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Associations Between Thyroid Hormones Levels and Gray Matter Volume of Frontal Lobe Involved into Violence in Male Schizophrenia Patients

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Background: Thyroid dysfunction and frontal lobe gray matter volume (GMV) alterations are associated with violence in schizophrenia (SCZ); however, little is known about the relationship between thyroid dysfunction and frontal lobe GMV. This study aimed to evaluate whether thyroid hormone levels were associated with frontal lobe GMV in male patients with schizophrenia and violence.

Methods: Fifty-five male patients with SCZ underwent triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) tests and structural magnetic resonance imaging (sMRI) scans. The sMRI data were processed using the FreeSurfer version 5.0. Multiple linear stepwise regression analysis was used to investigate the relationship between frontal lobe GMV and thyroid hormone levels in all patients.

Results: Patients with SCZ and violence exhibited lower GMV of the left frontal pole and higher TSH levels than those without violence. After controlling for potential covariates, the frontal pole GMV was negatively associated with TSH levels in all participants.

Conclusion: These findings expand our understanding of the influence of TSH on frontal pole GMV in patients with schizophrenia and violence.

Keywords: thyroid, schizophrenia, violence, gray matter volume, MRI, structures

Introduction

Schizophrenia (SCZ) is a severe mental disorder characterized by positive symptoms, negative symptoms, and cognitive deficits, and its lifetime prevalence is approximately 1%.[1] It has been reported that patients with SCZ are more likely to commit violence compared to the general population.[2] A recent meta-analysis indicated the prevalence of violence in SCZ individuals was approximately 33.3%.[3] A 38-year total population study performed in Sweden found the proportion of individuals with SCZ and related non-affective psychoses who were convicted of violent offenses within 5 years of their initial diagnosis was 10.7%.[4] The debilitating consequences of violence, without doubt, result in a heavy social burden and increased social stigmatization to individuals with SCZ.

Emerging evidence suggests that patients with SCZ have a higher prevalence of thyroid dysfunction than normal individuals because of the variation in the HOPA gene encoding the thyroid receptor co-activator protein and the presence of antithyroid antibodies associated with the occurrence of SCZ as well as antipsychotic treatment.[5–8] In addition, thyroid disorders are associated with a variety of neuropsychiatric symptoms, such as cognitive changes, delusions, and hallucinations, increasing the risk of patients with SCZ committing violent behavior.[9]

The frontal lobe is generally responsible for the regulation of affect, motivational processing, social-emotional behavior, and higher-order cognition.[10,11] Changes in frontal lobe gray matter volume (GMV) have been consistently reported in SCZ patients with violent behavior.[12–14] For example, Kumari et al found that SCZ patients with violence showed reduced GMV of the orbital frontal cortex compared to SCZ patients without violence.[15] Georgios et al revealed

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that the GMV in the left inferior frontal gyrus was associated with modified overt aggression scale and verbal aggression scores.[16] The results of other studies indicated the reduction of frontal lobe GMV in individuals with SCZ and violence.[2,17] Our previous research also found that the GMV of the left frontal pole in SCZ patients with a history of violence was decreased.[18] However, the potential mechanisms that contribute to alterations in the frontal lobe GMV are still unclear.

Thyroid hormones are widely known to participate in the development and maturation of the cerebrum.[19] Abnormal maternal thyroid function during pregnancy can influence fetal brain development. In addition, thyroid status is related to adult GMV.[20] A study showed that there was a small total brain GMV in older people with high fT4 levels.[21] A study using the voxel-based morphometry technique indicated that hyperthyroid patients had significantly lower GMVs in some brain regions, including bilateral hippocampus, parahippocampal gyrus, calcarine, lingual gyrus and left temporal pole, compared to healthy controls.[22] Another study found that patients with major depressive disorder and comorbid subclinical hypothyroidism exhibited a reduced GMV of the middle frontal gyrus than non-comorbid patients.[23] A study analyzed the data of 2557 individuals from two independent population-based surveys conducted in Germany and found that fT4 levels were related to the GMV of the middle frontal gyrus.[24] Thyroid-related gene variants were also reported to influence regional GMV.[25] Magnetic topography spectroscopy and positron emission topography have demonstrated that the frontal lobe is an important region for thyroid hormones.[10] Thus, decreased levels of thyroid hormones may lead to alterations of frontal lobe GMV due to thyroid hormones effects on neuronal proliferation, migration, differentiation and death.[26] We hypothesized that alterations in thyroid hormone levels might be implicated in the changes in the GMV of the frontal lobe associated with violence in individuals with SCZ.

Based on our previous research,[18] this study aimed to explore the relationship between GMV of the frontal lobe and thyroid hormone levels associated with violence in individuals with SCZ.

Materials and Methods

Subjects

From December 2021 to March 2022, 55 male inpatients with SCZ were enrolled from the general psychiatry ward of the Hefei Fourth People's Hospital in Anhui province and met the diagnostic criteria for SCZ according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). The patients underwent regular treatment after admission. Nineteen patients were taking risperidone, 8 patients taking paliperidone, 11 patients taking olanzapine, 8 patients taking sulfamethoxide, 16 patients taking clozapine, 5 patients taking ziprasidone, 5 patients taking piropilone, 3 patients taking aripiprazole, 2 patients taking quetiapine, and 2 patients taking perphenazine. The used antipsychotics were switched to equivalent chlorpromazine.[27] The inclusion criteria were male, right-handed, no alcohol or smoking and no neurological diseases. The exclusion criteria were substance dependence, history of severe head trauma, mental retardation, and MRI contraindications. Violent behavior was defined as aggression against objects, physical aggression against oneself, or aggression against others. The participants were divided into violent SCZ patients (VSPs) and non-VSPs (nVSPs) groups. The VSPs group comprised 29 individuals. The nVSPs group included 26 patients who had not experienced violence. This study was approved by the Ethics Committee of the Hefei Fourth People's Hospital, and all participants provided written informed consent.

Research Design

Within 24 hours after admission, Modified Overt Aggression Scale (MOAS) was used for evaluating aggressive manifestations in patients with SCZ. This scale contains four subscales (verbal aggression, aggression against objects, physical aggression against oneself, and physical aggression against others) and a 5-point rating system (0–4). The weighted total score of MOAS = verbal aggression × 1 + aggression against property × 2 + physical toward self × 3 + physical toward others × 4. Violent behavior was defined as a MOAS-weighted total score of ≥5.[28,29]

The fasting venous blood sample of each participant was collected by the nurses on the morning of the second day after admission and stored in an ethylenediaminetetraacetic acid (EDTA)-dipotassium anticoagulation tube. All samples were immediately sent to the laboratory at our hospital for testing. The serum concentrations of triiodothyronine (T3),

thyroxine (T4), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) were analyzed using Cobas e 602 (Switzerland).

Structural MRI data of all subjects were collected using a 3.0-Tesla Siemens MRI scanner at Hefei Fourth People's Hospital. T1-weighted images were collected with the following sequence: repetition time = 8.5 ms, echo time = 3.2 ms, inversion time (TI) = 450 ms, flip angle (FA) = 12°, field of view (FOV) = 256 mm × 256 mm, matrix size = 256 × 256, slice thickness = 1 mm, no graph, voxel size = 1 × 1×1 mm^3, 188 sagittal slices, and acquisition time = 296 s. Precautions were provided for noise attenuation and a birdcage head coil with foam padding was placed around subject's head to minimize movement. They were instructed to remain motionless and close their eyes during scanning.

Before processing the structural MRI data, we visually inspected the MRI images of all subjects and excluded those with motion artifacts. Finally, structural T1 images of 55 SCZ patients were converted to NIfTI format using dcm2nii and were processed using FreeSurfer version 5.0 (https://surfer.nmr.mgh.harvard.edu/).[30] The reconstruction of cortical surfaces was performed using a standard automatic reconstruction algorithm, which generated the GMV of each brain region, based on the Desikan–Killiany atlas.[31]

Data Analysis

SPSS 16.0 and R software were used for statistical analysis. Continuous variables were described as means and standard deviations and compared using *t*-tests. Categorical variables were expressed as rates, and the chi-squared test was used to compare the two groups. Logistic regression was used to control for potential covariates when the GMV was compared between the two groups. Cohen's *d* is a well-known effect size indicator used to compare two means with a normal distribution. About 0.2, 0.5 and 0.8 values of Cohen's *d* are considered small, medium, and large effect sizes, respectively.[32] The association between GMV and thyroid hormone levels was assessed using multiple linear stepwise regression analysis. $P<0.05$ was considered statistically significant.

Results

Comparison of Demographic Characteristics

There were significant differences in age and total brain volume between the two groups, with VSPs having increased age and decreased total brain volume compared to nVSPs (Table 1). We found no differences between the groups in the dosage of chlorpromazine, which was equivalent to that of the antipsychotics used by the patients (Table 1).

Comparison of Thyroid Hormones Levels

The T3, T4, TSH, fT3, and fT4 levels were within the reference range. VSPs had higher TSH levels than nVSPs, whereas T3, T4, fT3, and fT4 levels did not differ between the groups (Table 1).

Table 1 Comparison of Demographic Characteristics, Total Brain Volume and Antipsychotics Between Groups

Variables	VSPs (29)	nVSPs (26)	t value	P value	Cohen's *d*
Age (years)	40.07±11.15	29.65±9.20	3.752	<0.001	1.019
TSH (mIU/L)	2.81±1.91	1.88±1.25	2.128	0.038	0.576
T3 (pmol/L)	1.10±0.21	1.12±0.20	−0.419	0.677	–
T4 (pmol/L)	7.39±1.59	7.22±1.37	0.409	0.684	–
fT3 (pmol/L)	3.41±0.53	3.36±0.51	0.348	0.729	–
fT4 (pmol/L)	1.33±0.21	1.33±0.18	0.016	0.987	–
Left frontal pole volume (mL)	992.3±168.61	1204.81±170.60	−4.640	<0.001	−1.253
Total brain volume (mL)	1,122,735.74±116,154.84	1,203,069.42±85,842.89	−2.888	0.006	−0.787
Equivalent chlorpromazine	350.83±158.04	350.93± 214.22	−0.002	0.999	–

Abbreviations: VSPs, violent SCZ patients; nVSPs, non-VSPs.

Table 2 Association Between Left Frontal Pole Volume with Violence in SCZ

Variables	β	S.E	Wald	P value	OR (95% CI)
Left frontal pole volume (mL)	−0.006	0.002	7.024	0.008	0.994(0.989–0.998)

Notes: The association between GMV of left frontal pole and violence in SCZ was performed using logistic regression, with the total brain volume and age being covariates.

Table 3 Associations Between Left Frontal Pole Volume and TSH Levels

Variables	β	standard β	t value	P value
TSH	−33.316	−0.281	−2.307	0.025

Notes: The associations between GMV of left frontal pole and TSH levels were conducted using multiple linear stepwise regression analysis, with the total brain volume and age being covariates.

Comparison of Frontal GMV

VSPs were found to have reduced GMV in the left frontal pole compared with nVSPs (Table 1). After controlling for the total brain volume and age, the GMV of left frontal pole was still associated with violence in SCZ (Table 2).

Correlations Between TSH Levels and the GMV in Frontal Pole

The associations between GMV of the left frontal pole and TSH levels were determined using multiple linear stepwise regression analyses in all participants, in which total brain volume and age were considered as covariates. Multiple linear stepwise regression analysis showed that the GMV of the frontal pole was negatively associated with TSH levels (Table 3).

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between thyroid hormone levels and frontal lobe GMV associated with violence in male patients with SCZ. We found that compared to SCZ persons without violence, patients with violence had the reduced GMV in the frontal pole. There were no statistically significant differences in T3, T4, fT3, and fT4 levels between SCZ individuals with and without violence; however, TSH levels were higher in SCZ patients with violence than in those without violence. TSH levels were significantly and negatively associated with GMV of the frontal pole.

We found there are no differences in T3, T4, fT3 and fT4 levels between groups, inconsistent with other studies.[9,33–35] Previous research has reported alterations in thyroid hormone levels in individuals with violent behavior and antisocial personality disorder.[9] Alm et al reported former juvenile delinquents showed increased levels of T3.[33] A study performed in women with borderline personality disorder found that levels of T3 were associated with aggression scores.[34] Another study observed individuals diagnosed with antisocial personality disorder had higher levels of fT4 and aggression scores.[35] The possible reasons are that the definition of violence and the selection of subjects vary between studies. We used the MOAS to define violent behavior. Nevertheless, other studies have evaluated aggressive manifestations, including murder or conviction of violence. In addition, the present study aimed to explore the association between alterations in thyroid hormone levels and violence in patients with SCZ. However, other studies have analyzed thyroid function in patients with antisocial personality disorders, borderline personality disorders, or posttraumatic stress disorders. We found that patients with violence had higher TSH levels than patients without violence, and TSH levels were negatively associated with GMV in the frontal pole. Suggesting that alterations in TSH levels may be involved in violence in SCZ through changing the frontal pole GMV. The underlying mechanisms might be that the normal levels of TSH are crucial to the regulation of neuronal differentiation and synaptic plasticity.[36] In contrast, higher TSH levels might be harmful to brain structure.[37] Higher levels of TSH might result in lower levels of T3 or T4 in the brain.[38] T3 or T4 are closely related to neurotransmitter release, protein synthesis in mitochondria, and gene transportation.[39]

Considering that the density of thyroid hormone receptors is high in the frontal lobe, an inadequate supply of T3 or T4 may negatively influence the GMV in the frontal pole.[10] The frontal pole, also referred to as Brodmann Area 10, which is located in the human frontal lobe responsible for affective regulation, decision-making, and information processing, belongs to the rostral-most part of the human brain.[40–44] The reduced GMV of the frontal pole may lead to positive syndromes and increase the risk of committing violence among patients with SCZ.[45] Moreover, frontal pole plays an important role in many cognitive functions, such as decision-making and problem solving. When GMV becomes abnormal, individuals with SCZ present with persecutory delusions that are closely associated with violence.[46,47] Hence, our study demonstrates that higher TSH levels negatively affect the GMV in the frontal pole and further lead to violence in patients with SCZ.

The limitations of this study must be considered. First, the subjects recruited for this study were persons with SCZ taking antipsychotic medication in hospitals, which may influence brain GMV. Although no difference was found in equivalent chlorpromazine between groups, future research should recruit patients with first-episode schizophrenia and violence. Second, this study was conducted with a small sample size, and a larger sample size is required. Third, this study only investigated the association between thyroid hormones and frontal gray matter volume in male subjects. The results of male participants may not be generalized to female patients, but gender as a potential confounding factor should be controlled to yield reliable results. In addition, the associations between thyroid hormones and frontal poles are analyzed based on gender, eliminating the potential interaction effect. Future research conducted on female subjects is also needed. Fourth, the cross-sectional nature of the study limits causal interpretations.

In the present study, we aimed to explore the associations between thyroid hormone levels and brain GMV in patients with SCZ and violence. Our results indicated that SCZ patients with violence exhibited decreased GMV of the frontal pole and increased levels of TSH compared to those without violence. Moreover, GMV of the frontal pole was negatively associated with TSH levels. These findings provide valuable insights into the important role of reduced frontal GMV in violence among patients with schizophrenia. Additionally, the practical implications are that several potential factors that may lead to increased levels of TSH associated with violence in schizophrenia should be heeded to reduce the risk of violence in schizophrenia. Therefore, alterations in thyroid hormone levels in SCZ patients should be emphasized.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statements

All the procedures were performed in accordance with the Declaration of Helsinki of the National Institutes of Health. The study was approved by the Ethics Committee of Hefei Fourth People's Hospital (IRB-HFSY-YJ-LW-YT [2023-008-001]). All participants provided written informed consent.

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Disclosure

The authors report no conflict of interest in this work.

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