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# Association Between Frontotemporal Atrophy and Cognitive Impairment in Patients with Schizophrenia Based on Computed Tomography Imaging

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**Background:** Patients with schizophrenia (SZ) exhibit frontotemporal atrophy accompanied by cognitive impairment. However, the relationship between CT-derived structural changes and cognitive deficits remains underexplored. This study aimed to evaluate the association between frontotemporal atrophy and cognitive performance using routine cranial CT.

**Methods:** This retrospective cross-sectional case–control study included 120 patients with SZ and 100 healthy controls. Bifrontal ratio (BFR), frontal horn width (FHW), mean temporal horn width (THW_mean), sylvian fissure width (SFW), and frontotemporal atrophy index (FTAI) were measured. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) and the Trail Making Test (TMT). Group comparisons, Spearman correlation, and multivariable regression analyses were performed.

**Results:** Patients with SZ showed significantly increased atrophy indices and reduced cognitive performance. FTAI was negatively associated with global cognition, executive function, and attention. In multivariable models, FTAI remained significantly associated with cognitive outcomes and contributed to improved model fit ($\Delta R^2 = 0.319$).

**Conclusion:** CT-derived frontotemporal atrophy was significantly associated with cognitive impairment in SZ. These findings suggest that CT-based structural measures may provide a clinically accessible approach for characterizing brain changes related to cognitive dysfunction.

**Keywords:** schizophrenia, cognitive impairment, frontotemporal atrophy, computed tomography imaging, montreal cognitive assessment, trail making test, multivariable regression

## Introduction

Schizophrenia (SZ) is a severe psychiatric disorder characterized by disturbances in perception, thinking, emotion, and behavior, with a global prevalence of approximately 1%.[1,2] It is associated with substantial long-term disability and imposes a significant burden on affected individuals and society. Cognitive impairment is widely recognized as a core feature of SZ,[3,4] emerging early in the disease course and closely linked to functional outcomes and social recovery. However, clinically accessible imaging markers that can reliably quantify structural brain alterations and their association with cognitive impairment remain limited.

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Neuroimaging studies have consistently demonstrated widespread structural brain abnormalities in SZ.[5,6] Brain atrophy has been shown to correlate with cognitive decline,[7] with the frontal and temporal lobes being among the most consistently affected regions.[8–11] These alterations include enlargement of the frontal and temporal horns, cortical thinning, and widening of the sylvian fissure (SF). Magnetic resonance imaging (MRI) offers high sensitivity for detecting cortical and subcortical structural changes. However, its use in routine clinical practice and large-scale screening is constrained by high cost, longer acquisition times, and limited patient tolerance, particularly during acute psychiatric episodes.

In contrast, cranial computed tomography (CT) is widely used in psychiatric inpatient and emergency settings due to its accessibility, rapid acquisition, and cost-effectiveness. CT can provide several structural indicators related to brain atrophy.[12] Previous studies have explored CT-based measures such as frontal horn width (FHW) and sylvian fissure width (SFW),[13] but most have focused on single parameters, limiting their ability to comprehensively characterize frontotemporal structural alterations. Furthermore, studies investigating the association between CT-derived atrophy measures and cognitive function in SZ remain limited and have often lacked adjustment for key clinical confounders.

These gaps raise several important questions: (1) whether a composite index integrating multiple CT-based structural measures can more comprehensively characterize frontotemporal atrophy; (2) whether such structural alterations are consistently associated with impairments across different cognitive domains in SZ; and (3) whether these associations remain significant after accounting for relevant clinical and demographic factors.

To address these questions, the present study extracted multiple frontotemporal atrophy parameters from routine non-contrast cranial CT and constructed an integrated Frontotemporal Atrophy Index (FTAI). We systematically compared these measures between patients with SZ and healthy controls (HC) and examined their associations with cognitive performance, including domain-specific measures from the Montreal Cognitive Assessment (MoCA) and the Trail Making Test (TMT). Multivariable linear regression analyses were conducted to evaluate the independent associations between frontotemporal atrophy and cognitive outcomes. Unlike prior studies focusing on single CT-derived metrics, FTAI integrates multiple structural parameters to provide a more comprehensive representation of frontotemporal atrophy. This study aims to provide a clinically accessible and scalable structural framework for understanding cognitive impairment in SZ.

# Participants and Methods

## Study Design and Participants

This study adopted a single-center, retrospective cross-sectional case–control design. We systematically retrieved electronic medical records and the Picture Archiving and Communication System (PACS) of People's Hospital of Dali Bai Autonomous Prefecture from March 2023 to May 2025 to identify SZ patients and HC who had undergone non-contrast cranial CT during this period.

To ensure data completeness and consistency, all included participants were required to meet the following criteria: availability of complete raw cranial CT images for measurement of frontotemporal atrophy indices; presence of documented cognitive assessments from prior routine clinical evaluations, including MoCA and TMT; presence of complete clinical information, including age, sex, years of education, illness duration, body mass index (BMI), chlorpromazine-equivalent antipsychotic dosage (CPZeq), Brief Psychiatric Rating Scale (BPRS) score, and Clinical Global Impression–Severity (CGI-S) rating. All data were obtained from routine clinical care, and no additional interventions were performed.

Inclusion criteria for the SZ group: (1) diagnosis of SZ according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5);[14] (2) completed routine cranial CT within the study period with image quality adequate for atrophy measurement; (3) available historical cognitive assessment (MoCA, TMT-A, TMT-B); (4) complete clinical data including age, years of education, illness duration, BMI, CPZeq, BPRS, CGI-S, and smoking status; and (5) age between 18 and 60 years.

Exclusion criteria: (1) history of major organic brain disorders (traumatic brain injury, central nervous system infection, stroke, epilepsy, etc); (2) CT demonstrating intracranial mass lesions, large parenchymal injury, or poor scan

quality; (3) history of alcohol or other substance dependence; (4) missing or incomplete cognitive assessments, or an interval between CT and cognitive testing > 30 days; or (5) severe physical illness that might affect cognitive testing or the reliability of clinical data. (6) The HC group was screened using the same criteria, except that individuals with any psychiatric disorder or history of psychotropic medication use were excluded.

A total of 120 SZ patients and 100 HC participants were finally included.

## Cranial CT Acquisition and Measurement of Frontotemporal Atrophy Indices

All participants underwent routine non-contrast cranial CT scanning using the same multi-detector helical CT scanner. Scans were acquired in the supine position with the head centered, covering axial slices from the foramen magnum to the vertex. Slice thickness, interslice spacing, tube voltage, and tube current were maintained as consistent as possible to minimize technical bias.

Imaging data were imported into the PACS workstation. Two experienced neuroradiologists, blinded to all clinical data and group assignments, independently measured the following structural indices:

Bifrontal Ratio (BFR): the ratio of the inter-frontal-horn distance at the level of maximal frontal horn width to the corresponding intracranial diameter; FHW: the maximal distance between the left and right frontal horns on the same slice; Mean Temporal Horn Width (THW_mean): the mean of left and right temporal horn widths measured at the slice showing the most prominent temporal horn enlargement; SFW: the maximal width of one or both Sylvian fissures measured at the basal ganglia level; FTAI: a composite index integrating BFR, FHW, THW_mean, and SF to reflect the degree of frontotemporal atrophy, with higher values indicating more severe atrophy; Intracranial Volume Proxy (ICV_proxy): an estimated intracranial size parameter derived from skull inner-table cross-sectional area or volume, used as a covariate to adjust for differences in head size.

FTAI: definition and Z-standardization

FTAI was defined a priori as the primary imaging-derived exposure variable to quantify frontotemporal atrophy severity. Four CT-based morphometric indices were included: bifrontal ratio (BFR), frontal horn width (FHW), temporal horn width (THW), and sylvian fissure widening index (SFW) (abbreviated as BFR, FHW, THW_mean, and SFW, respectively). To ensure comparability across metrics with different units and ranges, each index was transformed into a $Z$ score using the healthy control (HC) group as the reference population. Specifically, for each participant and each metric $X \in \{BFR, FHW, THW\_mean, SFW\}$, we calculated: $Z\_X = (X - \mu\_HC)/\sigma\_HC$, where $\mu_{X,HC}$ and $\sigma_{X,HC}$ denote the mean and standard deviation of the metric in the HC group, respectively.

To ensure consistent interpretability, all variables were aligned such that higher values indicated greater atrophy. For metrics in which higher raw values reflected less atrophy (ie, protective direction), the values were first sign-inverted:

$$X' = -X$$

And then standardized using the same HC-based parameters. Finally, the FTAI was computed as the unweighted arithmetic mean of the four standardized components:

$$FTAI = (Z\_BFR + Z\_FHW + Z\_THW\_mean + Z\_SFW)/4$$

Thus, FTAI is a composite Z-score index centered on the HC distribution, with higher FTAI values representing greater frontotemporal atrophy burden.

If measurements by the two raters exceeded a predefined discrepancy threshold, a senior radiologist adjudicated the final value. Inter-rater and intra-rater reliability were assessed using intraclass correlation coefficients (ICC), with ICC values >0.75 considered good and >0.85 considered excellent reliability. The unweighted averaging approach was selected to ensure interpretability and to avoid overfitting, particularly given the moderate sample size and potential collinearity among component variables. To evaluate robustness, a sensitivity analysis using principal component analysis (PCA)-derived composite scores was performed, yielding consistent results (see Results section).

## Cognitive Assessment

All participants completed cognitive testing in a relatively stable clinical state. Assessments were conducted by trained evaluators in a quiet environment and scheduled within the shortest feasible time window before or after the CT scan.

MoCA: The Chinese version was used to evaluate global cognition, including executive function, attention, and memory.[15] Total MoCA score and domain-specific subscores (executive function, attention, memory) were recorded.

TMT A and B: TMT-A primarily evaluates processing speed and visual search, whereas TMT-B evaluates cognitive switching and executive control. Completion time (in seconds) was recorded.

For comparability across indices, MoCA domain scores and TMT results were standardized within the SZ group to generate Z_MoCA_total, Z_exec, Z_attention, and Exec_composite *Z* scores. When appropriate, TMT completion time was reverse-scored before Z-standardization so that higher scores consistently indicated better performance.

## Collection of Additional Clinical Variables

The following variables were obtained from medical records and face-to-face interviews: age, sex, years of education, smoking status, BMI, illness duration (years), antipsychotic dosage (converted to chlorpromazine equivalents, CPZeq mg/day), BPRS total score, and CGI-S score. These variables were included as covariates in regression analyses to control for potential confounding factors.

## Blinding Procedures

To minimize observer bias, blinding was implemented across imaging measurement, data processing, and statistical analyses. The two neuroradiologists independently measuring CT images were completely blinded to group status (SZ or HC), clinical characteristics, and cognitive performance. When discrepancies exceeded the predefined range, a senior neuroradiologist not involved in prior measurements adjudicated the final values. Personnel handling data cleaning and statistical analyses accessed only de-identified coded data and had no access to identifiable clinical information, ensuring objectivity and consistency throughout the study.

## Sample Size Considerations

As a retrospective case–control study, the sample size was determined by the number of eligible participants during the study period. To ensure adequate power for multivariable linear regression, we followed the event-per-variable principle (≥10–15 participants per independently associated factor) and the model-based sample size recommendations proposed by Riley et al.[16,17] With approximately nine associated factors in the final regression model, the theoretical required sample size ranged from 90 to 135. The present study included 120 SZ patients and 100 HC participants (total >200), exceeding the required threshold and providing sufficient statistical power. Additionally, power analysis based on moderate effect sizes ($\rho \approx 0.3$–$0.5$), $\alpha = 0.05$, and power = 0.80 indicated a required sample size of approximately 84–134, further supporting the adequacy of the sample.

## Ethical Approval

This study was conducted using data obtained from routine clinical care. All CT imaging, cognitive assessments, and clinical information were part of standard medical procedures, with no additional prospective examinations or interventions involved. The protocol was approved by the Ethics Committee of People's Hospital of Dali Bai Autonomous Prefecture (Approval No. MC20260010) and adhered strictly to the principles of the Declaration of Helsinki.[18] As the study was retrospective and all data were fully de-identified, the requirement for written informed consent was waived. Patient privacy and data security were protected throughout the research process.

## Statistical Analysis

All analyses and data visualizations were performed using GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA) and SPSS version 26.0 (IBM Corporation, Armonk, NY, USA).

For between-group comparisons, continuous variables were tested for normality. Normally distributed variables were expressed as mean ± standard deviation and compared using independent-sample t tests, while non-normally distributed variables were presented as median (interquartile range) and compared using the Mann–Whitney *U*-test. Categorical variables were reported as frequencies and percentages and compared using the $\chi^2$ test or Fisher's exact test. Where appropriate, Bonferroni correction was applied to control for multiple comparisons. The choice of statistical test and data presentation format was based on distribution normality.

Correlation between frontotemporal atrophy and cognition was analyzed, with FTAI serving as the primary structural indicator. Spearman rank correlation analysis was performed to examine associations between FTAI (primary structural index) and standardized cognitive variables (Z_MoCA_total, Z_exec, Z_attention, Exec_composite Z). Scatterplots with fitted regression lines were generated, and Spearman ρ coefficients with 95% confidence intervals were reported.

To evaluate the robustness of the composite FTAI, a sensitivity analysis was performed using principal component analysis (PCA). The four standardized structural variables (Z_BFR, Z_FHW, Z_THW_mean, Z_SFW) were entered into PCA, and the first principal component (PC1) was extracted as an alternative composite index of frontotemporal atrophy. Spearman correlation and multivariable regression analyses were repeated using PC1 to assess consistency with the original FTAI-based results.

Multivariable linear regression was conducted to assess association and independent contribution. To evaluate the independent contribution of frontotemporal atrophy to cognitive impairment: Step 1 (Model 1): baseline model including age, years of education, illness duration, BMI, CPZeq, BPRS total score, CGI-S, and ICV_proxy as associated factors. Step 2 (Model 2): FTAI was added to Model 1 to assess incremental explanatory value. Model fit ($R^2$, adjusted $R^2$), change in $R^2$ ($\Delta R^2$), and corresponding F-change were compared. Regression coefficients including unstandardized B, standard error SE(B), standardized β, t values, and 95% confidence intervals were reported. Multicollinearity was assessed using tolerance and the variance inflation factor (VIF), with VIF > 5 indicating possible collinearity.

A two-tailed $p < 0.05$ was considered statistically significant.

# Results

## Baseline Clinical and Psychopathological Characteristics

A total of 120 patients with SZ and 100 HC undergoing contemporaneous cranial CT were included. Baseline demographic and clinical characteristics were comparable between the two groups, including age, sex distribution, years of education, body mass index (BMI), smoking status, and intracranial volume proxy (ICV_proxy) (Table 1). The median ages of the SZ and HC groups were 39 (34–44) years and 42 (32–47) years, respectively ($p = 0.200$). Sex distribution was comparable (male: 50.83% vs 52.00%, $p = 0.863$). Years of education were identical at 11 (9–13) years ($p = 0.956$), and BMI did not differ (23.44 ± 2.92 vs 23.34 ± 3.10 kg/m$^2$, $p = 0.792$). Smoking rates were also similar (47.50% vs 43.00%, $p = 0.504$).

The ICV_proxy showed no significant group difference (139.67 ± 4.84 vs 140.19 ± 5.09, $p = 0.437$), suggesting adequate comparability in cranial size–related factors.

Regarding clinical symptoms, SZ patients exhibited markedly greater psychopathology severity than HC. BPRS total scores were 45.69 ± 7.84 vs 30.77 ± 5.29 ($p < 0.001$), and CGI-S scores were 4 (3–5) vs 1 (1–2) ($p < 0.001$). The median illness duration in SZ was 3 (1–6) years, and the median antipsychotic dose was 350.5 (247–463) mg CPZeq.

## Group Differences in CT-Based Frontotemporal Atrophy Measures

SZ patients showed significant abnormalities across CT-based frontal and temporal atrophy measures. Detailed comparisons of CT-derived frontotemporal atrophy indices between groups are presented in Table 2 and Figure 1. Compared with HC, the BFR was significantly increased in the SZ group [0.33 (0.30–0.35) vs 0.30 (0.28–0.32), $p < 0.001$], and FHW was markedly enlarged (3.66 ± 0.65 mm vs 2.98 ± 0.45 mm, $p < 0.001$). For temporal lobe–related indices, the SZ group demonstrated greater THW_mean (4.13 ± 0.64 mm vs 3.50 ± 0.62 mm, $p < 0.001$), and SFW was also significantly wider (4.72 ± 0.76 mm vs 4.07 ± 0.67 mm, $p < 0.001$). The composite FTAI, reflecting the overall degree of frontotemporal atrophy, was substantially elevated in SZ (1.09 ± 0.58) and close to zero in HC (0.00 ± 0.53), with

**Table 1** Baseline Demographic and Clinical Characteristics of Patients with SZ and HC

| Variable | SZ (n=120) | HC (n=100) | $t/\chi^2$ | p-value |
|---|---|---|---|---|
| Age, years | 39 (34, 44) | 42 (32, 47) | −1.283 | 0.2 |
| Sex, male (%) | 61 (50.83%) | 52 (52.00%) | 0.030 | 0.863 |
| Education, years | 11 (9, 13) | 11 (9, 13) | 0.339 | −0.956 |
| BMI, $kg/m^2$ | 23.44 ± 2.92 | 23.34 ± 3.10 | 0.264 | 0.792 |
| Smoking (%) | 57 (47.50%) | 43 (43.00%) | 0.445 | 0.504 |
| Illness duration, years | 3 (1, 6) | 0 | – | – |
| ICV proxy | 139.67 ± 4.84 | 140.19 ± 5.09 | −0.778 | 0.437 |
| CPZeq, mg | 350.5 (247, 463) | 0 | – | – |
| BPRS total | 45.69 ± 7.84 | 30.77 ± 5.29 | 16.207 | <0.001 |
| CGI-S | 1 (1, 2) | 4 (3, 5) | −12.997 | <0.001 |

**Note**: Data are presented as mean ± SD or median (interquartile range).

**Table 2** Comparison of Frontal and Temporal Atrophy Indices Between SZ and HC

| Variable | SZ (n=120) | HC (n=100) | t-value | p-value | Cohen's d |
|---|---|---|---|---|---|
| BFR | 0.33 (0.30–0.35) | 0.30 (0.28–0.32) | –5.558 | <0.001 | 0.75 |
| FHW, mm | 3.66 ± 0.65 | 2.98 ± 0.45 | 8.78 | <0.001 | 1.20 |
| THW_mean, mm | 4.13 ± 0.64 | 3.50 ± 0.62 | 7.36 | <0.001 | 1.00 |
| SFW, mm | 4.72 ± 0.76 | 4.07 ± 0.67 | 6.63 | <0.001 | 0.90 |
| FTAI | 1.09 ± 0.58 | 0.00 ± 0.53 | 14.37 | <0.001 | 1.95 |

**Note**: Cohen's d was calculated for continuous variables to estimate effect size.

a highly significant difference ($t = 14.37$, $p < 0.001$). The effect sizes for group differences were large, with Cohen's d values ranging from 0.75 to 1.95, indicating substantial between-group differences in frontotemporal atrophy measures.

Inter-rater reliability analysis demonstrated excellent agreement across all imaging measurements, with ICC values ranging from 0.86 to 0.92 (BFR: 0.88; FHW: 0.91; THW_mean: 0.89; SFW: 0.86).

These findings indicate prominent frontal and temporal structural atrophy in SZ, involving widening of both frontal and temporal horn and sylvian fissure.

## Cognitive Performance and Group Comparisons

SZ patients exhibited marked impairment in global cognition and multiple key cognitive domains. Group differences in cognitive performance across domains are summarized in Table 3. The median MoCA total score in the SZ group was 23 (21–24), significantly lower than the HC score of 26 (25–27) ($t = –8.709$, $p < 0.001$).

Across specific MoCA domains, SZ showed reduced performance in executive function [3 (2–3.5) vs 4 (3–5), $p < 0.001$], attention [4 (3–5) vs 5 (4–6), $p < 0.001$], and memory [4 (3–4) vs 5 (4.5–6), $p < 0.001$].

Processing speed and executive switching were also impaired. SZ patients had prolonged TMT-A times (43.75 ± 6.96 vs 39.62 ± 5.85 seconds, $p < 0.001$) and TMT-B times (99.81 ± 13.47 vs 91.09 ± 11.52 seconds, $p < 0.001$), indicating deficits in information processing speed, cognitive flexibility, and executive control.

Overall, SZ patients demonstrated pervasive impairment across global cognition, executive function, attention, memory, and processing speed.

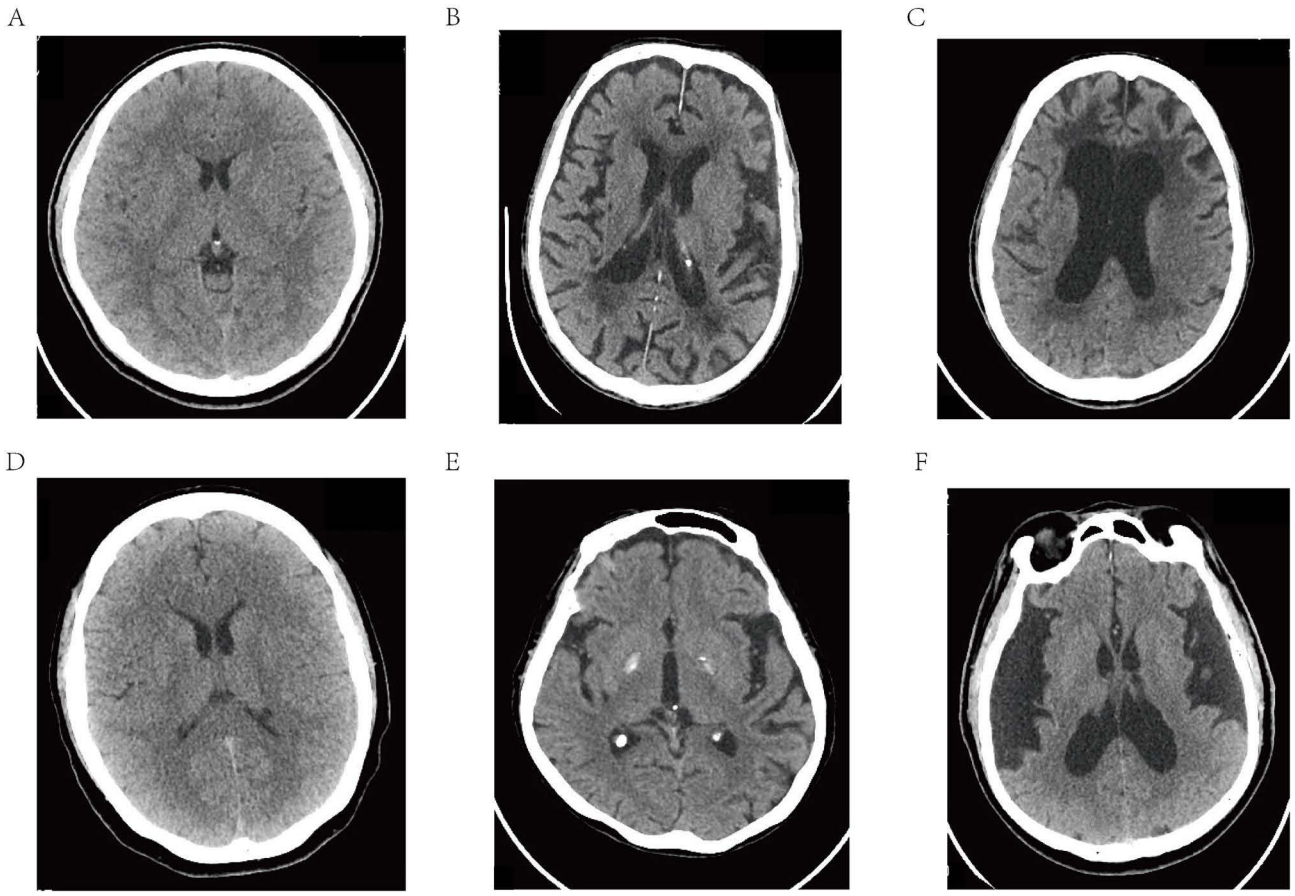


**Figure 1** Representative Cranial CT Images Illustrating Frontotemporal Structural Changes. (**A**) Normal frontal lobe on cranial CT, showing preserved frontal lobe volume with normal sulcal width and no ventricular enlargement. (**B**) Mild frontal lobe atrophy in patients with schizophrenia (SZ), characterized by slightly widened frontal sulci and subtle reduction in frontal lobe volume on CT. (**C**) Severe frontal lobe atrophy in SZ, demonstrated by marked widening of frontal sulci, obvious reduction in frontal lobe volume, and enlargement of the frontal horn of the lateral ventricle on CT. (**D**) Normal temporal lobe on cranial CT, with preserved temporal lobe volume and normal sulcal appearance. (**E**) Mild temporal lobe atrophy in SZ, indicated by mild widening of temporal sulci and subtle enlargement of the temporal horn of the lateral ventricle on CT. (**F**) Severe temporal lobe atrophy in SZ, characterized by pronounced reduction in temporal lobe volume and substantial enlargement of the temporal horn of the lateral ventricle on CT. All images are non-contrast cranial CT scans. Morphological assessment was based on sulcal width and ventricular size rather than cortical thickness.

## Correlations Between FTAI and Cognitive Function

Spearman correlation analyses revealed significant negative associations between FTAI and multiple cognitive indices in SZ (Figure 2). FTAI was moderately negatively correlated with MoCA total score (rho = –0.5544, 95% CI –0.6673 to –0.4166, $p < 0.0001$), indicating that greater frontotemporal atrophy was associated with poorer global cognition.

**Table 3** Comparison of Cognitive Function Between SZ and HC

| Variable | SZ (n=120) | HC (n=100) | t-value | p-value | Cohen's d |
|---|---|---|---|---|---|
| MoCA total | 23 (21–24) | 26 (25–27) | –8.709 | <0.001 | 1.20 |
| MoCA executive | 3 (2–3.5) | 4 (3–5) | –8.195 | <0.001 | 1.10 |
| MoCA attention | 4 (3–5) | 5 (4–6) | –7.751 | <0.001 | 1.05 |
| MoCA memory | 4 (3–4) | 5 (4.5–6) | –7.860 | <0.001 | 1.05 |
| TMT-A, sec | 43.75 ± 6.96 | 39.62 ± 5.85 | 4.72 | <0.001 | 0.65 |
| TMT-B, sec | 99.81 ± 13.47 | 91.09 ± 11.52 | 5.11 | <0.001 | 0.70 |

**Notes**: The effect sizes for group differences were moderate to large, with Cohen's d values ranging from 0.65 to 1.20, indicating substantial differences in cognitive performance between groups.

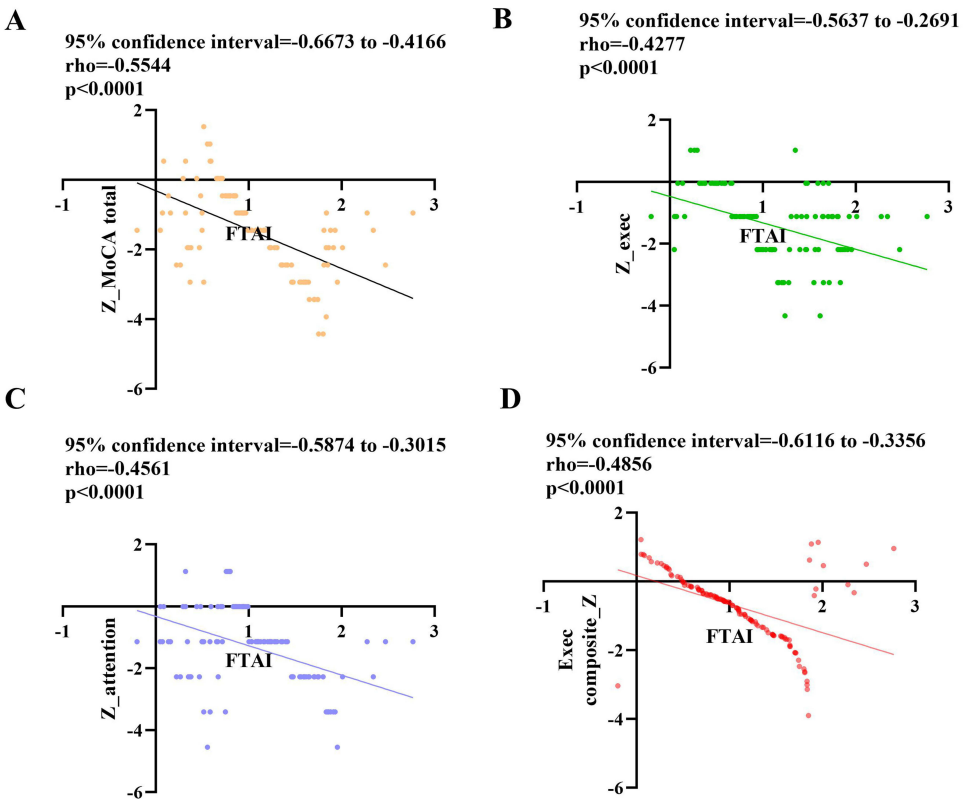


**Figure 2** Spearman Correlation Scatterplots Between FTAI and Cognitive Measures. (**A**) Association between FTAI and MoCA total score (rho = –0.5544, p < 0.0001). (**B**) Association between FTAI and executive function *Z* score (Z_exec) (rho = –0.4277, p < 0.0001). (**C**) Association between FTAI and attention *Z* score (Z_attention) (rho = –0.4561, p < 0.0001). (**D**) Association between FTAI and composite executive function score (Exec_composite Z) (rho = –0.4856, p < 0.0001).

Across cognitive domains, FTAI was significantly associated with executive function *Z* scores (rho = –0.4277, p < 0.0001) and attention *Z* scores (rho = –0.4561, p < 0.0001). Moreover, the composite executive function index (Exec_composite Z) was also strongly correlated with FTAI (rho = –0.4856, 95% CI –0.6116 to –0.3356, p < 0.0001).

In sensitivity analyses using PCA-derived composite scores, the first principal component (PC1) explained 68.4% of the total variance of the four structural indices. PC1 showed significant negative correlations with cognitive measures, including Z_MoCA_total (rho = –0.538, p < 0.001), Z_exec (rho = –0.401, p < 0.001), Z_attention (rho = –0.432, p < 0.001), and Exec_composite Z (rho = –0.462, p < 0.001).

In multivariable regression models, PC1 remained an independent factor associated with Z_MoCA_total (β = –0.552, p < 0.001) and Exec_composite Z (β = –0.487, p < 0.001), with effect sizes comparable to those obtained using FTAI.

These results demonstrate that FTAI shows consistent and robust associations with global cognition, executive control, attention, and composite executive performance in SZ.

## Independent and Incremental Effects of Frontotemporal Atrophy on Global Cognition

Using Z_MoCA_total as the dependent variable, Model 1 included age, years of education, illness duration, BMI, CPZeq, BPRS, CGI-S, and ICV_proxy. The model showed minimal explanatory power, with $R^2 = 0.019$ and adjusted $R^2 = –0.052$, indicating that demographic and clinical variables contributed very little to cognitive variance.

After adding FTAI to the model (Tables 4 and 5), model fit improved substantially. The $R^2$ increased to 0.338 and the adjusted $R^2$ to 0.284, while the standard error of the estimate decreased from 1.21 to 1.00. The increase in explained variance ($\Delta R^2 = 0.319$) was statistically significant ($\Delta F = 52.999$, df = 1110, p < 0.001), indicating that FTAI was strongly associated with global cognitive performance. This finding should be interpreted cautiously, as it reflects statistical association within the current sample rather than predictive performance.

**Table 4** Multivariable Linear Regression Analysis of Z_MoCA_total

| Variables | Unstandardized B | SE (B) | Standardized β | t | p | 95% CI Lower Limit | 95% CI Upper Limit |
|---|---|---|---|---|---|---|---|
| (Constant) | −4.161 | 2.95 | | −1.411 | 0.161 | −10.008 | 1.685 |
| Age | −0.003 | 0.01 | −0.021 | −0.268 | 0.79 | −0.023 | 0.018 |
| Education, years | 0.044 | 0.035 | 0.099 | 1.251 | 0.214 | −0.026 | 0.114 |
| Illness duration, years | −0.02 | 0.021 | −0.078 | −0.988 | 0.325 | −0.061 | 0.02 |
| BMI | 0.016 | 0.033 | 0.039 | 0.485 | 0.629 | −0.049 | 0.08 |
| CPZeq, mg | 0 | 0 | 0.024 | 0.304 | 0.762 | −0.001 | 0.001 |
| BPRS total | −5.30E-05 | 0.012 | 0 | −0.004 | 0.996 | −0.024 | 0.024 |
| CGI S | 0.01 | 0.089 | 0.009 | 0.118 | 0.907 | −0.165 | 0.186 |
| ICV proxy | 0.022 | 0.019 | 0.092 | 1.16 | 0.248 | −0.016 | 0.06 |
| FTAI | −1.144 | 0.157 | −0.568 | −7.28 | 0 | −1.456 | −0.833 |

**Notes**: The dependent variable is the standardized global cognitive score (Z_MoCA_total); negative B values indicate that higher values of the predictor are associated with poorer cognitive performance.

**Table 5** Model Fit and Incremental Effects for Multivariable Regression Models Predicting Z_MoCA_total

| Model | R | R square | Adjusted R Square | SE | $\Delta R^2$ | ΔF | P for ΔF |
|---|---|---|---|---|---|---|---|
| 1 | 0.138[a] | 0.019 | −0.052 | 1.207605 | 0.019 | 0.268 | 0.975 |
| 2 | 0.581[b] | 0.338 | 0.284 | 0.996539 | 0.319 | 52.999 | 0 |

**Notes**: [a]Model 1 includes age, years of education, illness duration, BMI, CPZeq, BPRS total score, CGI-S, and ICV_proxy. [b]Model 2 adds FTAI to Model 1. $\Delta R^2$ reflects the improvement in explanatory power contributed by the added variable; ΔF tests its statistical significance.

In the final model, FTAI was the only significant associated factor (B = –1.144, 95% CI –1.456 to –0.833, β = –0.568, $p < 0.001$), was associated with poorer global cognition independently of age, education, illness duration, BMI, medication dose, psychopathology severity, and ICV_proxy. All other covariates were nonsignificant. Collinearity diagnostics showed tolerances near 1 and VIF < 1.1, indicating no multicollinearity. The large $\Delta R^2$ should be interpreted cautiously, as it reflects statistical association within this sample rather than predictive performance.

## Multiple Linear Regression of Frontotemporal Atrophy on Composite Executive Function Scores

Using Exec_composite Z as the dependent variable, Model 1 included age, education, illness duration, BMI, CPZeq, BPRS, CGI-S, and ICV_proxy. As shown in Tables 6 and 7, age (B = –0.025, 95% CI –0.044 to –0.010, p = 0.002) and CGI-S (B = 0.198, 95% CI 0.053 to 0.343, p = 0.008) were significantly associated with executive function. Illness duration showed a non-significant trend toward association (B = –0.043, 95% CI –0.076 to –0.009, p = 0.013). Model fit was modest (R = 0.358, $R^2 = 0.128$, adjusted $R^2 = 0.065$), explaining only 12.8% of the variance [F(8111) = 2.039, p = 0.048]. Upon adding FTAI to form Model 2, FTAI emerged as a strong negative associated factor of Exec_composite Z (B = –0.859, 95% CI –1.116 to –0.603, β = –0.502, t = –6.640, $p < 0.001$). Age (B = –0.027, p = 0.002), illness duration (B = –0.043, p = 0.013), and CGI-S (B = 0.198, p = 0.008) remained significant or near-significant.

Model 2 showed markedly improved fit (R = 0.614, $R^2 = 0.378$, adjusted $R^2 = 0.327$), explaining 37.8% of variance in executive function. The $R^2$ increment was 0.249, with ΔF = 44.084 [df(1110), $p < 0.001$], indicating that adding FTAI substantially enhanced the model's explanatory performance. Collinearity diagnostics showed VIF values near 1, with no multicollinearity concerns.

**Table 6** Multivariable Linear Regression Analysis of Exec_composite Z

| Variables | Unstandardized B | SE (B) | Standardized β | t | p | 95% CI Lower Limit | 95% CI Upper Limit |
|---|---|---|---|---|---|---|---|
| (Constant) | 0.68 | 2.429 | | 0.28 | 0.78 | −4.133 | 5.493 |
| Age | −0.027 | 0.009 | −0.242 | −3.116 | 0.002 | −0.044 | −0.01 |
| Education, years | 0.016 | 0.029 | 0.043 | 0.557 | 0.579 | −0.041 | 0.073 |
| Illness duration, years | −0.043 | 0.017 | −0.192 | −2.525 | 0.013 | −0.076 | −0.009 |
| BMI | 0.02 | 0.027 | 0.058 | 0.736 | 0.463 | −0.033 | 0.073 |
| CPZeq, mg | 0 | 0 | 0.06 | 0.79 | 0.431 | 0 | 0.001 |
| BPRS total | −0.001 | 0.01 | −0.005 | −0.063 | 0.95 | −0.02 | 0.019 |
| CGI S | 0.198 | 0.073 | 0.208 | 2.711 | 0.008 | 0.053 | 0.343 |
| ICV proxy | −0.006 | 0.016 | −0.028 | −0.369 | 0.713 | −0.037 | 0.026 |
| FTAI | −0.859 | 0.129 | −0.502 | −6.64 | 0 | −1.116 | −0.603 |

**Notes**: The dependent variable is the standardized composite executive function score (Exec_composite Z); negative B values indicate that higher predictor values are associated with poorer executive performance.

**Table 7** Model Fit and Incremental Effects for Multivariable Regression Models Predicting Exec_composite Z

| Model | R | R square | Adjusted R Square | SE | $\Delta R^2$ | ΔF | P for ΔF |
|---|---|---|---|---|---|---|---|
| Model 1[a] | 0.358[a] | 0.128 | 0.065 | 0.96654 | 0.128 | 2.039 | 0.048 |
| Model 2[b] | 0.614[b] | 0.378 | 0.327 | 0.82036 | 0.249 | 44.084 | 0 |

**Notes**: [a]Model 1 includes age, years of education, illness duration, BMI, CPZeq, BPRS total score, CGI-S, and ICV_proxy. [b]Model 2 adds FTAI to Model 1. $\Delta R^2$ reflects the gain in explanatory power from the added variable; ΔF evaluates its statistical significance.

# Discussion

## Summary of Main Findings

Using routine cranial CT, this study systematically evaluated frontotemporal structural alterations in patients with schizophrenia. Significant abnormalities were observed across all atrophy indices (BFR, FHW, THW_mean, SFW, and FTAI), indicating widespread structural changes in the frontal and temporal regions. Patients with SZ also demonstrated impairments across multiple cognitive domains, including global cognition, executive function, attention, memory, and processing speed.

Correlation and multivariable regression analyses showed that FTAI was significantly associated with multiple cognitive outcomes, and these associations remained after adjustment for demographic and clinical variables. These findings suggest that frontotemporal structural alterations are closely related to cognitive impairment in SZ.

Due to the cross-sectional nature of this study, these findings should be interpreted as associations rather than causal or predictive relationships, and temporal directionality cannot be established.

## Potential Neurobiological Mechanisms

The frontal and temporal lobes are among the most consistently implicated regions in schizophrenia and play key roles in executive function, attention, memory, and language processing.[19–23] Structural abnormalities in these regions, including cortical thinning, ventricular enlargement, and synaptic dysfunction, have been associated with cognitive impairment in SZ.[24,25] The observed associations between FTAI and multidomain cognitive deficits in this study are consistent with previous findings and may reflect underlying structural and network-level alterations in the frontotemporal regions. As a composite index integrating multiple structural measures, FTAI may capture broader patterns of anatomical change that are not fully represented by single metrics. However, these potential mechanisms cannot be directly inferred from the present study and require further investigation.

## Clinical Implications and Potential Applications

This study has potential clinical relevance. CT is widely available, cost-effective, and feasible in routine psychiatric settings, particularly in patients who are unable to undergo MRI. In this context, CT-derived structural indices such as FTAI may provide a practical approach for characterizing brain structural changes associated with cognitive impairment.

However, given the cross-sectional design, these findings should not be interpreted as supporting predictive or diagnostic applications. Instead, FTAI should be considered an association-based structural marker that may be useful for research and exploratory clinical assessment. Further validation in longitudinal and multicenter studies is required before any potential clinical application can be established.

## Limitations and Future Directions

This study has several limitations. First, the retrospective cross-sectional design precludes causal inference and does not allow assessment of temporal relationships between structural alterations and cognitive decline.

Second, compared with MRI, CT has lower sensitivity for detecting subtle structural changes, including cortical thickness, subcortical volumes, and white matter integrity. Its relatively lower spatial resolution may introduce measurement bias when assessing fine anatomical structures, although CT remains clinically feasible and widely accessible.

Third, although several clinical variables were adjusted for, residual confounding cannot be excluded. Important factors such as antipsychotic class, treatment duration, negative symptom severity, and socioeconomic status were not comprehensively captured.

Fourth, cognitive assessment relied on MoCA and TMT, which may not fully capture the full spectrum of schizophrenia-related cognitive deficits. More comprehensive tools, such as the MATRICS Consensus Cognitive Battery (MCCB), should be considered in future studies.

Fifth, the FTAI was constructed using an unweighted approach. Although sensitivity analysis using principal component analysis (PCA) yielded consistent results, external validation and more advanced modeling strategies are needed.

Finally, the single-center design may limit generalizability. Future studies should incorporate multicenter cohorts and integrate multimodal imaging and biological markers to further elucidate the relationship between brain structure and cognitive dysfunction in SZ.

# Conclusion

In conclusion, this study provides preliminary evidence that CT-derived frontotemporal atrophy is associated with cognitive impairment in patients with schizophrenia. These findings support the potential value of CT-based structural measures for characterizing brain changes related to cognitive dysfunction. However, given the retrospective cross-sectional design, these results should be interpreted cautiously, and further validation in longitudinal and multicenter studies is required.

# Data Sharing Statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

# Ethical Approval and Consent to Participate

The protocol was approved by the Ethics Committee of People's Hospital of Dali Bai Autonomous Prefecture (Approval No. MC20260010) and adhered strictly to the principles of the Declaration of Helsinki. As the study was retrospective and all data were fully de-identified, the requirement for written informed consent was waived. Patient privacy and data security were protected throughout the research process.

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## Disclosure

The authors declare that they have no known competing interests in this work.

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