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RESEARCH

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Weight restoration in patients with anorexia nervosa after stereotactic surgery and brain morphometric insights

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Abstract

Background Bilateral anterior capsulotomy and deep brain stimulation (DBS) of the nucleus accumbens (NAc) represent investigational treatment options for severe, treatment-refractory anorexia nervosa (AN). However, follow-up studies evaluating postoperative outcomes in these patients remain limited, and the clinical and neuroanatomical characteristics associated with treatment response have yet to be elucidated.

Methods The retrospective study analyzed the preoperative imaging data of AN patients who underwent bilateral anterior capsulotomy or nucleus accumbens (NAc) DBS from 2019 to 2023. Voxel-based morphometry (VBM) was employed to assess structural differences between AN patients and healthy controls (HCs), as well as to identify brain regions associated with postoperative changes in body mass index (BMI).

Results Nineteen patients were included in the analysis, six of whom received NAc DBS. The mean (standard deviation, SD) BMI of patients significantly increased from 13.4 (2.5) kg/m^2 preoperatively to 20.7 (5.3) kg/m^2 postoperatively ($t = 5.45$, $p < 0.001$). A significant *smaller* gray matter volume was observed in widespread regions in AN patients compared to HCs including the cerebellum, the thalamus, the temporal, orbital frontal gyrus and the sensorimotor gyrus in VBM analysis ($P_{FWE} < 0.001$, cluster size > 30 voxels). After controlling for age, sex, surgical type, and total intracranial volume (TIV), no clusters passed the correction for multiple comparisons in the correlational analysis with BMI changes after surgeries. The volume of the left caudate and the right middle frontal gyrus showed a positive correlation with the percentage of BMI changes, while the volume of the right supplementary motor area, the right parahippocampal gyrus, the right precuneus, and the left cerebellum exhibited a negative correlation in peak-level analysis ($P_{uncorrected} < 0.001$).

Conclusions Both ablative and DBS surgeries demonstrate efficacy in promoting weight restoration in severe AN patients. The structural integrity of specific brain regions may play a role in predicting postoperative BMI recovery. Further studies with a larger number of patients are warranted to better evaluate the outcome of the surgeries and the predictive value of the imaging characteristics.

Keywords Anorexia nervosa, MRI, Functional neurosurgery

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Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by an abnormal pursuit of low body weight. Clinically, AN is classified into two primary subtypes: the restricting subtype (AN-RES), where individuals maintain low body weight primarily through dietary restriction and fasting, and the binge-purge subtype (AN-BP), which involves recurrent episodes of binge eating followed by compensatory behaviors such as self-induced vomiting, excessive exercise, or misuse of laxatives [1]. AN is associated with the highest mortality rate among all psychiatric disorders, often due to medical complications or suicide, and is frequently marked by a chronic, relapsing course that is resistant to treatment [2]. Up to now, no pharmacological treatments have been approved specifically for AN, and the efficacy of existing interventions, including psychotherapy and pharmacotherapy, remains limited. Notably, approximately 20% of patients with AN are refractory to conventional therapies [1], underscoring the urgent need for alternative, life-saving interventions such as neurosurgical approaches.

Efficacy and safety of bilateral anterior capsulotomy and nucleus accumbens (NAc) deep brain stimulation (DBS) in refractory AN patients have been demonstrated [3, 4]. Accumulating evidence reported symptom improvements in patients with AN after NAc DBS [5–7], including our previous study of 28 patients showing not only weight gain but also an improvement of psychiatric comorbidities with no severe adverse effect [7]. The stereotactic ablation of the anterior limb of the internal capsule (ALIC) has also been shown to be both effective and safe, as evidenced by our long-term follow-up study involving 74 patients [8–10]. In clinical practice, the choice between these surgical approaches is typically guided by disease severity and patient preferences. However, a comparison between the two techniques has not yet been conducted, leaving critical questions unanswered regarding their relative effectiveness, safety profiles, and long-term outcomes.

Neurobiological studies have shown an abnormality in the pathway of hedonic reward, cognitive control and habitual responding in AN patients. The cortico-striatal-thalamo-cortical pathway, a brain circuit consisting of prefrontal cortex, dorsal striatum, the presupplementary motor area etc., controls movement execution, habit formation and reward, which is believed to underlie OCD and AN [11]. Stimulation of regions involving NAc modulates the reward circuit of the CSTC pathway [12], while the ablation of ALIC directly interrupts connections between the prefrontal cortex and subcortical regions [13]. Imaging studies have implicated the involvement of these regions in the reward processing of AN patients during food restrictions [14]. Yet it was unclear whether they had an influence during weight restoration following surgeries. VBM analysis reveals gray matter volumes that correlate with the disease course. Consistent findings in difference between AN patients and healthy controls (HCs) were found in regions including cerebellum, cingulate gyrus, thalamus and sensorimotor cortex, yet the results were not related with the treatment outcome [15–17].

Follow-up studies for patients who received DBS or ablation surgeries are lacking. Biomarkers that characterize AN and correlate with the treatment outcome remain to be explored. Our study retrospectively reviewed the BMI changes of AN patients after two different surgical approaches in a single center [18]. Exploratory VBM analysis was conducted to identify brain morphometric indexes that may correlate with BMI changes. The goal was to reveal more information regarding the relative effectiveness of the two surgical approaches and the underlying neuroimaging characteristics that may help explain for the mechanism of weight restoration after surgeries.

Methods

Participants

Twenty patients who had met the inclusion criteria received NAc DBS or bilateral anterior capsulotomy between 2019 and 2023 in Ruijin Hospital. One patient was lost to contact. Overall, nineteen patients were included in the analysis. The study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (ethics committee reference number: 201212) in accordance with the Declaration of Helsinki. Patients were individually assessed by a group of psychiatrists, neurosurgeons, and neurologists. All patients provided a written informed consent for their enrolment in the investigation.

The inclusion criteria were as follow: (1) a diagnosis of AN by independent psychiatrists in either the Department of Psychiatry of our hospital or the Yangpu District Mental Health Center according to the DSM-V; (2) disease duration > 3 years with persistent functional impairment; (3) age > 16 years; (4) resistance to combined pharmacotherapy and psychotherapy (i.e., prescription of at least 2 selective serotonin reuptake inhibitors and antipsychotics as well as augmentation for 12 weeks at the maximum tolerable dosage and psychotherapy conducted by an experienced therapist for at least 3 months); (5) a life-threatening situation, with patients referring to either their physiological state or their mental state (e.g., past suicide attempts); and (6) the ability and willingness to provide informed consent.

In contrast, the following exclusion criteria were considered: (1) presence of contraindications to neurosurgery, (2) presence of contraindications to magnetic resonance imaging (MRI), (3) presence of a metabolic pathology interfering with eating or digestion (e.g., diabetes) and (4) history of a psychotic disorder.

Surgical selections and procedure

Different surgical approaches were considered according to the clinical features of AN patients. Based on our previous researches, patients with AN-BP subtype tend to benefit less from DBS surgeries compared to patients with AN-RES [7]. Compared with DBS, anterior capsulotomy may be more effective and rapid in restoring weight [8]. Ablative surgeries were considered for patients with extremely low body weight, a long disease duration, binge-purge subtype or severe psychiatric comorbidities. Patients' preference was also taken into considerations in clinical practice. Detailed surgical procedure was previously described [7, 8]. In general, the target was defined directly under the guidance of co-registered image. For ablative surgeries, the target was localized between the anterior and middle thirds of the ALIC, as defined in MR images at the approximate level of the foramen of Monro. Stereotactic target coordinates and the trajectory angle for the target region were calculated according to the stereotactic MRI. The radiofrequency lesions were generated by radiofrequency ablation with a 2 mm diameter electrode at 75℃ for 60s. A lesion region 4–5 mm in diameter and 10–12 mm in length along the contoured target was produced.

For DBS surgeries, electrodes were implanted bilaterally in the NAc region using stereotactic frame-based, magnetic resonance technique using SR1210-40 4-contact leads (SceneRay, Suzhou, China) with a spacing of 1.5 mm and an electrode length of 1.5 mm. Targets were located approximately 3 mm anterior to the anterior commissure, 4 mm from the midline, and 6 mm below the anterior commissure-posterior commissure line. Electrodes were connected to a subcutaneous stimulator in a subclavicular pocket. The stimulator was activated 2–3 days after the operation. Safety of each electrode contact was assessed during postoperative programming by asking patients' instant feelings timely. Typically, the closest contacts to the anatomic NAc (identified on the postsurgical MRI images) were chosen as initial stimulating contacts. The target contacts were activated bilaterally at 2.5 V, 160 Hz, and 120 ms (i.e., pulse width) for all patients. The stimulation parameters were then kept unchanged for approximately 1 month to determine both the therapeutic effects and potential complications. Patients were readmitted several times for re-programming. The optimal stimulation parameters were the following: 2.5–4.0 V, 160–180 Hz, and 120–150 µs. Medication changes were not performed during the first 6 months following the surgery.

Clinical evaluation and image acquisitions

We collected BMI of all patients before surgery and at one-year follow up. BMI is closely related to total body fat, and is calculated using the following computational formula: (body weight [kg]/body height [m]^2). Due to the influence of the COVID-19 pandemic, most of the BMI data at one-year follow up were collected through communication with patients and their families through telephone. The psychometric data of patients were not collected for the same reason.

Fourteen patients involved in the studies had whole-brain MRI scan before surgeries and were included in the imaging analysis. Scans were acquired on a 3.0-T MRI scanner (Philips Ingenia 3.0T). T1 weighted 3D-magnetization-prepared rapid acquisition, gradient-echo sequence of patients was as follows: TR: 6.9 ms, TE: 3.4 ms, flip angle: 7°, slice thickness: 1.0 mm, matrix: 256×256; voxel size: $1 \times 1 \times 1$ mm^3). T1 imaging of age and gender matched healthy controls (HC) was downloaded from the Imaging Chinese Young Brains (I See Your Brain) [19].

Voxel based morphometry

Anatomical T1 images were analyzed using the Computational Anatomy Toolbox (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) of Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) [20]. The default settings were used which were described in detail in the CAT12 manual. We used the ICBM space template - East Asian brains for Chinese patients. The images were spatially normalized and segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) according to the Geodesic Shooting in Montreal Neurological Institute (MNI) space. Normalized maps were modulated and smoothed with a 8-mm full width half maximum (FWHM) Gaussian kernel [21]. For group-level comparisons, a two-sample t-test was performed to assess differences in regional brain volumes between AN patients and age- and gender-matched healthy controls (HCs). Total intracranial volume (TIV) and age were included as covariates to account for potential confounding effects. To investigate the relationship between preoperative brain structures and postoperative BMI changes, multiple regression analysis was conducted with TIV, age, sex, and surgical type as covariates. Statistical significance was assessed using a primary threshold of $p < 0.001$ at the voxel level, followed by cluster-level family-wise error (FWE) correction at $p < 0.05$, with a minimum cluster size of 30 contiguous voxels. Exploratory results were also reported at a peak-level uncorrected threshold of $p < 0.001$. Region-of-interest (ROI) analysis was performed using the Automated Anatomical Labeling Atlas 3 (AAL3) [22], which parcellates the brain into 166 distinct regions. We applied false discovery rate (FDR) correction both across all ROIs and within a predefined subset of regions. This subset was selected based on prior evidence implicating these areas in the pathophysiology of AN and on observed group differences between AN patients and HCs. The subset included bilateral superior, middle, and inferior frontal gyri; supplementary motor area; paracentral gyrus; olfactory cortex; orbital gyrus; anterior cingulate and paracingulate gyri; amygdala; nucleus accumbens; hippocampus; precuneus; superior temporal gyrus; angular gyrus; thalamus; caudate; putamen; pallidum; and cerebellar regions. Additionally, regions showing associations with $P_{uncorrected} < 0.05$ in preliminary analyses were further examined to explore potential effects, while preserving appropriate statistical rigor.

Statistical analysis

Data were first tested for distribution using the shapiro-Wilk test. Then the parametric (two-sample t-test or Pearson's correlation coefficient) or non-parametric (paired Wilcoxon rank-sum test or Spearman's correlation coefficient) statistic was used to assess potential differences or correlations. Partial correlation analysis was conducted when considering covariates. The continuous variables were expressed as the mean ± standard deviation (SD). Two-tailed p-value < 0.05 was considered as significant.

Results

Demographic information and surgery outcome

Nineteen patients were included in the analysis who had completed one-year follow-up (Supplementary Table 1). A significant increase of BMI was observed after bilateral anterior capsulotomy (t = 5.08, $p < 0.001$) and after NAc DBS (t = 2.77, $p = 0.039$, Table 1; Fig. 1). Eleven patients (57.9%) reached a BMI of 18.5 kg/m^2 one year after surgery. Among these, four patients became overweight (> 24.5 kg/m^2). Acute epidural hematoma occurred in one patient after NAc DBS who received craniotomy evacuation of hematoma subsequently and recovered without complications. Apart from this case, no severe adverse event was observed in patients. Lethargy was reported by two patients after anterior capsulotomy. 7/8 patients with AN-BP subtype still had binge-purge behavior one year after surgery while 1 patient receiving anterior capsulotomy had the purging behavior cured. No fatalities occurred in this study. No significant correlations were found between the AN subtype, age and disease duration with BMI changes. Two patients did not experience a significant BMI increase (less than 5%) one year after surgeries. They are, one male patient of AN-BP subtype receiving bilateral anterior capsulotomy with a disease duration of 10 years, and one female patient of AN-RES subtype receiving NAc DBS with also a disease duration of 10 years. These two had the longest disease duration among the patients involved (Supplementary Table 1). No difference was observed in the pre- and post- operative BMI, BMI changes between different AN subtypes or different surgical approaches. A borderline significant difference was observed in the percentage of BMI changes between the two surgical approaches (t = 1.79, p = 0.092), with ablative surgeries showing a greater tendency for BMI increase.

Structural difference between AN patients and HCs

Significant differences were observed between the AN and HC group in the TIV value (AN: 1352.1 ± 108.0, HC: 1447.1 ± 97.1, t = 2,46, $p = 0.021$) and the gray matter volume (AN: 614.0 ± 68.4, HC: 705.8 ± 39.2, t = 4.36, $p < 0.001$). No difference was observed in the CSF and white matter volume between the two groups.

In the VBM analysis comparing AN patients with age and gender matched HCs, smaller gray matter volume was observed in AN patients in wide-spread regions involving left and right cerebellum, sensorimotor gyrus, inferior temporal lobe, thalamus and orbital frontal gyrus compared with HCs ($P_{FWE} < 0.05$, cluster size > 30 voxels, Fig. 2, Supplementary Table 2). No significantly greater

Table 1 Demographic information and BMI characteristics of patients

Variables	Ablation	DBS	Total [Min/Max]
Age (yrs)	26.7 ± 7.9	22.3 ± 4.4	25.3 ± 7.2 [17/42]
Gender (Female)	11/13	6/6	17/19
Disease duration (yrs)	5.2 ± 2.4	5.0 ± 2.6	4.9 ± 2.6 [3/10]
Subtype (AN-BP)	6/13	2/6	8/19
Days of hospital stay (d)	9.5 ± 3.0	10.5 ± 4.6	10.2 ± 4.1
BMI_pre (kg/m^2)	15.0 ± 1.5***	12.7 ± 2.5*	13.4 ± 2.5*** [8.8/17.1]
BMI_post_1y (kg/m^2)	19.2 ± 3.4***	21.3 ± 6.0*	20.7 ± 5.3*** [10.6/27.6]
Pct change of BMI	73.4 ± 57.9%	28.7 ± 26.6%	59.3 ± 53.7% [0/175.9%]
No. of pts reaching BMI of 18.5 kg/m^2	8/13	3/6	11/19
No. of pts with BMI > 24.5 kg/m^2	4/13	0/6	4/19

Note. Significance levels: ***$p < 0.001$, $p < 0.05$. BMI was compared before and after surgery

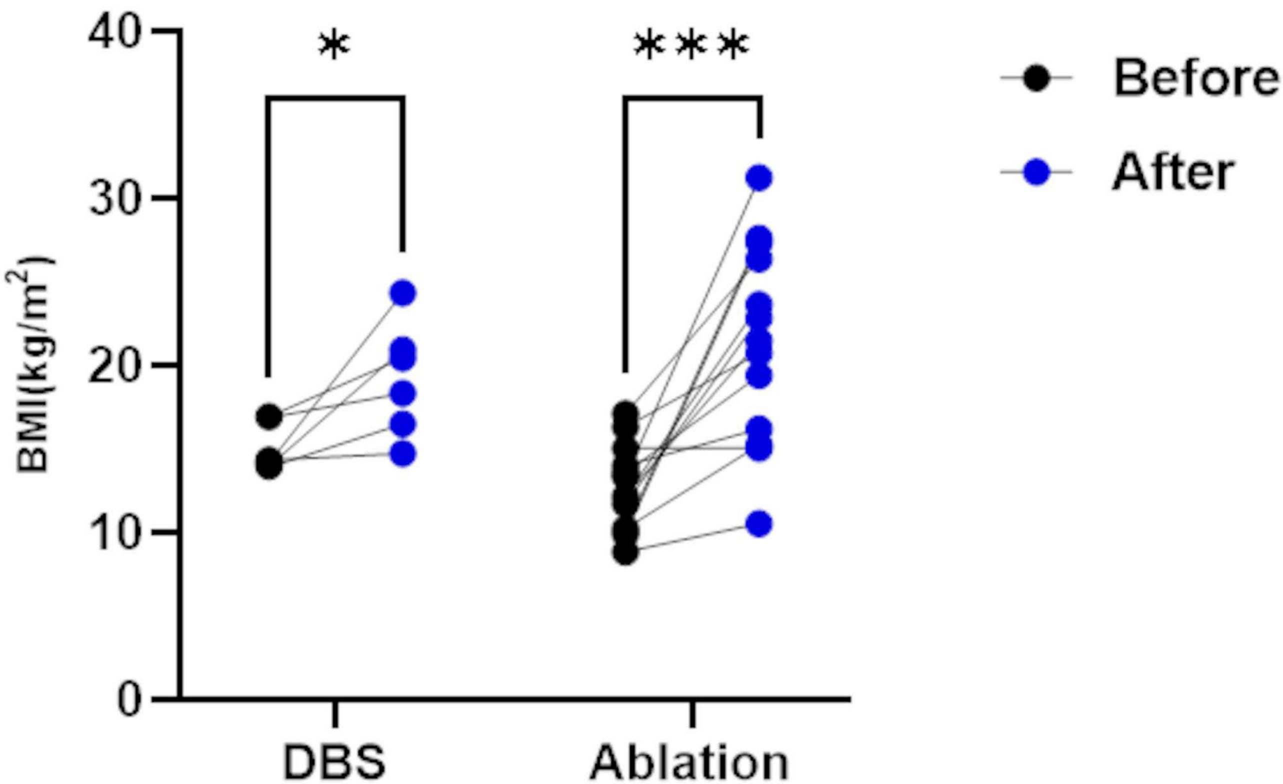

Fig. 1 Changes of BMI value before and after surgeries

gray matter volume was observed in AN patients in cluster-level analysis. An enlargement of gray matter volume was observed in the left and right extra nuclear area in the limbic region in AN patients in peak-level analysis ($P_{uncorrected}$ < 0.001, Fig. 2). Further ROI analysis did not observe a significant enlargement of gray matter volume in AN patients compared with HCs. No significant difference in gray matter volume was observed between different AN subtypes.

Correlations between Gray matter volume and BMI changes

In the multi-regression analysis controlling for age, sex, types of surgeries and TIV, no significant clusters were found in cluster-level analysis. Peak-level analysis revealed a positive correlation between the left caudate, the right middle frontal gyrus and the percentage of BMI changes after surgeries ($P_{uncorrected}$ < 0.001, Fig. 3, Supplementary Table 3). Negative correlations were observed in the right supplementary motor area, the right parahippocampal gyrus, the right precuneus and the left cerebellum in peak-level analysis ($P_{uncorrected}$ < 0.001). In the ROI analysis, no significant effects remained after applying FDR correction, either across the full set of 166 AAL3 regions or within the hypothesis-driven subset (all P_{FDR} > 0.05). At an uncorrected threshold ($P_{uncorrected}$ < 0.05), we observed trend-level positive associations with the percentage of BMI changes in the bilateral caudate and putamen, and negative associations in the right paracentral gyrus, right lateral orbitofrontal cortex, and several cerebellar subregions, including lobule VI, lobule X, and crus I. However, none of these associations survived FDR correction in the analysis within the ROI subset.

Discussion

Our study reviewed the BMI changes of AN patients who received bilateral anterior capsulotomy or NAc DBS from 2019 to 2023. Potential clinical factors and gray matter characteristics that may correlate with BMI changes were analyzed. All but two patients with a disease duration of 10 years experienced a weight gain of over 5%. An overall less gray matter volume was exhibited in AN patients compared with HC, specifically in regions in the cerebellum, the sensorimotor gyrus, the inferior temporal lobe, the thalamus and the orbital frontal gyrus. No clusters were found correlated with BMI changes after surgeries while positive correlations of the left caudate and the right middle frontal gyrus were shown in peak-level analysis with BMI increase after correcting for age, sex, types of surgeries and TIV.

Our findings corroborate the therapeutic efficacy of surgeries in improving the BMI status of AN patients. Ablative surgeries may bring about a greater weight gain, meanwhile bear the risks of patients being overweight

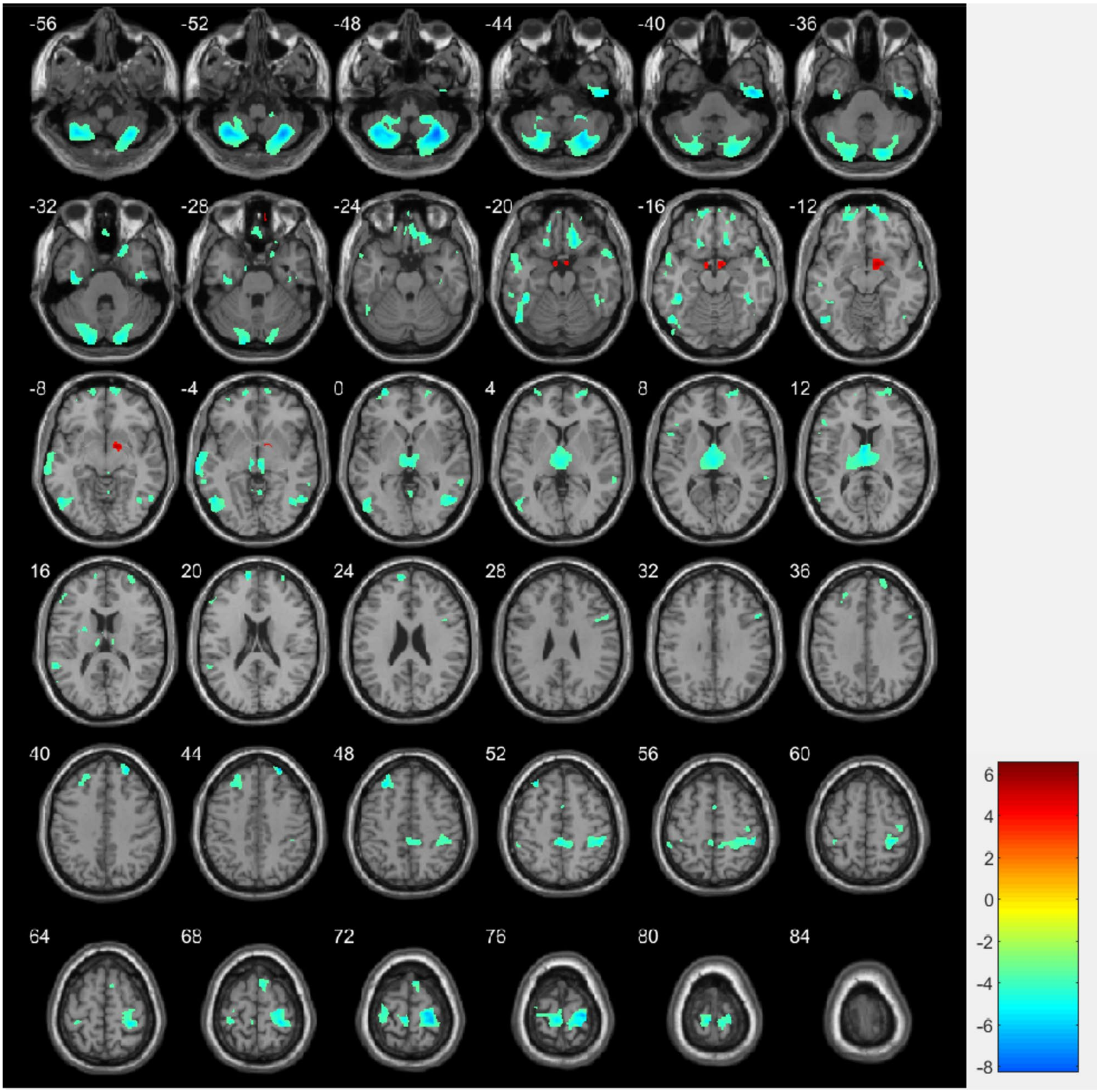

Fig. 2 Difference of gray matter volume observed in AN patients compared with HCs. A significantly smaller gray matter volume (labeled in green) was observed in AN patients in the left and right cerebellum, sensorimotor gyrus, inferior temporal lobe, thalamus and orbital frontal gyrus controlling for TIV and age in cluster level analysis ($P_{FWE} < 0.05$, cluster size > 30 voxels). Greater gray matter volume was observed in the left and right extra nuclear area in the limbic region in peak-level analysis ($P_{uncorrected} < 0.001$)

[8]. Four of our patients receiving ablative surgeries became overweight one year after surgery, who reported to experience a period of time craving for food. The potential mechanism may involve the loss of inhibitory control over nucleus accumbens after bilateral anterior capsulotomy [23], Interestingly, the behavior can be mediated by NAc DBS [23]. The effect of DBS can be more adjustable and relatively reversible, although it may not bring a rapid and substantial change. Considerations of the surgical selections were based on the AN subtype, disease duration, severity of psychiatric comorbidities, and patients' BMI status. For patients with extremely low body weight, or binge-purge subtype, or long disease durations, or severe psychiatric comorbidities, we would consider bilateral anterior capsulotomy. The decision was made ultimately by patients themselves, since some patients were reluctant to have implanted devices while some favored the relative reversibility of DBS. In this study, lethargy was reported by 2/13 patients after the ablative surgery in one-year follow up. No occurrence of

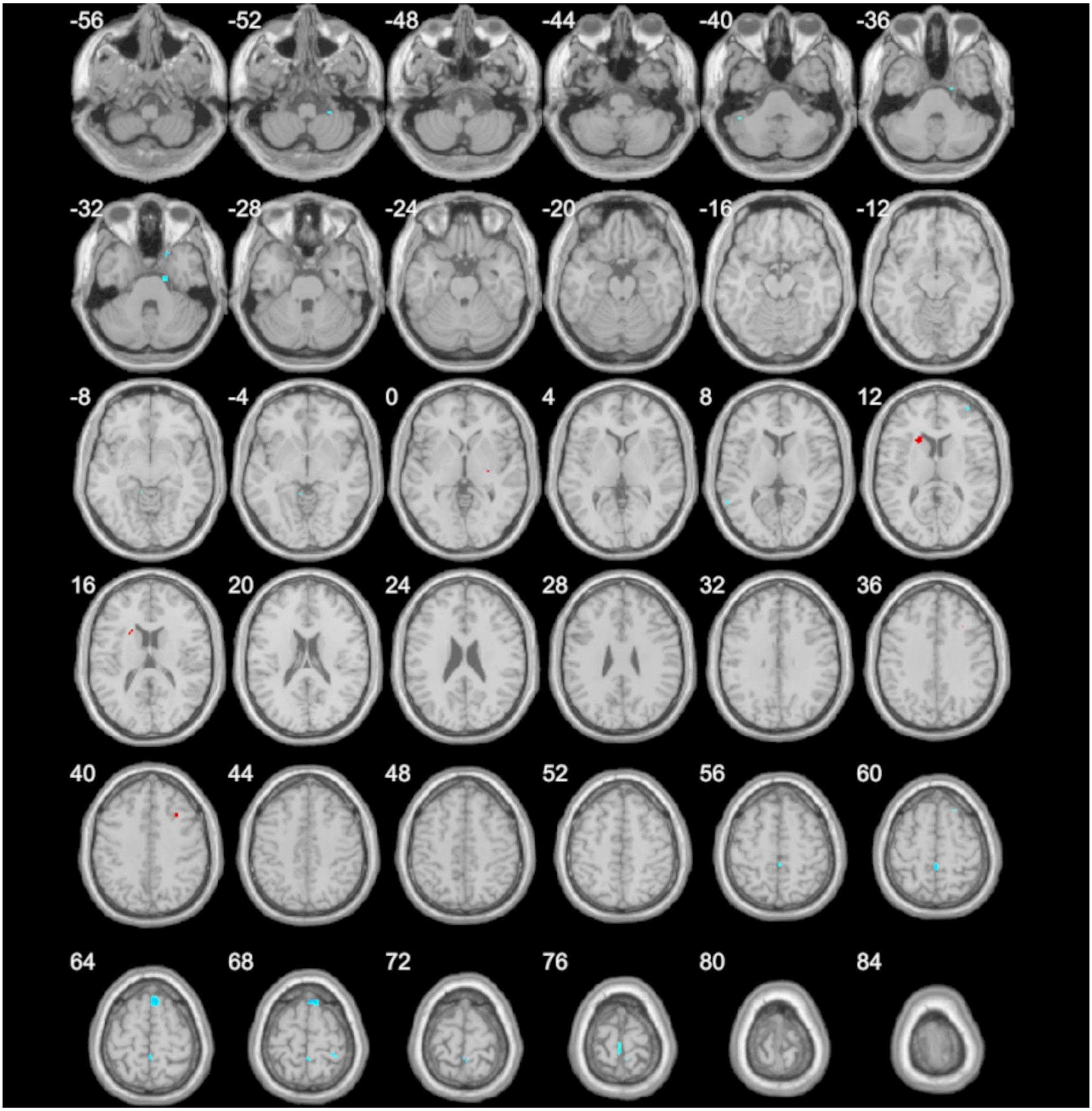

Fig. 3 Correlations between gray matter volume and percentage change of BMI. Positive correlations were observed between the left caudate, the right middle frontal gyrus and the BMI changes after surgeries ($P_{uncorrected} < 0.001$). Negative correlations were observed in the right supplementary motor area, the right parahippocampal gyrus, the left cerebellum and the right precuneus in peak-level analysis ($P_{uncorrected} < 0.001$)

other long-term adverse effects was reported. The surgical approach has been shown to be generally safe when targeting at the correct position [24, 25]. Nevertheless, serious adverse events such as apathy and personality changes were still reported in other studies, emphasizing the careful selection of surgical approaches in patients with treatment-resistant psychiatric disorders [26]. For intractable and life-threatening cases like AN, ablative surgeries may be considered as a life-saving approach.

Our study supported previous findings in showing the difference of gray matter volume between AN patients and HCs. A recent multi-center imaging study showed a systematic reduction of gray matter volume in AN patients in bilateral cerebellum, supplementary motor cortex, precentral gyrus and thalamus [15], which was also found in our study. In correlational analysis, we found the preoperative volume of the dorsal striatum, specifically, the caudate and the right middle frontal gyrus positively correlated with BMI increase in peak-level analysis. Alterations in the dorsal striatum volume predicted sensitivity to reward in patients with anorexia nervosa and bulimia nervosa [27] while lower cortical thickness in the middle frontal gyrus correlated with the cognitive restraint in eating [28]. Nevertheless, none of the observed associations survived cluster-level thresholding or passed the correction for multiple comparisons. Therefore, these findings should be considered preliminary and require further validation in larger, independent patient cohorts to establish their robustness and clinical relevance.

This study had several limitations. First, our study did not include the psychometric data and measurements of other core symptoms characterizing AN due to the influence of the pandemic. While BMI restoration serves as a key indicator of treatment efficacy, it may not fully capture the broader spectrum of symptom improvement in AN patients [29]. Additionally, psychiatric comorbidities, which are prevalent in AN, could significantly influence long-term weight restoration outcomes [30]. Future studies should prioritize the inclusion of detailed psychiatric assessments to better understand the trajectory of psychological recovery following surgical interventions. Second, although a majority of past VBM studies also had a small number of patients (less than 20) [31], the number of patients enrolled in this study, especially patients receiving DBS surgeries, was limited. To address this limitation, we combined the number of patients receiving DBS or ablative surgeries in VBM analysis and used the surgical selection as a covariate. Future studies with larger cohorts should aim to conduct separate analyses for each surgical approach to better delineate their unique effects. Third, most of the postoperative BMI data were collected through self-reported telephone follow-ups. Although self-reported data may be subject to inaccuracies, we believe these self-reports provide a reasonable approximation of patients' overall physical condition. Our study failed to identify associated clinical factors and differences in surgical outcomes after ablative or DBS surgeries. This may be partly attributable to baseline differences in disease severity between the two surgical groups. Notably, despite the fact that patients undergoing ablative surgeries generally presented with more severe psychiatric comorbidities, they achieved significant weight gain and even demonstrated a trend toward greater improvement compared to DBS patients. This underscores the robust efficacy of ablative surgeries in promoting weight restoration, even in complex cases.

Conclusions

This study highlights the significant impact of bilateral anterior capsulotomy and NAc DBS surgeries on the weight restoration of AN patients. VBM analysis showed smaller gray matter volume in regions in the cerebellum, the sensorimotor gyrus, the inferior temporal lobe, the thalamus and the orbital frontal gyrus in AN patients compared with HC. No clusters were found correlated with BMI changes after surgeries while positive correlations of the left caudate and the right middle frontal gyrus were shown in peak-level analysis. The results point out potential involvement of specific areas in the modulation of AN symptoms, and may help to identify predictive factors for BMI changes after surgeries.

Abbreviations

AAL3	Automated anatomical labeling atlas 3
ALIC	Anterior limb of the internal capsule
AN	Anorexia nervosa
AN-BP	Anorexia nervosa binge–purge subtype
AN-RES	Anorexia nervosa restricting subtype
BMI	Body mass index
CAT12	Computational anatomy toolbox (version 12)
CSF	Cerebrospinal fluid
CSTC	Cortico–striato–thalamo–cortical
DBS	Deep brain stimulation
DSM-V	Diagnostic and statistical manual of mental disorders, 5th edition
FDR	False discovery rate
FWE	Family–wise error
FWHM	Full width at half maximum
GM	Gray matter
HCs	Healthy controls
ICBM	International consortium for brain mapping
IPG	Implantable pulse generator
MNI	Montreal neurological institute
MRI	Magnetic resonance imaging
NAc	Nucleus accumbens
PFWE	Family–wise error–corrected p–value
Puncorrected	Uncorrected p–value
ROI	Region of interest
SD	Standard deviation
SPM12	Statistical parametric mapping (software version 12)
TIV	Total intracranial volume
TR/TE	Repetition time/echo time
VBM	Voxel–based morphometry
WM	White matter
COVID-19	Coronavirus disease 2019

Supplementary Information

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Supplementary Material 1

Author contributions

FW, WL, YL, BS and SZ contributed to the conception and design of the study. FW, WL, ZL, DL, HP, TW, YL, BS and SZ contributed to acquisition, post-processing and analysis of the data. FW, KY and ZL drafted the text and prepared the figures. All authors approved the final version of the manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. All patients provided a written informed consent for their enrolment in the investigation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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