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Research report

Hypothalamic subunit volumes in schizophrenia with comorbidity of metabolic syndrome

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ABSTRACT

Schizophrenia and metabolic syndrome (MS) are common conditions that frequently co-occur, yet the neurobiological mechanisms underlying their comorbidity remain unclear. This study aimed to investigate whether hypothalamic structural alterations contribute to this comorbidity. A total of 194 participants were included and categorized into four groups based on diagnoses of schizophrenia and MS: schizophrenia patients with/without metabolic syndrome (SZ-wMS and SZ-nMS), and healthy controls with/without metabolic syndrome. T1-weighted structural magnetic resonance imaging (MRI) was acquired. Clinical assessments included metabolic indicators, cognitive function tests, and the Positive and Negative Syndrome Scale. Based on structural MRI, the hypothalamus was segmented into five subunits in each hemisphere. We examined the interaction effects of schizophrenia and MS on the volumes of hypothalamic subunits and conducted partial correlation and moderation analyses to explore clinical relevance. An interaction effect was found in the volume of the right superior tubular subunit (supTub), with SZ-wMS showing the greatest volume reduction. Reduced right supTub volume was associated with elevated fasting blood glucose level and higher negative symptom scores. The association between right supTub volume and negative symptom scores was moderated by triglycerides level. In the SZ-wMS group, reduced right supTub volume was associated with cognitive function scores. These findings suggest that reduced volume of the right supTub may represent a potential mechanism contributing to the comorbidity of schizophrenia and MS. The observed associations with cognitive dysfunction highlight the right supTub as a possible translational target for clinical interventions aimed at improving cognitive deficits in schizophrenia patients with comorbidity of MS.

1. Introduction

Schizophrenia is one of the most serious mental disorders, yet its etiopathogenesis remains poorly understood (Jauhar et al., 2022). Exposure to the chronic psychosocial stress during the early neurodevelopment has been shown to contribute to the risk of developing

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schizophrenia (Stilo and Murray, 2019). According to the diathesis–stress model, hypothalamic-pituitary-adrenal (HPA) axis is a major neural system mediating effect of psychosocial stress on schizophrenia (Walker et al., 2008). The hypothalamus plays a central role in regulating the HPA axis, as well as the synthesis of oxytocin and neuroendocrine regulators of energy homeostasis, which are thought to be affected in schizophrenia (Walker et al., 2008; Lengton et al., 2022).

Metabolic syndrome (MS) is a common condition with major public health implications, including an increased risk of cardiovascular disease, type 2 diabetes, and a significant burden on healthcare systems, that tends to co-occur with schizophrenia (Mitchell et al., 2013). Evidence suggests a bidirectional relationship between the two diseases, with the presence of one increasing the risk for developing the other. Therefore, it is crucial to gain a better understanding of the mechanisms underlying this comorbidity between both diseases (Milaneschi et al., 2019). The hypothalamus is also known to play key roles in regulating satiation, circadian feeding, energy homeostasis and the risk of progression to adiposity (Lengton et al., 2022; Han et al., 2023). Overactivity of the HPA axis and nonadaptive unabated release of cortisol may induce both psychotic symptoms and metabolic dysregulation (Cullen et al., 2022). Moreover, preclinical and clinical studies have reported that the dysregulation of endogenous oxytocin and leptin circuit contributes to obesity and symptoms in schizophrenia spectrum disorders (Ghazy et al., 2023; Li et al., 2024). Hypothalamus may mediate the effects of leptin gene variations and peripheral leptin levels on the development of antipsychotic-induced metabolic syndrome in schizophrenia (Chen et al., 2018; Zhou et al., 2022). These findings collectively suggest that structural and functional abnormalities within the hypothalamus may constitute a shared neurobiological substrate responsible for the comorbidity between schizophrenia and MS.

Structural alterations of the hypothalamus from magnetic resonance imaging (MRI) studies have been reported in schizophrenia. Early studies reported increased volumes of the paraventricular nucleus and mammillary bodies, which have been found to correlate with negative symptoms and anxiety (Goldstein et al., 2007; Tognin et al., 2012). However, more recent research has observed reduced paraventricular nucleus volume (Ruggeri et al., 2024). The hypothalamus is composed of distinct nuclei with specialized physiological functions. The inconsistent findings across studies highlight the need for a standardized tool for reproducible hypothalamic segmentation to enable nucleus-level analyses of hypothalamic structural changes in schizophrenia. Additionally, abnormal volume of hypothalamus can disrupt food intake behaviors and is associated with the risk of progression to metabolic syndrome (Pane et al., 2024; Le et al., 2020). However, whether hypothalamic volume is implicated in the neurobiological mechanisms underlying the comorbidity between schizophrenia and MS remains unclear. In addition, prior studies have not examined subunit-specific hypothalamic alterations mediating the comorbidity between schizophrenia and MS.

In this study, we categorized a cross-sectional sample into four groups according to diagnoses of schizophrenia and MS. We used a recently developed automated Bayesian segmentation method to identify hypothalamic subunits (Billot et al., 2020).The framework enables accurate and robust hypothalamic segmentation and permits a subunit-level analysis for hypothalamus. Thus, we explored whether volumetric abnormalities in these subunits represent a potential mechanism underlying the comorbidity between schizophrenia and MS based on the two-factor experimental design. Finally, the associations between hypothalamic subunit volumes and metabolic indicators, psychiatric symptoms, and cognitive performance were investigated.

2. Methods

2.1. Participants

A total of 194 participants were included in this study, comprising 51 schizophrenia patients with comorbidity of MS (SZ-wMS; mean age = 45.02 ± 8.95 years; 8 females), 66 schizophrenia patients without comorbidity of MS (SZ-nMS; mean age = 43.36 ± 10.46 years; 17 females), 39 healthy controls with MS (HC-wMS; mean age = 42.29 ± 11.18 years; 10 females), and 38 healthy controls without MS (HC-nMS; mean age = 42.26 ± 10.27 years; 6 females) (Table 1). All schizophrenia patients were recruited from the Clinical Hospital of Chengdu Brain Science Institute and The Third People's Hospital of Wenjiang District, Chengdu. These patients were diagnosed according to the Diagnosis and Statistic Manual of Mental Disorders, fourth edition (DSM-IV). Healthy controls (HC) were recruited from the local community through advertisements (Supplemental material). Metabolic syndrome was diagnosed for all participants according to a slightly modified criteria based on that proposed by the International Diabetes Federation in 2005 (Alberti and Shaw, 2006; Lee et al., 2007; Deurenberg-Yap and Deurenberg, 2002) (Supplemental material). After a complete description of the study was given to all participants and/or their guardians, written informed consent was obtained. The Ethics Committee of the Clinical Hospital of Chengdu Brain Science Institute in accordance with the Helsinki Declaration approved this study. Demographic characteristics are summarized in Table 1.

2.2. Behavior measures

The severity of psychiatric symptoms in patients with schizophrenia was assessed using the Positive and Negative Syndrome Scale (PANSS). Cognitive function in all participants was evaluated using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE).

2.3. Laboratory tests

Blood samples were collected between 7:00 and 9:00 AM following an overnight fast of 12 h. For each participant, the blood sample was collected at approximately the same time, which was immediately taken to the hospital's laboratory center and analyzed on the same day. Specifically, samples were centrifuged at 3200 rpm for 10 min to separate serum and plasma. Fasting blood glucose (FBG) levels in plasma, as well as serum levels of triglycerides (TG) and high-density lipoprotein (HDL),

Table 1
Demographic information and clinical characteristics of four groups of participants (n = 194).

Characteristic	SZ-wMS (n = 51) Mean (SD)	SZ-nMS (n = 66) Mean (SD)	HC-wMS (n = 39) Mean (SD)	HC-nMS (n = 38)	Unadjusted p-value
Sex (male/female)	43/8	49/17	29/10	32/6	0.309
Age (years)	45.02 (8.95)	43.36 (10.46)	42.29 (11.18)	42.26 (10.27)	0.55
Education (years)	10.4 (3.72)	10.94 (3.1)	11.85 (3.96)	11.95 (3.66)	0.13
Disease duration (years)	18.77 (8.53)	16.74 (9.89)	-		0.25
Medicine dosage	338.04 (162.75)	321.13 (134.2)	-		0.27
PANSS total score	59.89 (16.92)	61.68 (15.56)	-		0.58
PANSS positive symptoms score	11.81 (5.45)	14.68 (5.89)	-		0.01*
PANSS negative symptoms score	19.47 (7.07)	18.77 (6.02)	-		0.59
PANSS general symptoms score	28.62 (7.68)	28.23 (6.54)	-		0.78

Note: We did not collect complete clinical data for 117 schizophrenia patients. Only 100 patients' PANSS scales were collected.

were measured using enzymatic photometric assays.

2.4. Imaging data acquisition

All MRI data were acquired on a 3.0 Tesla scanner (GE DISCOVERY MR750, USA) at the Center of Information Medicine Research in University of Electronic Science and Technology of China. High-spatial-resolution T1-weighted images were acquired using a three-dimensional fast spoiled gradient-echo sequence. The main parameters included repetition time [TR]/ echo time [TE] = 6.008/1.984; flip angle [FA] = 9°; field of view [FOV], 256 × 256 mm^2; matrix = 256 × 256; section thickness, 1 mm (no gap).

2.5. Imaging processes

High-spatial-resolution T1-weighted images were processed using FreeSurfer (v7.4.1; https://surfer.nmr.mgh.harvard.edu/). First, all images were checked for artifacts. Second, the Sequence Adaptive Multimodal SEGmentation (SAMSEG) tool in FreeSurfer was used to compute the segmentation-based Total Intracranial Volume (TIV). Third, a fully automated tool for the segmentation of the whole hypothalamus released by Billot et al. (2020) was applied. This method employs a 3D convolutional neural network based on manually labeled T1-weighted scans, which was performed using a Bayesian segmentation included in FreeSurfer (v7.4.1).

The whole hypothalamus was segmented into five hypothalamic subunits in each hemisphere (Billot et al., 2020): (1) the anterior-inferior subunit (a-iHyp), which includes the suprachiasmatic and the supraoptic nucleus, (2) the anterior-superior subunit (a-sHyp), which includes the preoptic area and the paraventricular nucleus, (3) the posterior subunit (posHyp), composed of the mammillary bodies (including the medial and lateral mammillary nuclei), the lateral hypothalamus, and the tuberomammillary nucleus, (4) the inferior tubular subunit (infTub), which includes the arcuate nucleus, ventromedial nucleus, lateral tubular nucleus, and the tuberomammillary nucleus, and (5) the superior tubular subunit (supTub), which includes the dorsomedial nucleus, the paraventricular nucleus, and the lateral hypothalamus (Table S1 and Fig. 1). The volumes of the total hypothalamus and each of the five subunits in both hemispheres were extracted and used for subsequent statistical analyses.

2.6. Statistical analysis

To compare demographic and clinical variables across the four groups, one-way analysis of variance (Kandilarov et al., 2023) and chi-square tests were performed for continuous (age and education level) and categorical (sex) variables, respectively. Between the SZ-wMS and SZ-nMS groups, two-sample *t*-tests were performed to compare disease duration, medicine dosage and PANSS scores. A two-way analysis of covariance (ANCOVA) was conducted to examine the main effects and interaction effects of schizophrenia and MS diagnoses on the volumes of the total hypothalamus and hypothalamic subunits, with age, sex, education level, and TIV included as covariates. Pairwise post-hoc comparisons were performed using the Least Significant Difference (LSD) test.

To examine the clinical relevance of hypothalamic volumes, partial correlation analyses were performed between hypothalamic volumes and clinical measures, including PANSS scores and metabolic indicators. Age, sex, and education level were included as covariates in a linear regression model. Associations between hypothalamic volumes and cognitive scores (MoCA and MMSE) were evaluated using Spearman's rank correlation analysis. Consistent with our previous study (Zhou et al., 2023), we conducted moderation analyses to examine the moderation effect of metabolic indicators on the associations between hypothalamic volumes and PANSS, MoCA, and MMSE scores. These analyses were performed separately for each group using Hayes's PROCESS macro (Model 1) (Hayes, 2013).

To assess the impact of current medication dosage on hypothalamic volumes, we fitted regression models for SZ-wMS and SZ-nMS groups, separately. Chlorpromazine equivalent dose was included as the variable of interest, with age, sex, and education level included as covariates.

3. Results

3.1. Demographics and clinical characteristics

Demographic and clinical characteristics of the four groups are presented in Table 1. No significant between-group differences were found in sex, age, or education level. Additionally, there were no significant differences in disease duration, medication dosage, negative symptom scores or general symptom scores between the SZ-wMS and SZ-

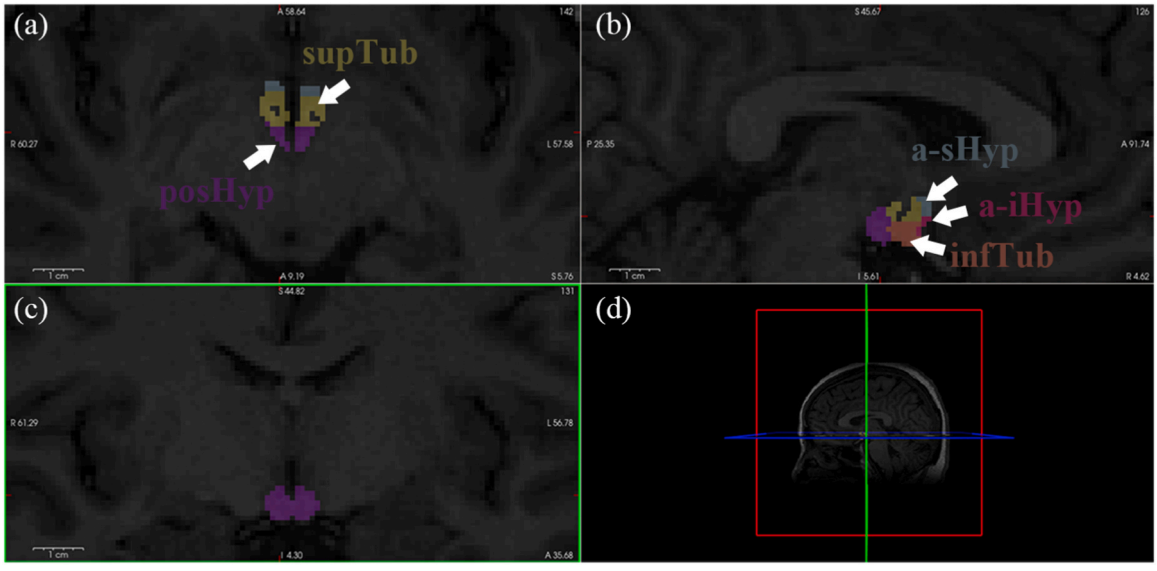

Fig. 1. Example of segmented five hypothalamic subunits (a) Axial views; (b) Sagittal views; (c) Coronal views; (d) 3D location of the hypothalamus. a-sHyp, anterior-superior subunit; a-iHyp, anterior-inferior subunit; posHyp, posterior subunit; infTub, inferior tubular subunit; supTub, superior tubular subunit.

nMS groups. However, the SZ-wMS group showed lower positive symptom scores compared to the SZ-nMS group ($t = -2.35$, $p = 0.01$, $n = 100$). The antipsychotic types prescribed for patients were presented in Table S2. Metabolic indicators for each group are presented in Table S3.

3.2. Volume evaluation of hypothalamus and subunits

First, no significant main effects or interaction effects were observed on total volume of the left or right hypothalamus (Table 2). However, a main effect of MS was observed on the left a-sHyp (Table 2, $F = 4.37$, $p = 0.03$, $\eta^2 = 0.023$). Compared to the HC-nMS group, the HC-wMS group showed a larger volume of the left a-sHyp (Fig. 2b, $p < 0.05$). No significant main effect of schizophrenia was observed on the left a-sHyp. Second, A main effect of schizophrenia was found on the volume of the left posHyp (Table 2, $F = 6.11$, $p = 0.01$, $\eta^2 = 0.032$) and the right a-sHyp (Table 2, $F = 19.30$, $p = 1 \times 10^{-5}$, $\eta^2 = 0.094$). Compared to both HC-wMS and HC-nMS groups, the SZ-wMS group showed larger volumes of the left posHyp (Fig. 2d, $p < 0.05$) and smaller volumes of right a-sHyp (Fig. 2h, $p < 0.05$). However, no significant differences in the two subunits were found in the SZ-nMS group.

Importantly, an interaction effect between schizophrenia and MS was found on the volume of the right supTub (Table 2, $F = 4.62$, $p = 0.03$, $\eta^2 = 0.024$). The SZ-wMS group exhibited a smaller volume of the right supTub compared with both HC-wMS and HC-nMS groups (Fig. 2l, $p < 0.05$). Additionally, the SZ-wMS group had a smaller volume of the right supTub compared to the SZ-nMS group (Fig. 2l, $p < 0.05$).

3.3. Clinical relevance of volumes of hypothalamic subunits

Partial correlation analysis revealed a negative correlation between the volume of the right supTub and peripheral FBG levels in the schizophrenia group (SZ-wMS and SZ-nMS combined; Fig. 3a, $r = -0.19$, $p = 0.04$). A negative correlation was also revealed between the volume of the right supTub and PANSS negative symptom scores (Fig. 3b, $r = -0.25$, $p = 0.01$). Importantly, this correlation was moderated by serum levels of TG. (Fig. 3c, Table S4). Additionally, in the SZ-wMS group, positive correlations were found between the volume of the right supTub and multiple cognitive function scores, including visuospatial and executive function (Fig. 3d, $r = 0.46$, $p = 0.04$), naming (Fig. 3e, $r = 0.51$, $p = 0.02$), attention and working memory (Fig. 3f, $r = 0.56$, $p = 0.01$), delayed recall (Fig. 3g, $r = 0.54$, $p = 0.01$), attention and calculation (Fig. 3h, $r = 0.57$, $p = 0.008$), and language (Fig. 3i, $r = 0.45$, $p = 0.04$). However, none of these associations were significant in the SZ-nMS group.

3.4. Relationships with current medication dosage

No significant correlations were observed between the volumes of any hypothalamic subunits and current medication dosage in the SZ-wMS group, the SZ-nMS group or the schizophrenia group. Similarly, no significant correlation was found between the total hypothalamic volume and current medication dosage (Table S5).

4. Discussion

In this study, five hypothalamic subunits in each hemisphere were identified for each participant. Although no significant main effects or interaction effects were observed on total volume of the left or right hypothalamus, we found that schizophrenia and MS exerted main effects on the volumes of distinct, non-overlapping hypothalamic subunits. Importantly, an interaction effect between schizophrenia and MS was revealed on the volume of the right supTub. Compared to the SZ-nMS, HC-wMS, and HC-nMS groups, the SZ-wMS group exhibited a smaller volume of right supTub. This reduced volume was associated with elevated FBG levels and greater negative symptom severity in patients with schizophrenia. The association between right supTub volume and negative symptoms was moderated by TG levels. In addition, more specific associations were identified between reduced right supTub volume and impairments across multiple cognitive domains in the SZ-wMS group, whereas no such associations were found in the SZ-nMS group. Finally, no significant correlations were observed between the volumes of any hypothalamic subunits and current medication dosage.

Abnormalities in hypothalamic volume may be more severe in individuals with comorbidity of schizophrenia and MS (Goldstein et al., 2007; Pane et al., 2024). However, whether such structural abnormalities represent a potential neurobiological mechanism underlying the comorbidity between schizophrenia and MS remains unclear. The current study employed a two-factor experimental design and identified a significant interaction effect between schizophrenia and MS on the volume of the right supTub. Compared to SZ-nMS, HC-wMS, and HC-nMS groups, the SZ-wMS group exhibited a smaller right supTub volume. Our findings indicate a synergistic reduction in the volume of the right supTub (which includes the dorsomedial nucleus and the paraventricular nucleus) in the two disease conditions, which may represent a potential neurobiological mechanism underlying the comorbidity between schizophrenia and MS. Both the dorsomedial nucleus and paraventricular nucleus are known to play key roles in regulating satiation, circadian feeding, and energy homeostasis (Tang et al., 2023; Xing et al., 2024). Activity of leptin receptor-expressing neurons and glucagon-like peptide-1 (GLP-1) receptor neurons in the two nuclei may regulate the risk of weight gain and progression to the adiposity (Han et al., 2023; Faber et al., 2021; Kim et al., 2024; Shi et al., 2020).

Table 2
Main effects and interaction effects of volumes of hypothalamus and subunits.

Hypothalamus subunit	Main effect of SZ			Main effect of MS			Interaction effect (SZ × MS)		
	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2
Left whole hypothalamus	0.55	0.46	0.003	0.23	0.63	0.001	0.36	0.54	0.002
Left anterior superior	0.34	0.56	0.002	4.37	0.03*	0.023	3.2	0.08	0.017
Left anterior inferior	0.12	0.73	0.001	0.05	0.82	0.001	0.98	0.32	0.005
Left posterior	6.11	0.01*	0.032	0.97	0.32	0.005	0.14	0.71	0.001
Left tubular inferior	1.06	0.31	0.006	0.1	0.82	0.001	0.18	0.67	0.001
Left tubular superior	3.74	0.06	0.02	0.6	0.81	0.001	0.44	0.5	0.002
Right whole hypothalamus	1.12	0.27	0.007	0.12	0.73	0.001	0.38	0.54	0.002
Right anterior superior	19.3	1.0×10^{-5}*	0.094	1.92	0.17	0.01	0.31	0.58	0.002
Right anterior inferior	0.25	0.62	0.001	1.46	0.23	0.008	3.08	0.08	0.016
Right posterior	0.76	0.78	0.001	0.33	0.57	0.002	0.75	0.39	0.004
Right tubular inferior	0.11	0.74	0.001	1.32	0.25	0.007	0.01	0.97	0.001
Right tubular superior	3.11	0.08	0.02	0.41	0.84	0.001	4.62	0.03*	0.024

Note: Partial η^2 indicates the effect size. SZ: schizophrenia; MS: metabolic syndrome.
* $p < 0.05$.

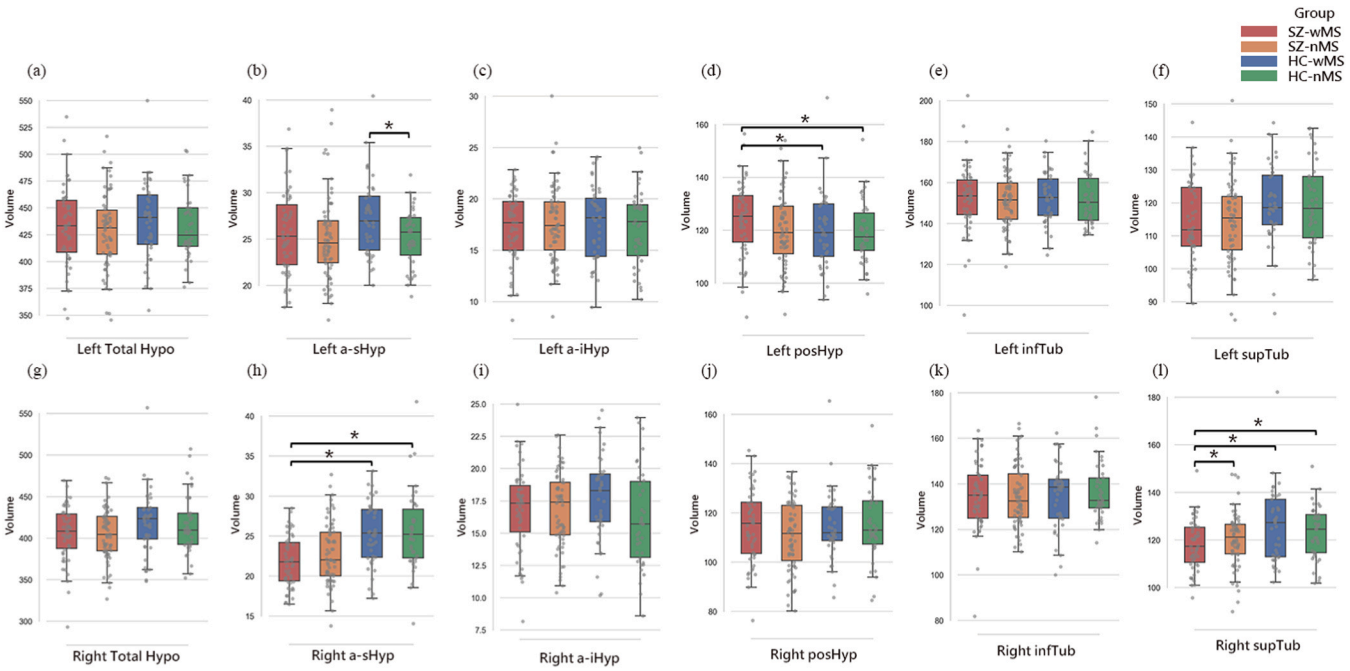

Fig. 2. The post-hoc tests of volumes of the whole hypothalamus and subunits among four groups. Bar plots show the volumes of the bilateral whole hypothalamus and five subunits in post-hoc tests among SZ-wMS, SZ-nMS, HC-wMS and HC-nMS groups, represented in red for SZ-wMS group, in orange for SZ-nMS group, in blue for HC-wMS group and in green for HC-nMS group. total hypo, total hypothalamus; a-sHyp, anterior-superior subunit; a-iHyp, anterior-inferior subunit; posHyp, posterior subunit; infTub, inferior tubular subunit; supTub, superior tubular subunit.

Additionally, a glutamatergic pathway from the prefrontal cortex to the dorsomedial hypothalamus drives behavioral stress responses to the psychological stress, which is thought to increase the vulnerability to schizophrenia during early development (Walker et al., 2008; Kataoka et al., 2020). As a center hub of neuroendocrine stress regulation, the paraventricular nucleus synthesizes and secretes the corticotropin-releasing factor (CRF) and oxytocin, both of which are critical for regulating responses to the stressful challenges (Ramot et al., 2017; Carcea et al., 2021). Importantly, disrupted brain-expression of transient receptor potential channel 5 in oxytocin neurons within the paraventricular nucleus has been shown to induce both obesity and psychosis-related behaviors (Li et al., 2024). Therefore, the reduced volume of right supTub may reflect the loss of multiple neuronal populations, including leptin receptor-expressing neurons, GLP-1 receptor neurons and oxytocin neurons, which may contribute to the neurobiological basis of comorbidity between schizophrenia and MS.

The clinical relevance of the right supTub volume provides additional evidence supporting our hypothesis. Specifically, the volume of the right supTub was associated with typical clinical symptoms of both schizophrenia and MS, including elevated FBG levels and higher negative symptom scores. Moreover, the moderating effect of TG levels on the association between right supTub volume and negative symptoms suggests that schizophrenia patients with elevated TG may have reduced right supTub volume and consequent exacerbation of negative symptoms. Thus, these findings indicate that reduced right supTub volume may contribute to the pathophysiology of hyperglycemia, hyperlipidemia, and negative symptoms in schizophrenia with comorbidity of MS.

More importantly, positive correlations between right supTub volume and multiple cognitive functions were revealed in the SZ-wMS group. Although previous literature supports that the comorbidity of MS is associated with cognitive impairment in schizophrenia and can potentially contribute to functional disability throughout the course of illness (Hagi et al., 2021; Bora et al., 2017), the underlying neurobiological mechanisms are unclear. In several neurological disorders, abnormalities in the volume of hypothalamic subregions have been linked to impairments in working memory, verbal comprehension, and processing speed (Spencer et al., 2023). In schizophrenia, the paraventricular nucleus has been implicated in the regulation of social reward processing, working memory, and executive function by neuroendocrine signaling pathways involving leptin, oxytocin, arginine-vasopressin, and HPA axis-derived cortisol (Walder et al., 2000; Lei et al., 2022; Hung et al., 2017). Our findings indicate that the volume of the right supTub, as a specific hypothalamic subunit, rather than total hypothalamic volume, is associated with impairments across multiple cognitive domains in SZ-wMS. The absence of such correlations in the SZ-nMS group suggests that these relationships may be specific to individuals with comorbid conditions. In addition, reduced volume of right supTub may represent a stable trait marker in schizophrenia with comorbidity of MS, which is independent of the current dosage of antipsychotics. Therefore, our findings highlight the right supTub as a potential translational target for clinical interventions aimed at improving cognitive impairments in schizophrenia with comorbidity of metabolic syndrome.

In addition, findings from MRI studies on structural alterations of the hypothalamus remain controversial in schizophrenia. Some early studies reported increased hypothalamic volume, particularly in the paraventricular nucleus and mammillary body nuclei (Goldstein et al., 2007; Tognin et al., 2012). However, recent research has observed reduced volume of anterior-superior subunit, which includes the paraventricular nucleus (Ruggeri et al., 2024). Another research did not find significant difference in volumes of the hypothalamus (Klomp et al., 2011). In the present study, we employed a recently developed automated image segmentation technique relying on a deep convolutional neural network to achieve reliable and reproducible hypothalamic segmentation (Billot et al., 2020). Consistent with prior findings (Ruggeri et al., 2024), we found the main effects of schizophrenia on the volumes of the left posterior and right anterior-superior subunits, but not on total hypothalamic volume. Our findings underscore the importance of subunit-level analysis in elucidating hypothalamic structural pathology in schizophrenia. Moreover, we found that schizophrenia and MS exerted main effects on the volumes of distinct, non-overlapping hypothalamic subunits. Compared to HC groups (HC-wMS and HC-nMS),

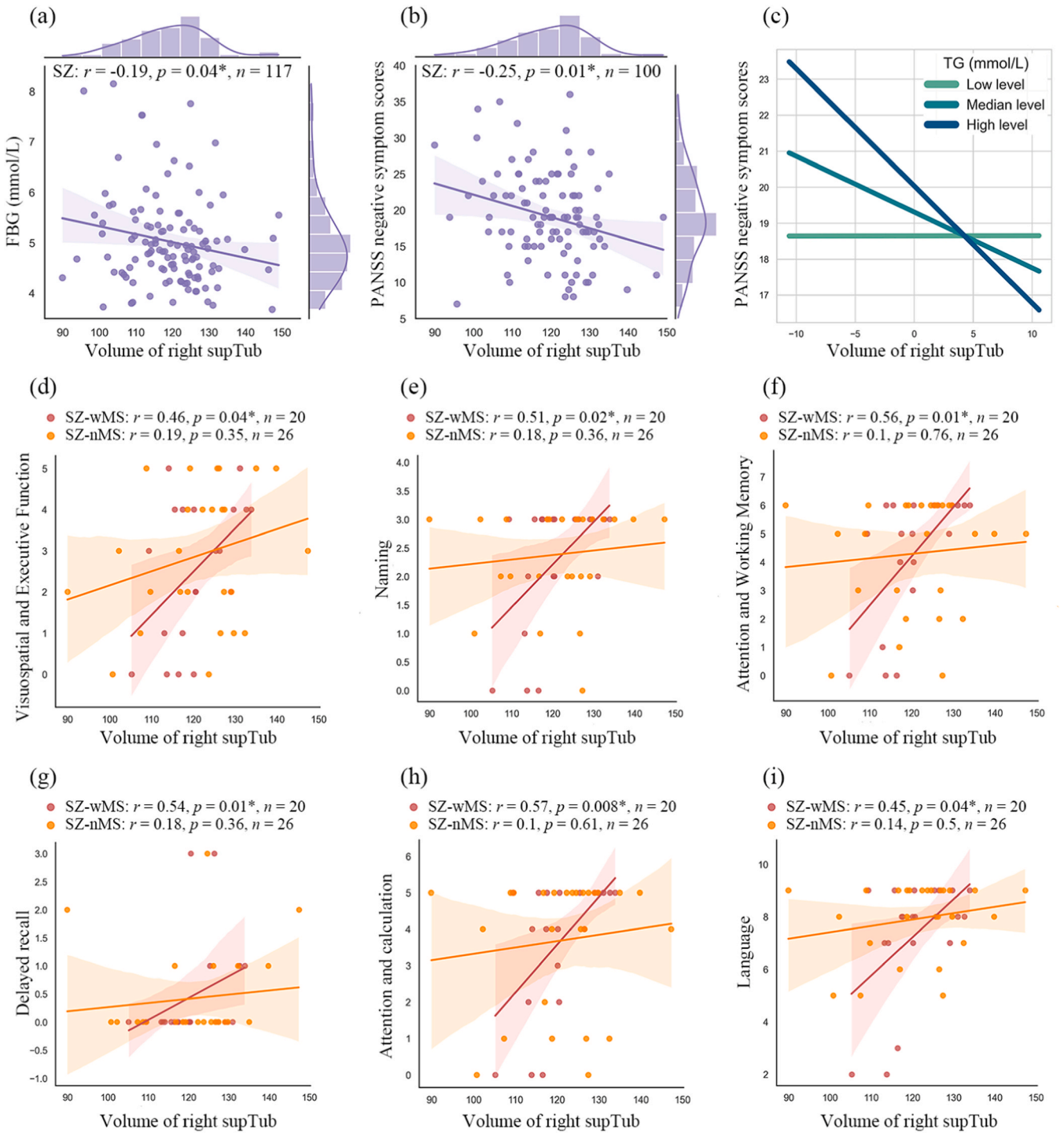

Fig. 3. Relationships between volume of right supTub and clinical symptoms, metabolic indicators and cognitive functions (a) Scatter plot shows correlation between volume of right supTub and peripheral FBG level in schizophrenia group (SZ-wMS and SZ-nMS). (b) Scatter plot shows correlation between volume of right supTub and PANSS negative symptom score in schizophrenia group. (c) Moderation effect of serum level of TG on the correlation between volume of right supTub and PANSS negative symptom scores in schizophrenia group. (d) Scatter plot shows correlation between volume of right supTub and score of visuospatial and executive function in MoCA scale, represented in red for SZ-wMS group, in orange for SZ-nMS group. (e) Scatter plot shows correlation between volume of right supTub and score of naming in MoCA scale. (f) Scatter plot shows correlation between volume of right supTub and score of attention and working memory in MoCA scale. (g) Scatter plot shows correlation between volume of right supTub and score of delayed recall in MoCA scale. (h) Scatter plot shows correlation between volume of right supTub and score of attention and calculation in MMSE scale. (i) Scatter plot shows correlation between volume of right supTub and score of language in MMSE scale. supTub, superior tubular subunit; SZ: schizophrenia. *$p < 0.05$.

increased volume of left posterior subunit (which includes mammillary bodies nucleus) and reduced volume of right a-sHyp (which includes paraventricular nucleus) were observed in the SZ-wMS group, but not in the SZ-nMS group. These findings may help explain inconsistent results reported in schizophrenia regarding the volume of the hypothalamic mammillary body and paraventricular nucleus (Tognin et al., 2012; Bernstein et al., 2007), and highlight the independent impact of metabolic dysfunction to hypothalamic volume. In light of the high

prevalence of MS among individuals with schizophrenia (Mitchell et al., 2013), prior reports on hypothalamic volume alterations in schizophrenia may have been confounded by unaccounted metabolic status. Accordingly, our findings suggest that MS should be considered a critical stratification factor in investigations of hypothalamic volume in schizophrenia.

This study has several limitations. First, previous studies have reported pronounced sexual dimorphism in the volumes of hypothalamic nuclei (Ruggeri et al., 2024). However, due to the unbalanced distribution of male and female participants in the current sample, we were unable to perform sex-stratified analyses to validate our findings. Second, although we did not observe significant associations between current medicine dosage and hypothalamus volumes, a previous study has found larger volume of the inferior tubular subunit in antipsychotic-treated patients with bipolar disorders (Ruggeri et al., 2024). The type of antipsychotic drugs and cumulative medicine dosage should be considered as potential confounding factors in future research. Third, while we found the associations between volume of the right supTub and multiple cognitive functions in the SZ-wMS group, the underlying neurobiological mechanisms linking right supTub volume to cognitive behaviors remain unknown. Future studies should incorporate measurements of peripheral neuroendocrine hormones, such as leptin, oxytocin, and cortisol, to explore these mechanisms. Finally, longitudinal studies with larger and more demographically balanced samples are needed to replicate and validate our findings.

5. Conclusion

In summary, reduced volume of the right supTub of the hypothalamus may represent a potential neurobiological mechanism underlying the comorbidity between schizophrenia and metabolic syndrome. The observed associations with cognitive dysfunction highlight the right supTub as a possible translational target for clinical interventions aimed at improving cognitive deficits in schizophrenia patients with comorbidity of metabolic syndrome.

CRediT authorship contribution statement

Lan Yang: Investigation. **Jiangyan Liao:** Investigation. **Dezhong Yao:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Huan Huang:** Conceptualization. **Chao Mu:** Investigation. **Mingjun Duan:** Resources. **Jingyu Zhou:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Hui He:** Supervision, Resources. **Xianmei Luo:** Investigation. **Cheng Luo:** Writing – review & editing, Supervision, Conceptualization. **Hongyuan Deng:** Resources, Investigation. **Sisi Jiang:** Supervision, Resources. **María Luisa Bringas Vega:** Supervision, Conceptualization. **Xueguo Wang:** Resources, Investigation. **Gang Yao:** Resources. **Yufan Zhou:** Visualization, Methodology.

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Code availability

Automated Bayesian segmentation method were performed on the FreeSurfer (v7.4.1; https://surfer.nmr.mgh.harvard.edu/).

Declaration of Competing Interest

The authors declare that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2025.111569.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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