon Rank Sum Test and chi-square test according to the data type. The statistical significance level was set at 0.05. The correlation of MoCA and relative volume of limbic cortex were evaluated using Spearman Correlation. Univariate and multivariate Logistic regressions were used to explore the relationship of MoCA and volumetric data. C-statistic were used for evaluation of regression model, and a nomogram was built based on the regression model. All the statistical analysis were performed using R Program (version 4.0.3).

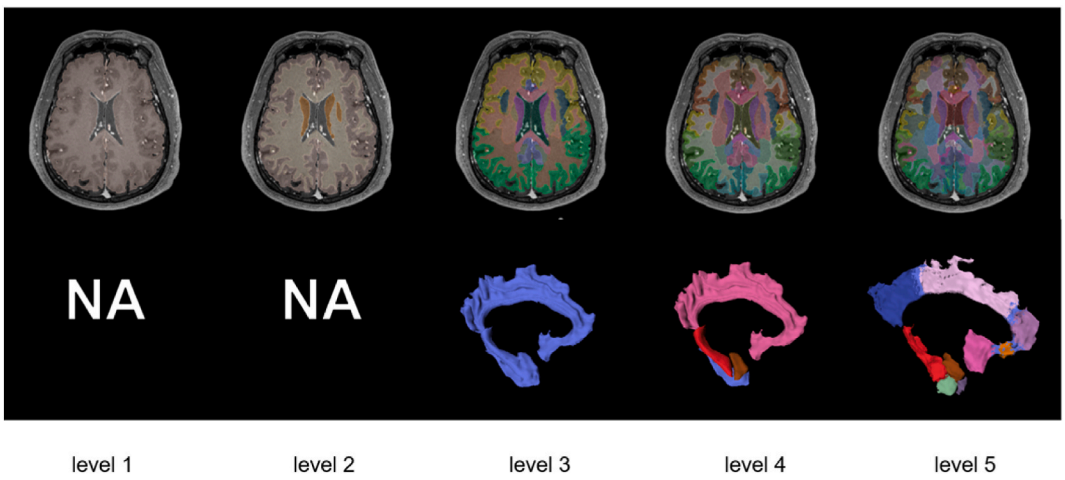

Fig. 1. Images were segmented at five different levels of granularity.

3. Results

3.1. Auto-segmentation of brain region and limbic subregions

After the images were uploaded to the cloud-based platform, the T1-weighted structural images were automatically segmented using the platform's automatic brain region segmentation module, and the segmentation results are obtained after about 10–15 min per patient. Based on the atlas, the whole brain was segmented into 5 granularity levels with a total of 283 brain regions (Fig. 1). The limbic system structure can be shown above the 3rd granularity level. Since the higher the granularity level, the larger the segmentation error may be (e.g., many regions segmented at the 5th level granularity cannot be calculated for volume), we chose to calculate the volume of each limbic cortex on the image under the 4th granularity level, including hippocampus, amygdala, limbic cortex (parahippocampal gyrus and internal olfactory area) and cingulate gyrus. The volume data of each brain region were also generated automatically by the cloud platform.

3.2. Baseline information of patients with NFPAs and GHPAs

48 patients with GHPAs and 43 patients with NFPAs were included in this study, and all baseline data are shown in Table 1. Notably, there was a significant difference in the scores on the MOCA scale between the two groups, while there was no significant difference in the MMSE scores, considering that patients with pituitary adenomas are usually mildly cognitively impaired and the MOCA scale is more sensitive than the MMSE scale for detecting mild cognitive impairment. There were also no significant differences between two groups in terms of age, gender percentage, and sex hormone levels, while there were significant differences in the volume of gray matter of the whole brain and the relative volume of each sub-region of the limbic system (Fig. 2). No significant differences in the absolute value of the volume of each sub-region were found.

Table 1
Baseline information of patients with NFPAs and GHPAs.

	GHPA	NFPA	p
	N = 48	*N = 43*	
gender:			0.903[b]
Female	24 (50.0 %)	20 (46.5 %)	
Male	24 (50.0 %)	23 (53.5 %)	
Age (years)	40.5 (11.3)	44.4 (7.98)	0.054[a]
Duration (months)	60.0 [34.5; 97.0]	12.0 [3.00; 30.0]	<0.001[a]
Knosp Grade			0.5542[b]
0 -2	34 (70.8 %)	27 (62.8 %)	
3-4	14 (29.2 %)	16 (37.2 %)	
MoCA	24.0 (2.18)	25.1 (2.28)	0.031[a]
MMSE	26.2 (2.27)	26.3 (2.19)	0.872[a]
GH (ng/ml)	19.0 [7.69; 35.5]	0.11 [0.05; 0.30]	<0.001[c]
St IGF-1	2.43 [1.713; 2.772]	NA	
PRL (ng/ml)	14.9 [10.9; 22.1]	14.4 [10.4; 34.3]	0.855[c]
Absolute volume (mm^3)			
gray.matter	760337 (97244)	680382 (70700)	<0.001[a]***
CSF	167169 (107799)	210708 (70189)	0.024[a]*
Amyg_L	1731 (233)	1755 (262)	0.652[a]
Amyg_R	1922 (270)	1967 (307)	0.457[a]
Cingulate_L	22385 (3251)	23442 (3729)	0.156[a]
Cingulate_R	24464 (3528)	26099 (4107)	0.046[a]*
Hippo_L	3888 (441)	3773 (582)	0.296[a]
Hippo_R	3930 (571)	3729 (626)	0.115[a]
Limbic_L	1020 (421)	952 (310)	0.381[a]
Limbic_R	1193 (453)	1056 (387)	0.123[a]
Relative volume adjusted by whole brain gray matter			
rel.Amyg_L	0.0023 (0.0003)	0.0026 (0.0003)	<0.001[a]***
rel.Amyg_R	0.0025 (0.0003)	0.0029 (0.0004)	<0.001[a]***
rel.Cingulate_L	0.0299 (0.0056)	0.0345 (0.0048)	<0.001[a]***
rel.Cingulate_R	0.0326 (0.0058)	0.0384 (0.0049)	<0.001[a]***
rel.Hippo_L	0.0052 (0.0007)	0.0056 (0.0007)	0.010[a]**
rel.Hippo_R	0.0052 (0.0007)	0.0055 (0.0007)	0.067[a]
rel.Limbic_L	0.0013 (0.0006)	0.0014 (0.0004)	0.606[a]
rel.Limbic_R	0.0016 (0.0006)	0.0016 (0.0006)	0.824[a]

For the absolute and relative volume in each brain region, the standard deviation is shown in the parenthesis. CSF = cerebrospinal fluid, Amyg = amygdala, Hippo = hippocampus, Limbic = parahippocampal gyrus and internal olfactory area, rel = relative volume. a: *t*-test. b: chi-square test. c: Wilcoxon Rank Sum Test. * p-value <0.05. ** p-value <0.01. *** p-value <0.001.

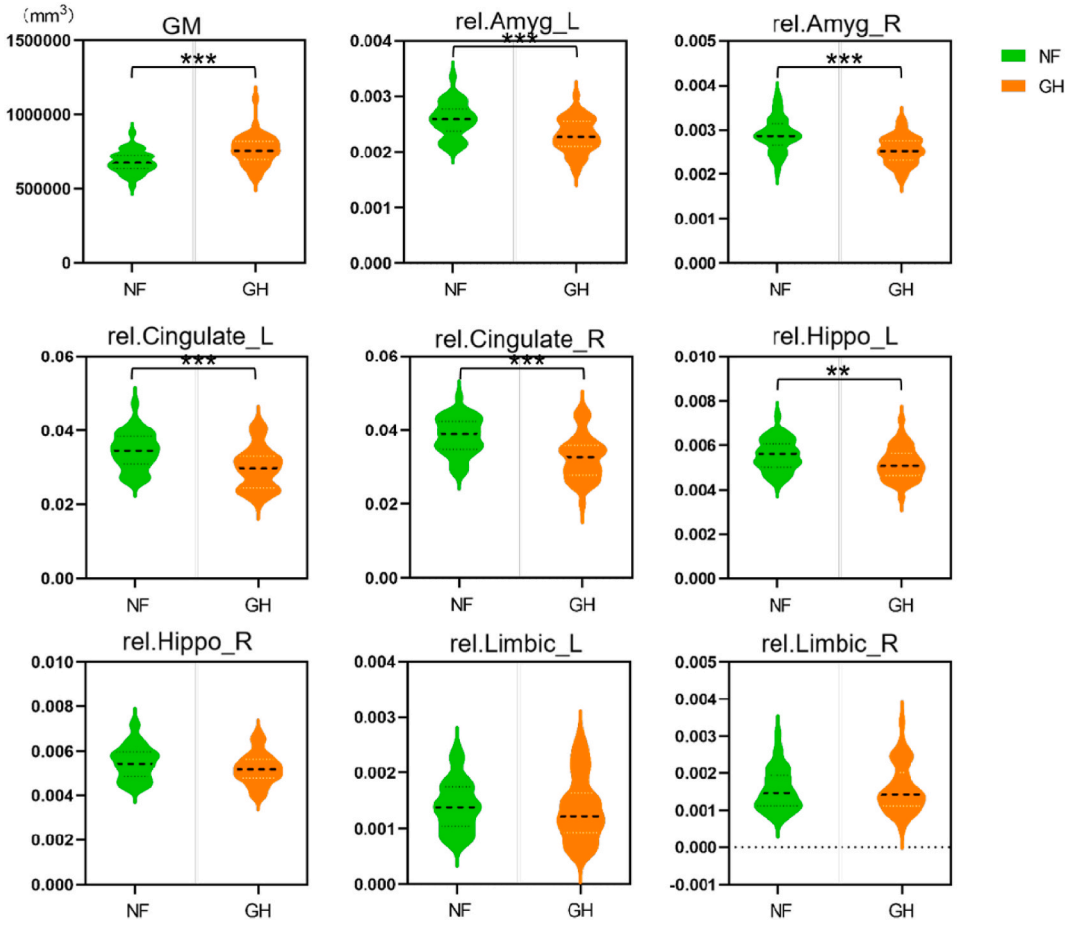

Fig. 2. The whole brain gray matter volume and the relative volumes of limbic system sub-regions in patients with GHPAs and NFPAs. * p-value <0.05; ** p-value <0.01; *** p-value <0.001.

3.3. Correlation analysis of MoCA and sub-region of limbic cortex

Correlation analysis of MOCA scale scores, growth hormone and relative volume of each sub-region revealed no significant correlation between MOCA scores and serum GH or IGF-1 levels, but a significant correlation between MOCA scores and relative volume of each sub-region. Correlation matrix was shown in Fig. 3.

3.4. Logistics regression of MoCA and volume of limbic cortex and nomogram for mild cognitive impairment

According to the internationally accepted standard, those with MOCA scores less than 26 were considered to have cognitive impairment [28]. Therefore, patients were divided into two groups using a cut-off score of 26. First, a univariate Logistic regression was done for the relative volumes of each sub-region, and results showed that the relative volumes of all sub-regions were significant except for the right cingulate gyrus (Table 2). After that, multivariate Logistic regression was done using those factors with significance, and it was found that only left hippocampus and left limbic cortex (parahippocampal gyrus and entorhinal cortex) volumes were significantly associated with MOCA scores (Table 3). Using predictive values of MOCA scores based on the volumes of the two regions to make ROC curves, the C-statistic value could reach 0.90 (Fig. 4), after which we made a nomogram using the relative volumes of these two regions to visualize the effect on occurrence of MCI in patients with GHPAs (Fig. 5).

4. Discussion

In this study, we explored for the first time the changes in the gray matter volume of the limbic system due to GHPAs, by measuring the gray matter volume of the limbic system in patients with GHPAs in comparison with that in patients with NFPAs. We found that the relative limbic gray matter volume was significantly reduced in patients with GHPAs compared to patients with NFPAs. Moreover, we found that the reduced relative volume of the left hippocampus and limbic cortex (parahippocampal gyrus and internal olfactory area) was strongly associated with the occurrence of MCI in patients with GHPAs. In addition, we measured the white matter volume of the

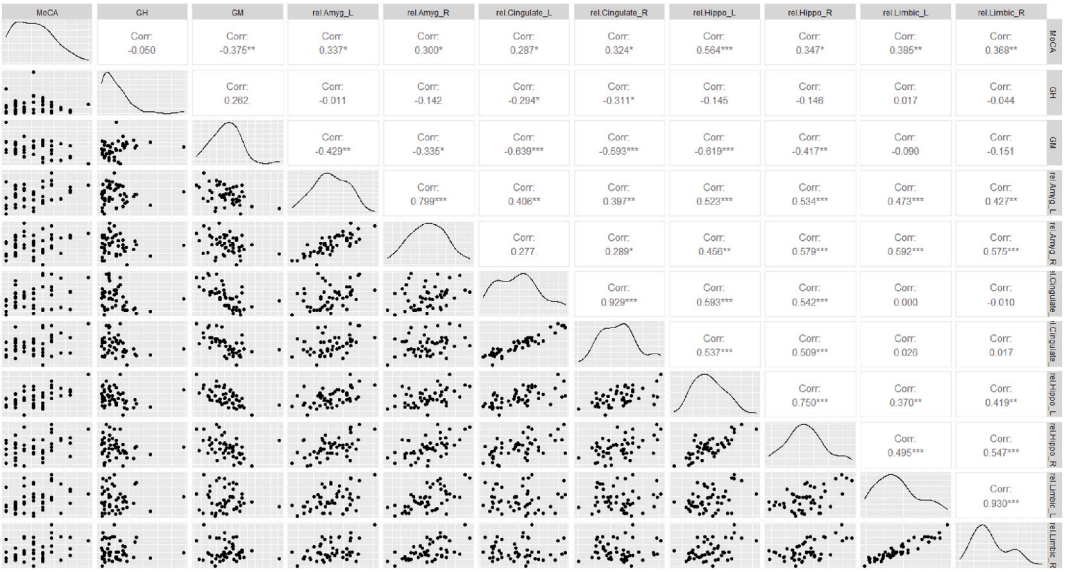

Fig. 3. Correlation between MOCA Scores, growth hormone, and relative volume of each gray matter subregion. The diagonal subplots are histograms of each metric. The subplots in lower left corner show the scatter plots between MOCA scores, growth hormone, and each subregion volume. The subplots in upper right corner show the corresponding correlation coefficients and statistical significance. Corr = Pearson's correlation coefficients, * p-value <0.05; ** p-value <0.01; *** p-value <0.001.

Table 2
Univariate Logistics regression of relative volume and MCI.

	OR	95 % confidence interval		P
rel.Amyg_L	−1.69420	−2.990800	−0.39759	0.0104[a]
rel.Amyg_R	−1.25870	−2.385100	−0.13219	0.0285[a]
rel.Cingulate_L	−0.98211	−1.89290	−0.071328	0.0346[a]
rel.Cingulate_R	−0.89291	−1.88180	0.096001	0.0768
rel.Hippo_L	−2.848100	−4.55540	−1.14070	0.0011[b]
rel.Hippo_R	−1.50100	−2.52800	−0.47393	0.0042[b]
rel.Limbic_L	−1.14850	−2.0318	−0.26514	0.0108[a]
rel.Limbic_R	−1.40950	−2.398400	−0.42053	0.0052[b]

[a] p-value <0.05.
[b] p-value <0.01.

Table 3
Multivariate Logistics regression of relative volume and MCI.

	Estimate	Std. Error	z value	Pr (>|z|)
rel.Amyg_L	−6645.66	5164.52	−1.287	0.1982
rel.Amyg_R	11831.15	8657.37	1.367	0.1718
rel.Cingulate_L	2811.08	1446.62	1.943	0.052
rel.Cingulate_R	−3179.99	1588.77	−2.002	0.832
rel.Hippo_L	−15022.3	7343.17	−2.046	0.0408[a]
rel.Hippo_R	2374.35	2583.19	0.919	0.358
rel.Limbic_L	1022.8	4820.5	0.212	0.0453[a]
rel.Limbic_R	−10057.7	5885.47	−1.709	0.0875

[a] p-value <0.05.

limbic system and yet found no significant statistical differences in both the absolute and relative volumes (sub-region/whole brain) of the limbic system's white matter between the two groups of patients (Supplementary Materials). Therefore, we did not further explore the white matter volume.

Many studies have demonstrated that memory loss and reduced emotional control are closely related to structural alterations in the hippocampus region. In most cases, reduced hippocampus volume is often indicative of reduced memory and emotional control [19, 30–33]. Structural MRI analysis has shown a significant correlation between brain atrophy and neurological dysfunction in diseases such as Alzheimer's disease, Parkinson's disease, and infection of prions [34]. For example, restricted regional gray matter atrophy

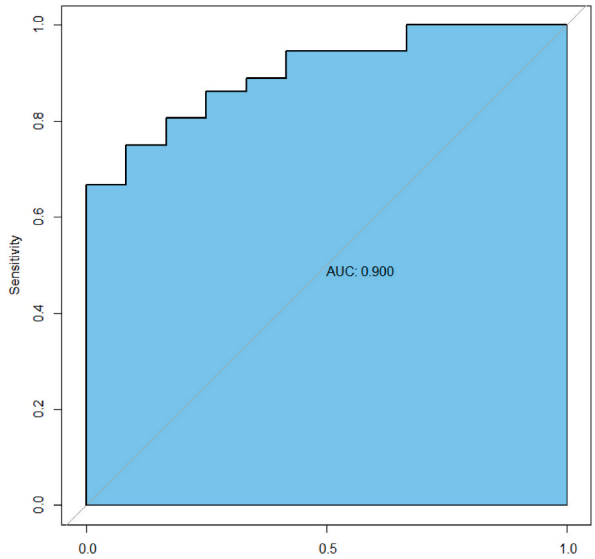

Fig. 4. ROC for MOCA scores based on relative volumes of left hippocampus and left limbic cortex.

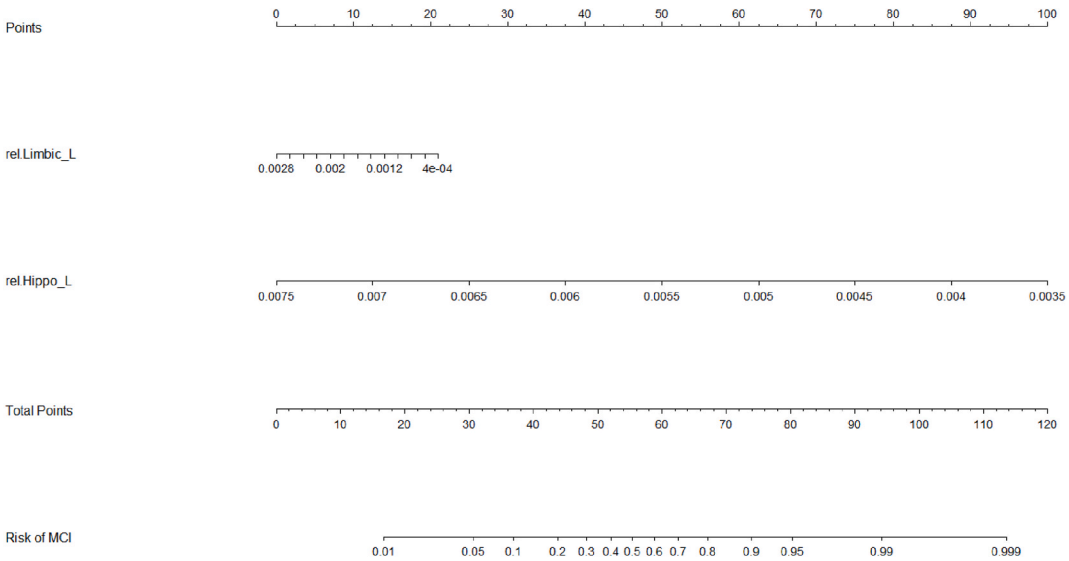

Fig. 5. The nomogram using relative volumes of left hippocampus and left limbic cortex to evaluate the risk of MCI in patients with GHPAs.

occurs mainly in medial temporal lobe structures, including the bilateral hippocampus, parahippocampal gyrus, amygdala and internal olfactory cortex, cingulate gyrus and medial thalamus [12,35]. In patients with Alzheimer's disease, there were diffuse gray matter volume reduction in bilateral primary motor cortex, frontotemporal regions, cerebellum and basal ganglia [36,37]. Furthermore, Zhou et al. found that alterations in gray matter volume in the hippocampus/parahippocampus are associated with subthreshold depression, suggesting that early structural atrophy in these regions may serve as a risk indicator for depression [38]. As early as 2009, Professor Sievers' team found changes in brain structure in patients with GHPAs, more specifically, an increase in gray matter volume in the whole brain and a compression of the ventricles, reducing the amount of cerebrospinal fluid and gaining space [20]. In later studies, it was observed that these structural changes in the brain could predict the degree of cognitive dysfunction, and the predictive analysis was extended to the hippocampus, which is significantly related to memory and attention processes [39–41]. In the present study, we also found an increase in the absolute volume of regions such as whole gray matter and hippocampus in patients with GHPAs.

To evaluate the brain volume alterations in GHPAs, Yuan et al. used voxel morphometry and region-based morphometry cross-sectional studies to obtain the ratio of each brain region's absolute volume to the total intracranial volume, and performed structural MRI evaluations in 48 patients with GHPAs, 48 age- and sex-matched patients with clinical NFPAs, and 48 age- and sex-matched healthy controls [19]. They showed that the whole brain gray matter volume and white matter volume were significantly increased

and correlated significantly with blood GH/IGF-1 levels, and region-based morphometry showed increased white or gray matter volume in 54 of 68 brain regions in GHPAs. To further study correlations of brain volumes and neuropsychological activity impairments in patients, we calculated the relative volume in each region normalized by using the whole brain gray mater volume, instead of the total intracranial volume, to increase the sensitivity in the present study. We found that the absolute volume of gray matter was increasing with growth hormone, whereas the relative volume of limbic regions was significantly decreasing with growth hormone, which may be an important factor contributing to the MCI of the patients. The relative volume and its alterations may be more meaningful than the absolute volume. In addition, our results showed no significant association between the level of serum GH/IGF-1 and MOCA scores, which may be related to the volatility of the hormones on the one hand. The results may be more accurate using GH levels after the OGTT test. On the other hand, the duration of the patient's disease may play a role in the patient's cognitive function, and the time the patient under high GH/IGF-1 level may affect the volume of brain areas subsequently, causing cognitive impairment.

Previous studies also demonstrated that the connections between the posterior cingulate and hippocampus were important for memory encoding and recognition in humans [42–44]. Guo et al. have analyzed cingulate metabolism using magnetic resonance spectroscopy and found significant metabolic alterations in people with MCI [45]. One study in Alzheimer's disease patients found that as hippocampal neurons were damaged, the circuits between the posterior cingulate and hippocampus were damaged in parallel [46]. The results of the multifactorial regression in the present study also showed that hippocampus and limbic cortex volumes in the dominant hemisphere alone were significantly associated with MCI in patients. We did not analyze the changes in hippocampus and limbic cortex subregions at a granularity of 5 because the increase of automatic segmentation bias was associated with the increase of granularity. Specialized hippocampus MRI could be used in the future to perform more accurate analyses.

We used the automatic segmentation method based on the previous studies [21,24]. The algorithm uses structural image of T1WI MRI sequences as the basis for segmentation, and combines multiple standard atlases for segmentation. Not only does it have the efficiency and accuracy provided by the advanced automatic segmentation methods, but because it matches and incorporates 90 atlases from 4 to 90 years of age in the algorithm for the general population. It can be applied to segment brain regions of subjects in all ages, reducing segmentation errors due to brain structural alterations related with development and aging. Since pituitary adenomas themselves are usually confined to the sellar region, they basically do not produce occupation effects in other brain regions. Therefore, automatic segmentation based on this algorithm is possible for the assessment of brain region alterations in patients with pituitary adenomas. Overall, automatic segmentation significantly enhances work efficiency compared to manual segmentation, reduces human labor, and avoids the human bias that can occur from different individuals during manual segmentation. In the future, by integrating tumor segmentation with brain region segmentation, we will be able to jointly segment brain regions with pathological occupancy.

This study has some limitations. First, the sample size is relatively small, and future studies with larger sample sizes are required to confirm these findings. Second, it requires more post-operative follow-up data to clarify whether this relative volume change condition in patients is reversible after hormonal remission. Third, in this study we considered patients with NFPAs as the control group, while mild elevations in PRL are commonly observed in NFPAs and GHPAs patients. In future studies, we will compare the GHPAs group with the normal population to corroborate the results.

5. Conclusions

Our study found that patients with GHPAs exhibit atrophy in the limbic gray matter volume when compared to the overall gray matter volume of the brain. This atrophy is associated with a mild cognitive decline. Additionally, we observed that this relationship does not correlate linearly with the levels of GH and IGF-1 in the serum. This highlights the need to focus more on the potential changes in brain structure and cognitive function impairments in patients with existing or possible high GH/IGF-1 exposure, such as those with GHPAs or patients requiring GH replacement therapy.

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Ethical approval

This study was reviewed and approved by the ethic committee for Clinical Research and Animal Trials of Sun Yat-Sen University with the approval number: [2023]127, dated 2023-04- 17. For this retrospective analysis, the requirement for informed consent was waived due to the de-identified nature of the data and the absence of any additional interventions.

Data availability statement

Data not available due to the authors do not have permission to share data.

CRediT authorship contribution statement

Chengbin Duan: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mengqi Wang:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal

analysis, Data curation. **Shun Yao:** Writing – review & editing, Validation. **Haijun Wang:** Writing – review & editing, Project administration. **Hong-Hsi Lee:** Writing – review & editing, Supervision, Funding acquisition. **Wenli Chen:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35867.

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