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Structural asymmetries in the planum temporale in patients with schizophrenia: A meta-analysis

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ABSTRACT

Research on planum temporale (PT) asymmetries in schizophrenia has yielded inconsistent findings: Some studies suggest a link between atypical PT asymmetries and schizophrenia, their conclusions are often limited by low statistical power or limited representativeness, while others find no association. The PT, a region crucial for auditory and language processing, seems particularly relevant in schizophrenia because of the disorder's symptomatology regarding changes in language processing. This meta-analysis synthesizes literature on structural PT asymmetries in schizophrenia compared to controls, employing robust meta-analytical methods. Following PRISMA guidelines, we conducted a systematic search process in 2024 with the keywords (schizophrenia) OR (schizophrenic) OR (psychosis) AND (planum temporale) OR (asymmetries) OR (asymmetry) OR (laterality) on the databases PubMed, PubPsych, GoogleScholar, and ResearchGate. This search yielded 28 results with a total of $n = 1409$ participants (760 schizophrenia patients, 649 unaffected controls). Studies fulfilled the inclusion criteria: reporting of primary MRI/CT data on PT asymmetry in schizophrenia and controls; DSM/ICD schizophrenia diagnosis; sufficient PT size data for analysis and specification of measurement units, peer-reviewed and published in English, French, German, or Greek. Random effects meta-analyses revealed a significant atypical asymmetry and a significant size reduction of the left PT in patients with schizophrenia relative to controls. Further analyses did not identify any significant moderating effects. Risk of Bias assessment (following the Newcastle-Ottawa scale) revealed that most studies were of moderate to high quality with relatively low bias. The findings extend our understanding of the neurobiological underpinnings of schizophrenia.

1. Introduction

The left and right hemisphere of the human brain show several structural and functional differences, so-called hemispheric asymmetries. Hemispheric asymmetries are related to various cognitive, behavioral, and emotional processes (Hugdahl, 2011). Importantly, neuroscientific research has suggested that atypical hemispheric asymmetries might show an increased prevalence in various psychiatric disorders, including schizophrenia (Ocklenburg et al., 2024). Atypical asymmetries are defined as hemispheric asymmetries that are less common in the general population (Ocklenburg et al., 2024). For example, the typical left-hemispheric dominance for language functions observed in the general population is reduced in schizophrenia (Crow, 1997). Such atypical laterality patterns have further been found in

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certain brain areas supporting language functions, such as the planum temporale (PT) (Ocklenburg and Güntürkün, 2017). However, literature on atypical asymmetries of the PT in schizophrenia often yields inconsistent findings and has not been comprehensively summarized in a quantitative manner using meta-analytic techniques.

Different approaches and measures exist to examine differences between the two hemispheres of the brain: One approach is to obtain structural measures of asymmetry, e.g., size differences for a given brain region for the left and right hemispheres (Mundorf et al., 2021). Alternatively, research can focus on functional asymmetry which can be assessed either directly, e.g., based on activation differences between the left and right hemispheres, or inferred indirectly based on associations between different types of asymmetries. For instance, handedness, which describes both hand preference and differences in hand skill, is a behavioral index that somewhat reflects the underlying brain organization (Szaflarski et al., 2012). Indeed, hand preference gives information about the localization and processing of language in the brain: Specifically, right-handedness is associated with left-lateralized language processing, and this asymmetry is substantially reduced in non-righthandedness (Ocklenburg and Güntürkün, 2017). Importantly, non-right handedness has a higher prevalence in patients with psychiatric or neurodevelopmental disorders (Packheiser et al., 2025), such as schizophrenia (Mundorf et al., 2025), post-traumatic stress disorder (Borawski et al., 2023), or autism spectrum disorder (Markou et al., 2017), compared to unaffected controls. In addition and consistent with the above described link between handedness and language lateralization, neuroimaging studies have demonstrated atypical asymmetry patterns in schizophrenia patients compared to unaffected controls (Chance et al., 2008; Oertel et al., 2010), for example in the PT, as mentioned earlier.

The PT is an area located in the temporal lobe of the brain, which overlaps with Wernicke's area and is connected to Brodmann's area 22 (Shapleske et al., 1999). In individuals without schizophrenia, the PT is on average larger in the left hemisphere than in the right hemisphere (Ocklenburg and Güntürkün, 2017). In contrast, in schizophrenia, findings partly indicate the presence of a rightward asymmetry (Altamura et al., 2020). This atypical asymmetry is marked by a significantly larger PT surface area on the right side and a somewhat smaller area on the left side compared to unaffected individuals (Barta et al., 1997; Hasan et al., 2011). Despite the increased surface area on the right, the gray matter volume in this region is reduced, indicating substantial cortical thinning (Barta et al., 1997). This gray matter reduction of the left PT in schizophrenia patients has been found independent of age, sex, and years of education (Oertel et al., 2010). Rund has even suggested that schizophrenia can be considered as a neurodevelopmental disorder due to the nature of the atypical PT asymmetry (Rund, 2018). Nevertheless, not all findings clearly support the theory of atypical asymmetry patterns in patients with schizophrenia: Some findings underline hypoactivity in the left hemisphere (Lewis et al., 1992), while others report typical laterality patterns in the left PT which do not differ from patterns in the control group (Kulynych et al., 1995). One study revealed that the atypical asymmetry of the PT was exclusively observed in female patients, while asymmetry patterns in male patients were indistinguishable from the unaffected control group (Delvecchio et al., 2017). An evaluation of post-mortem brains showed thinning of upper cortical layers in the left hemisphere in schizophrenia patients but could not reveal any difference in whole PT volume (Smiley et al., 2009).

The PT primarily processes speech and other language functions (Preis et al., 1999), making it a key structure underlying speech-related symptoms in psychotic disorders such as the auditory hallucinations frequently observed in schizophrenia (Petty et al., 1995). Atypical asymmetries in the PT are particularly relevant in this context as research has demonstrated a connection between PT structure and the presence of positive symptoms, including auditory hallucinations (Altamura et al., 2020; Chance et al., 2008). Moreover, the degree of atypical laterality in the PT has been linked to the severity of auditory hallucinations among individuals with schizophrenia (Ratnanather et al., 2013). Kwon and colleagues further specified this relationship by associating atypical PT asymmetry with certain delusional elements such as persecution and mistrust, reporting that a reduced size of the left PT correlated with higher scores on relevant subscales of symptom questionnaires (Kwon et al., 1999).

Given that the previous findings on asymmetry in the PT in schizophrenia are somewhat conflicting and based on the apparent link between atypical asymmetries in the PT and hallucinations, it seems especially relevant to comprehensively review and integrate these findings for a more elaborate understanding of the neurobiology of the symptoms.

Another argument for the relevance of integrative research in this field lies in the ongoing replication crisis where psychological and neuroscientific research still faces critique: The results of individual published studies frequently seem to be difficult to replicate, often due to insufficient statistical power. Within this discourse, meta-analysis has emerged as a statistical tool which allows researchers to synthesize results from empirical studies on a specific topic, and to potentially offer a more comprehensive view of the evidence. This is particularly relevant to the investigation of atypical structural hemispheric asymmetries in schizophrenia, since some findings are predicted based on small sample sizes or selective and not entirely representative sample compositions (Sommer et al., 2001). Furthermore, although handedness meta-analyses have robustly shown a link between schizophrenia and atypical hemispheric asymmetries, it should be noted that handedness represents a more direct measure of behavioral lateralization when it comes to motor tasks but only represents an indirect index for brain lateralization for language (Karlsson et al., 2023). Directly assessing structural PT asymmetries using a meta-analytic approach will yield more concrete insights in this regard. Given the ambiguity of results reported earlier, meta-analytic integration seems crucial to identify robust and replicable result patterns. Moreover, meta-regression with relevant moderator variables can improve the understanding of the between-study heterogeneity (Markou et al., 2017) in research on PT asymmetries in schizophrenia. To our knowledge, there is no existing meta-analysis in which the severity of positive and negative symptoms is considered. Furthermore, meta-analytic research on structural PT asymmetries and schizophrenia has not been updated in the past years (Sommer et al., 2001). Moreover, no combination of frequentist and Bayesian statistics has been used to examine the potential PT and schizophrenia relationship. As shown in a recent large-scale meta-analysis (Packheiser et al., 2025), incorporating both frequentist and Bayesian statistical approaches can offer a more comprehensive interpretation of statistical results. Frequentist methods provide established tools for hypothesis testing and confidence interval estimation, while allowing for comparability with most published meta-analyses. Bayesian methods, in contrast, allow for the integration of prior knowledge and expectations to evaluate probabilities of different hypotheses, thereby enabling the estimation of strength of evidence of an absence of an effect, rather than merely the absence of evidence for an effect (Pek and Van Zandt, 2020).

The present work is intended to fill this gap: Using robust meta-analytic methods, data from primary studies on structural hemispheric PT asymmetries in patients with schizophrenia compared to healthy controls were included. We further examined the literature for heterogeneity and attempted to explain it through moderator variables analysis, namely through the variables: *year, age, sex ratio, classification system, symptom severity*, *instrument,* and *medication* (for further details see the 2.4 *Data extraction*). Moreover, the presence of small study bias and publication bias, as well as the quality of the individual studies were analyzed by means of Risk of Bias assessment.

We put forward the following preregistered research questions:

1) Do patients with schizophrenia show increased atypical structural asymmetries in the PT compared to controls?

2) Does the severity of positive and negative symptoms moderate the relationship between diagnosis and asymmetries in the PT?

Based on the previously mentioned research questions, the following preregistered hypotheses were examined:

H1: Patients with schizophrenia show increased atypical structural asymmetries in the PT compared to controls.

H2: Positive symptoms will have a moderating effect in the putative schizophrenia - PT asymmetry relationship.

H3: Negative symptoms will have a moderating effect in the putative schizophrenia - PT asymmetry relationship.

2. Methods

This meta-analysis followed PRSIMA guidelines (Page et al., 2021). The PRISMA 2020 Main Checklist (see Table S1) as well as the PRISMA 2020 Abstract Checklist (see Table S2) can be found in the supplementary material.

2.1. Search strategy

Literature search aimed for completeness and was performed in June 2024 via a multi-step process:

The electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov), PubPsych (https://www.pubpsych.eu), Google Scholar (first 200 results) (https://scholar.google.com), and ResearchGate (https://www.researchgate.net) were searched. The keywords used were identical on all databases: (Schizophrenia) OR (schizophrenic) OR (psychosis) AND (planum temporale) OR (asymmetries) OR (asymmetry) OR (laterality). The same standalone keywords were used on ResearchGate without applying the search term format. No other databases or automation tools were used. Reference lists of the identified meta-analyses were screened to search for more potentially fitting articles. Furthermore, the research team made efforts to obtain missing data by contacting the authors from two of the included studies via email. We did not receive any answer after two weeks and then proceeded with the analyses.

2.2. Study selection

The study selection process was performed by two independent researchers [J.B. and S.O.] with an interrater reliability score of Cohen's $K = 0.935$, indicating an almost perfect strength of agreement (Landis and Koch, 1977). Any inconsistencies were resolved through discussion in the full-text stage. An initial screening based on titles and abstracts yielded 96 potential articles, from which, after detailed reviews, 28 were included in this meta-analysis. Details about literature search are shown in Fig. 1.

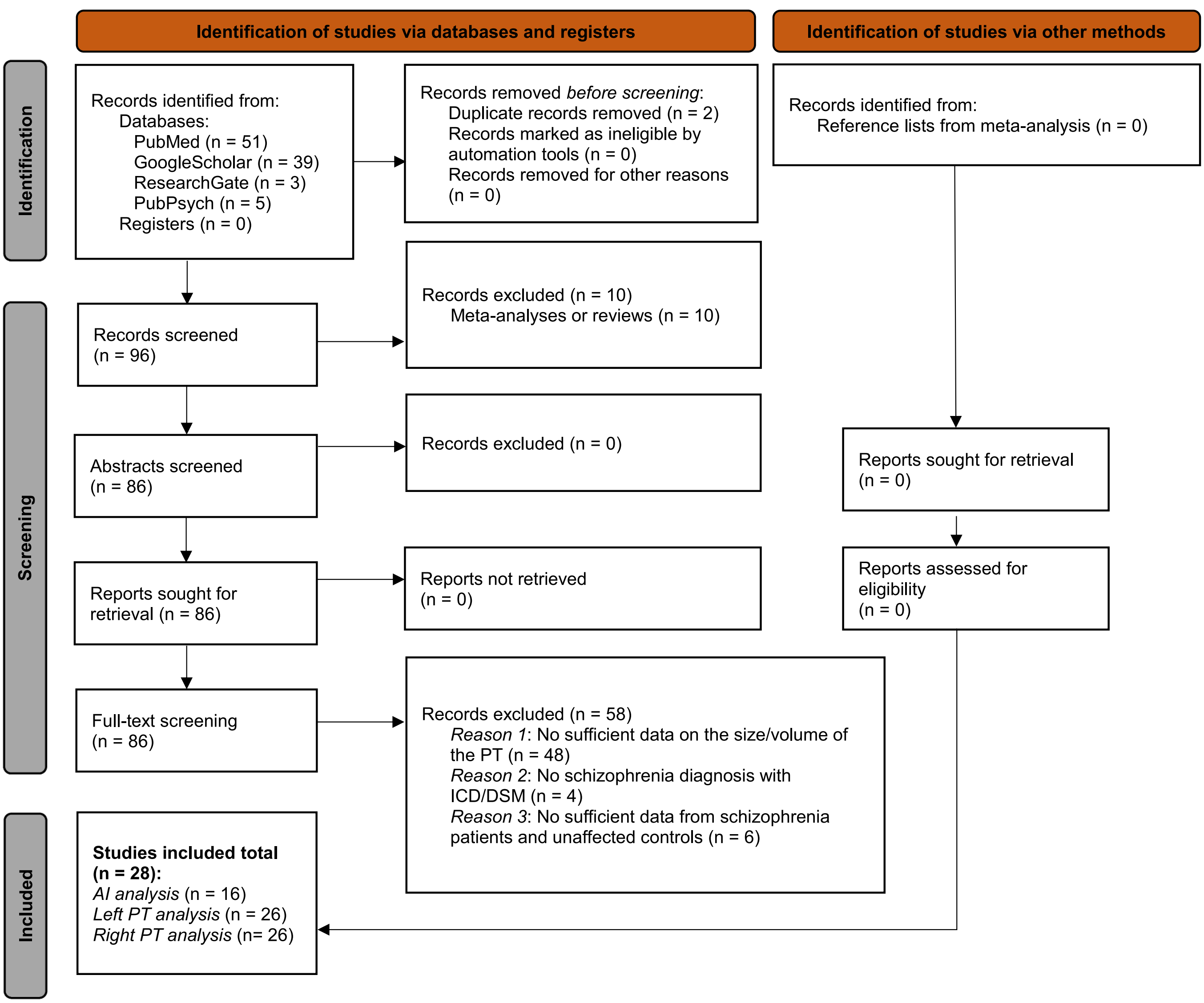

Fig. 1. Flow diagram of the search and selection process, adapted from the PRISMA flow diagram (Page et al., 2021).

2.3. Inclusion and exclusion criteria

The full texts of the studies were assessed for eligibility based on the following criteria:

1. Studies: Studies needed to include primary MRI or CT data on PT asymmetry in individuals with schizophrenia and controls. No case studies, reviews, or meta-analyses were included.
2. Participants: Patients needed to be diagnosed with schizophrenia based on DSM/ICD criteria. If studies reported mixed samples (e.g., schizophrenia and schizoaffective patient group) they were included as well but there were no further analyses regarding mixed samples and other diagnoses since we aimed at schizophrenia.
3. Sufficient data: Studies needed to report sufficient data on the size of the PT between schizophrenia patients and controls, and to have presented this data in a usable way for the analysis, or the data had to be provided by the authors. This either had to be reflected in sufficient raw data provided separately for patients and controls, or in means and standard deviations of the left and right PT provided separately for both patients and controls. The unit of measurement used in the neuroscientific data (e.g., mm^3, mm^2, mL) had to be specified in the study.
4. Publication language: Studies from peer-reviewed journals written in English, French, German, or Greek were included.
5. Studies with human subjects were integrated. Simulation data or animal studies were not included.

2.4. Data extraction

Data extraction was performed by [J.B. and S.O.] independently and any inconsistencies were resolved by discussion. Missing data were not replaced. The number of patients and unaffected controls, the means and standard deviations of the asymmetry indices, and the size of the PT were extracted. In addition, the following data were extracted to examine a potential moderating influence on the PT asymmetry and schizophrenia relationship:

- *Year.* Year of publication was examined to check for potential historical influences.
- *Age.* Literature shows a strong influence of age on the onset or emergence of the disorder (McGrath et al., 2008). We consequently integrated this factor by extracting means and standard deviations of the participants' ages from each study.
- *Sex ratio*. As the influence of sex on the development of schizophrenia is not clear (Li et al., 2022), it seemed relevant to shed light on potential sex-related differences. The sex ratio was calculated from the number of male and female participants reported in the studies. This was done since not all primary studies presented data broken down by sex.
- *Classification system*. The ICD (International Statistical Classification of Diseases and Related Health Problems) (World Health Organization, 2016) and the DSM (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association, 2013) are two different approaches in the classification of mental disorders. Although the ICD, in its latest, eleventh edition, has moved closer to the dimensional assessment system of the DSM, significant differences between the systems remain, which can also affect the assignment of a diagnosis. We extracted whether a study used a version of the ICD or DSM to diagnose the patient group.
- *Symptom severity and instrument.* As described earlier, the presence of positive symptoms in the schizophrenia spectrum is often associated with the PT (Altamura et al., 2020). The severity of the symptoms (positive and negative) was thus included in the analysis. Therefore, the type of instrument/questionnaire as well as the respective scores were extracted. The following instruments were cited across various articles: Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1986, 1989), and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). All instruments include items regarding certain aspects of positive and negative symptoms (e.g., hallucinations). To make the scores from the different questionnaires comparable, all values were converted to the PANSS scale. This conversion was carried out using an existing conversion tool(van Erp et al., 2014), which transformed the mean scores from SAPS/SANS to the PANSS scales for positive and negative symptoms. To transform the BPRS subscale scores to PANSS scores an unpublished conversion table was provided from the lab of Stefan Leucht and colleagues (provided in 2024 via personal communication) which links positive PANSS items with positive BPRS items and items from the negative PANSS subscale with items from the negative BPRS scale. We also included the type of instrument in addition to symptom severity and coded it with consecutive numbers independently of their scales or values.
- *Medication.* The inclusion of medication as a potential moderating factor seemed pertinent, as literature documents brain-related changes associated with long-term antipsychotic medication (Ho et al., 2011). The intake of antipsychotic drugs was coded in two categories: 1) All patients in the study received medication, 2) Mixed patient group in which some received medication and others did not. No article includes a patient group with no kinds of antipsychotic medication intake.

2.5. Data preparation

If a study reported results separately for sex, the data for male and female participants were extracted separately and treated as two distinct samples (Chance et al., 2008; Delvecchio et al., 2017; Falkai et al., 1995; Kleinschmidt et al., 1994). Measurements reported in cm^3 , cm^2, or mL were converted to mm^3 and mm^2. If the standard error (SE) was reported, it was converted to the standard deviation (SD) using the formula $SD = SE \times \sqrt{N}$. If articles did not provide asymmetry indices using the formula (R-L) / (R+L), these were calculated from the raw data. In the formula, R denotes the neuroimaging parameter for the right hemisphere and L denotes the neuroimaging parameter for the left hemisphere (for example volume in mm^3, surface area in mm^2, or similar measures). The analysis focused on the average AI scores across groups, rather than the differences in variance between them.

In one article (DeLisi et al., 1994), the subgroups had to be summarized by calculating pooled means following the formula $\frac{n_1 x_1 + n_2 x_2}{n_1 + n_2}$ and pooled standard deviations following the formula $\sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1+n_2}}$. For later regression analyses, the standardized mean differences (SMD) and confidence intervals of the frequentist analyses were included in the formula $\frac{(\text{upper limit} - \text{lower limit})}{3.92}$ to calculate the standard error (Higgins et al., 2019). The characteristics of each study are shown in Table 1.

2.6. Statistical analysis

All analyses were conducted in R and RStudio by two independent researchers [J.B. and S.M.] following Harrer and colleagues guide for meta-analyses (Harrer et al., 2021).

For the frequentist analyses, we used the metafor package (Viechtbauer, 2010) and calculated random effects models with SMD/Cohen's d as effect size and restricted maximum-likelihood estimator for τ^2, Hartung-Knapp adjustments, and Hedges' g for small sample size Risk of Bias correction. The asymmetry indices or left or right PT anatomical measures were used as dependent variables in these random effects models. Heterogeneity was examined using Cochran's Q test, I^2 index, and τ^2. Besides confidence intervals, prediction intervals were also calculated to show the range in which effects of future studies are expected to fall based on current evidence. Furthermore,

Table 1
Study characteristics of the integrated articles.

Study	*n* total (SCH)	Age M(SD)		Sexratio (m: (m+f))		Medi-cation	Diagnostic manual	Details on MRI method	Unit of measure	Symptom scores
		SCH	C	SCH	C					
Barta et al., (1997)	60(28)	41.57 (12.93)	44.34 (19.39)	0.75	0.719	Mixed	DSM-3-R	1.5-Tesla, manual tracing, MEASURE software	Surface	n/a
Chance et al., (2008)						All	DSM-4	(post-mortem)	Surface	n/a
Female	21(11)	71.6 (14.5)	73.2 (12.4)	0	0					
Male	17(10)	59.5 (15.8)	59.9 (11.9)	1	1					
Crespo-Facorro et al., (2004)	60(30)	33.5 (10.6)	33.7 (7.9)	1	1	All	DSM-3-R	1.5-Tesla, automated segmentation, BRAINS software	Surface	SAPS/ SANS
De Lisi et al., 1994	125(85)	26.94 (7.25)	27.1 (7.26)	0.589	0.6	n/a	DSM-3-R	1.5-Tesla, manual tracing	Surface	n/a
Delvecchio et al., (2017)						All	DSM-4-R	1.5-Tesla, manual tracing, BRAINS2 software	Volume	BPRS
Female	45(18)	40.7 (11.3)	41(10.9)	0	0					
Male	72(40)	40.5 (12.1)	40.4 (11.3)	1	1					
Falkai et al., (1995)						All	ICD-9 & DSM-3-R	(post-mortem)	Volume	n/a
Female	26(14)	58(-)	55.2(-)	0	0					
Male	22(10)	51(-)	55.3(-)	1	1					
Frangou et al., 1997	71(32)	37.5 (12.3)	33.4(12)	0.656	0.69	Mixed	DSM-3-R	1.5-Tesla, manual tracing, MEASURE software	Volume	n/a
Hasan et al., (2011)	46(20)	31.54 (7.56)	33.04 (10.53)	0.565	0.478	All	DSM-4	1.5-Tesla, manual tracing, MRIcro software	Volume	PANSS
Hirayasu et al., (2000)	42(20)	27.3 (7.0)	24.5 (4.7)	0.8	0.909	Mixed	DSM-3-R	1.5-Tesla, semi-automated segmentation, coronal protocol	Volume	n/a
Jacobsen et al., (1997)	32(16)	13.5 (2.4)	13.9 (2.1)	0.5	0.5	n/a	DSM-3-R	1.5-Tesla, manual tracing and segmentation	Surface	n/a
Kasai et al., (2003)	35(13)	27.3 (7.0)	25(4.3)	0.769	0.909	All	DSM-4	1.5-Tesla, manual tracing, 3D slicer	Volume	n/a
Kleinschmidt et al., (1994)						All	DSM-3-R	1.5-Tesla, manual tracing	Surface	SAPS/ SANS
Female	54(26)	29.7(-)	24.9(-)	0.5	0.5					
Male	54(26)	29.7(-)	24.9(-)	0.5	0.5					
Kulynych et al., (1995)	24(12)	29.5 (5.5)	25.9 (4.1)	1	1	n/a	DSM-3-R	1.5-Tesla, semi-automated segmentation, NIH Image software	Surface	n/a
Kwon et al., (1999)	32(16)	45.1 (6.5)	42.6(8)	1	1	All	DSM-4	1.5-Tesla, semi-automated segmentation	Volume	n/a
Mazánek et al., (1997)	53(38)	27.2(-)	27.1(-)	0.605	0.6	n/a	ICD (edition n/a)	1.5-Tesla, manual tracing	Surface	n/a
McCarley et al., (2002)	33(15)	27.6 (7.6)	24.9 (4.9)	0.8	0.833	Mixed	DSM-3-R	1.5-Tesla, semi-automated segmentation	n/a	n/a
Oertel et al., (2010)	31(16)	37.57 (7.84)	39.31 (10.98)	0.563	0.533	All	DSM-4	3-Tesla, manual segmentation	Volume	PANSS
Park et al., (2004)	38(17)	n/a	n/a	n/a	n/a	n/a	DSM-3-R/ DSM-4	1.5-Tesla, manual tracing	Volume	n/a
Petty et al., (1995)	28(14)	36.6 (17.2)	36.6 (15.6)	0.643	0.643	-	DSM-3-R	1.5-Tesla, manual tracing	Surface	n/a
Ratnanather et al., (2013)	58(31)	41.4 (9.5)	44(15.6)	0.548	0.444	All	DSM-4-R	1.5-Tesla, automated segmentation, ANALYZE and FreeSurfer 3.0.5 software	Surface	n/a
Rossi et al., (1992)	28(17)	31.76 (6.25)	33.54 (9.21)	0.824	0.727	All	DSM-3-R	0.5-Tesla, manual tracing, Autocad software v2.64	Surface	n/a
Rossi et al., (1994)	45(22)	30.27 (4.68)	31.52 (4.54)	0.591	0.565	All	DSM-3-R	0.5-Tesla, semi-automated, multiplanar reconstruction program	Surface	n/a
Sallet et al., (2003)	60(40)	34(8)	31.5 (10.8)	0.6	0.6	All	DSM-4	1.5-Tesla, manual tracing, Gyroview software HR 2.1	Volume	PANSS
Shapleske et al., (2001)	106(74)	34.1 (8.5)	33.5 (8.5)	1	1	All	DSM-4	1.5-Tesla, automated segmentation, ANALYZE software	Volume	SANS
Smiley et al., (2009)	37(19)	49(16)	53(17)	1	1	Mixed	DSM-4	(post mortem)	Volume	n/a
Sumich et al., (2002)	41(25)	24(4.7)	27(5.9)	1	1	All	DSM-3-R	1.5-Tesla, manual tracing	Volume	n/a
Yamasaki et al., (2007)	39(17)	29.5 (5.5)	29.1 (2.8)	1	1	All	DSM-4	1.5-Tesla, manual tracing, 3D slicer	Volume	PANSS
Yamasue et al., (2004)	32(13)	29.8 (6.1)	27.3(7)	0.538	0.684	Mixed	DSM-4	1.5-Tesla, manual tracing, 3D slicer	Volume	PANSS

Note. SCH=schizophrenia, C=control group, M(SD) = means (standard deviation), Sexratio = male: (male+female), n/a = information not available meta-regression analyses and sensitivity analyses were also performed. No multiple comparison correction was performed. Robust Bayesian meta-analyses with help of the RoBMA (Maier et al., 2023) package were used including tests for publication bias with precision-effect test and precision-effect estimate with standard errors (PET-PEESE). Due to contradictory results on PT asymmetries and schizophrenia in the literature, a conservative prior of zero was initially chosen for Robust Bayesian meta-analyses.

The interpretation of the Bayesian results follows a scale of evidential strength (Jeffreys and Jeffreys, 1998):

- Bayes factor (BF_{10}) of 0.10–0.33: Moderate evidence for the null hypothesis
- BF_{10} of 0.33–1: Anecdotal evidence for the null hypothesis
- BF_{10} of 1: No evidence
- BF_{10} of 1–3: Anecdotal evidence for the alternative hypothesis
- BF_{10} of 3–10: Moderate evidence for the alternative hypothesis

2.7. Risk of bias assessment

In accordance with the current PRISMA guidelines (Page et al., 2021), a Risk of Bias Assessment was also performed to evaluate the primary studies as transparently and precisely as possible. To this end, the Newcastle-Ottawa Scale (Wells et al., 2000) was used by two independent researchers [J.B. and S.M] with an interrater reliability score of Cohen's $K = 0.732$. Disagreements were resolved by discussion. The interpretation of assessment follows the cut offs: 0–3 indicating low study quality, 4–6 moderate and 7–9 high quality.

2.8. Pre-registration and data availability

To transparently present this research, the project was preregistered in the Open Science Framework (https://osf.io/th564/?view_only=2c208a293afa4b33bf36f8075cc2cd4f) in July 2024. All data and R Codes were uploaded to the Open Science Framework as well, shortly before submission in July 2025.

2.9. Deviations from pre-registration

It seemed relevant to consider not only the asymmetry index, but also which hemisphere might be driving the asymmetry. For this reason, in addition to the preregistered analysis of the PT asymmetry indices in patients with schizophrenia and controls, we added two further hemisphere-specific analyses. Furthermore, antipsychotic medication was considered as a potential moderating factor of the putative PT and schizophrenia relationship. Since the studies only reported PT data obtained from MRI, no comparison between MRI and CT could be performed. In addition, three post-mortem studies were integrated which provided sufficient data on the PT in schizophrenia patients compared controls, which has not been part of the pre-registration. Moreover, we preregistered leave-one-out analyses to check for sensitivity, but in the end performed data-driven sensitivity checks based on the Risk of Bias analyses, as this seemed to be more informative for the purpose of this project.

3. Results

The multi-step literature search process, performed independently by two researchers [J.B. and S.O.] resulted in the identification of 28 eligible studies (and 32 samples as a result of four studies that reported data separately for males and females and were consequently rated as two distinct samples, see Methods section for this). These studies were published over a span of 25 years, from 1992 to 2017. In summary, the 28 studies included a total number of $n = 1409$ participants, with 760 individuals diagnosed with schizophrenia and 649 unaffected control subjects. In twelve studies, the PT was assessed using surface area, while fifteen reported volume measurements and one study did not specify the unit used (see Table 1). The detailed results of each individual analysis are presented below:

3.1. Hypothesis 1

For testing the first hypothesis, the asymmetry index (AI) was examined. In 16 articles and 19 samples (due to sex separated data as mentioned above), the AI could either be extracted or calculated. We used a random-effects model with the effect size Cohen's *d*, including 19 samples and an overall of $n = 840$ participants (459 schizophrenia patients and 381 controls), resulting in a SMD of 0.38 between schizophrenia patients and controls [95 % CI: 0.03;0.73] (95 % prediction interval: −0.98;1.74). Controls had an overall mean of −0.117 (SD = 0.2915) and patients a mean of 0.09 (SD = 0.3872). The model reached significance ($p = 0.03$), indicating a weaker leftward asymmetry of the PT in patients with schizophrenia compared to controls (see Fig. 2).

With an I^2 index of 77.3 % [95 % CI: 64.9 %;85.3 %], $\tau^2 = 0.3911$ [95 % CI: 0.1757;1.0366], and $Q(18) = 79.20$, $p = 0.0001$, heterogeneity and inconsistency between studies can be considered high. Robust Bayesian analysis with a prior of zero suggested anecdotal evidence for no difference in the asymmetry index of patients with schizophrenia compared to controls ($BF_{10} = 0.793$), and anecdotal evidence for the presence of publication bias ($BF_{10} = 1.409$). Since the results of the Bayes Analysis were in contradiction with the frequentist meta, we performed robustness analyses by including wider priors. This resulted in evidence in favor of the alternative hypothesis (prior = 0.3, BF_{10} =1.960; prior 0.5, $BF_{10} = 1.659$; prior = 0.707, $BF_{10} = 1.368$). To test for small study bias, we conducted funnel plots and Egger's *t* test. This assessment showed no significant funnel plot asymmetry for the AI analysis ($t(17) = 1.88$; $p = 0.776$) (see Fig. 3).

3.2. Hypothesis 2 and 3

To test if positive or negative symptoms influence the PT asymmetry and schizophrenia relationship or might explain the high-heterogeneity scores, multiple meta-regressions were performed separately (for AI, left PT and right PT with the predictors positive symptoms, negative symptoms, and symptom scale). It should be noted that of the total of 28 studies, only 15 mentioned the assessment of symptomatology and only 9 articles provided the exact scores for positive and negative symptoms. Three studies used SAPS/SANS (Crespo-Facorro et al., 2004; Kleinschmidt et al., 1994; Shapleske et al., 2001), one study used BPRS (Delvecchio et al., 2017), and five used PANSS (Hasan et al., 2011; Oertel et al., 2010; Sallet et al., 2003; Yamasaki et al., 2007; Yamasue et al., 2004) to assess symptomatology. Throughout the analyses, both symptom predictors showed only low R^2 scores and all models failed to reach significance (see Table 2).

3.3. Exploratory analyses

For the left PT, the random-effects model, shown in Fig. 4, was calculated using $k = 26$ studies with a total of 29 samples and $n = 1319$ participants (717 schizophrenia patients and 602 controls). The results show a SMD of −0.45 [95 % CI: −0.68;-0.21], (95 % prediction interval: −1.44;0.55), and the model reached significance ($p = 0.0005$), which demonstrates that the size of the left PT in patients with schizophrenia is significantly smaller compared to controls.

This result is partly supported by anecdotal evidence ($BF_{10} = 0.616$) for the presence of this effect in Bayes analysis with a prior of zero. As the results of the frequentist and the Bayes analyses were in line, we did not perform additional robustness checks. Again, there was high heterogeneity and between studies inconsistency with an I^2 index of 66.3 % [95 % CI: 50.3 %;77.2 %], $\tau^2 = 0.2243$ [95 % CI: 0.1154;0.6411] and $Q(28) = 83.19$, $p = 0.0001$, and moderate evidence for publication bias ($BF_{10} = 4.952$). The assessment of small study bias showed a statistically

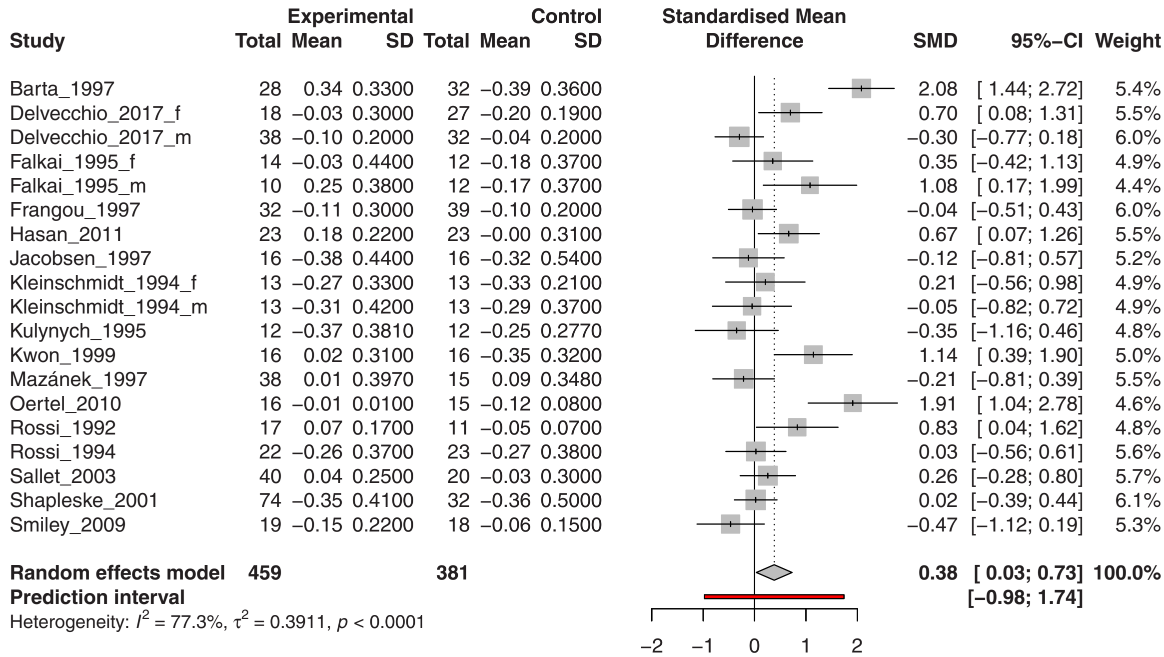

Fig. 2. Forest plot for the asymmetry index analysis.

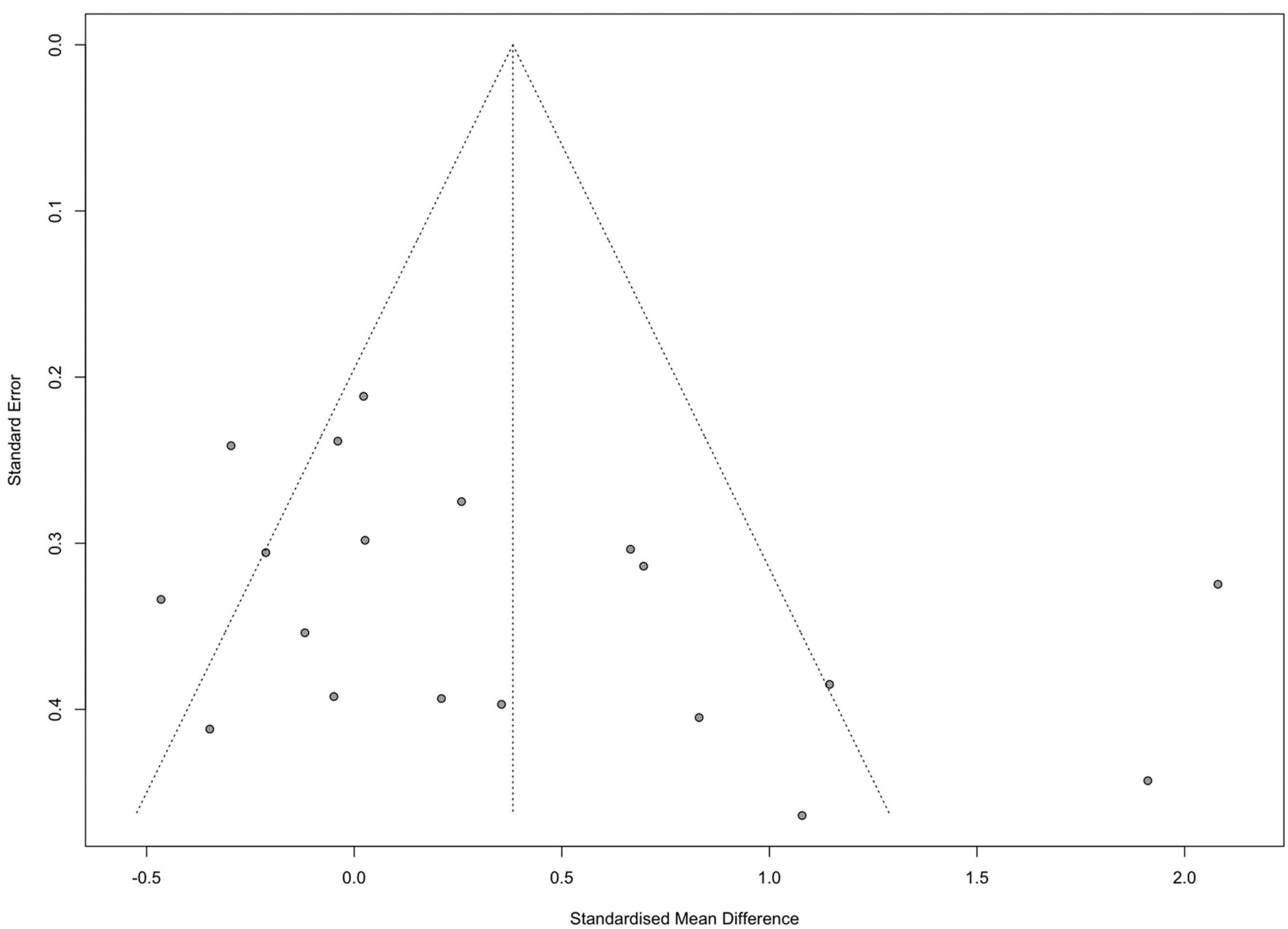

Fig. 3. Funnel plot for the asymmetry index analysis.

Table 2
Detailed results of meta-regression analyses.

Moderators	*Age*	*Year*	*Sexratio*	Classification system	*Positive symptoms*	Negative symptoms	Symptom scale	Unit of measurement	*Medication*
Asymmetry Index Analysis									
R^2 coefficent	21.18 %	0.00 %	26.12 %	4.20 %	2.17 %,	0.66 %	11.46 %	0.00 %,	0.83 %
p-value	0.22	0.95	0.21	0.41	0.58	0.62	0.38	0.79	0.80
Left PT Analysis									
R^2 coefficent	5 %	0.01 %	21.43 %	7.27 %,	2.08 %	0.05 %	1.36 %	18.92 %	0.15 %
p-value	0.69	0.76	0.25	0.35	0.76	0.84	0.66	0.06	0.97
Right PT Analysis									
R^2 coefficent	0.51 %	8.73 %	0.15 %	0.46 %	10.67 %	10.01 %	17.06 %	13.12 %	14.53 %
p-value	0.82	0.16	0.99	0.75	0.40	0.40	0.16	0.08	0.08

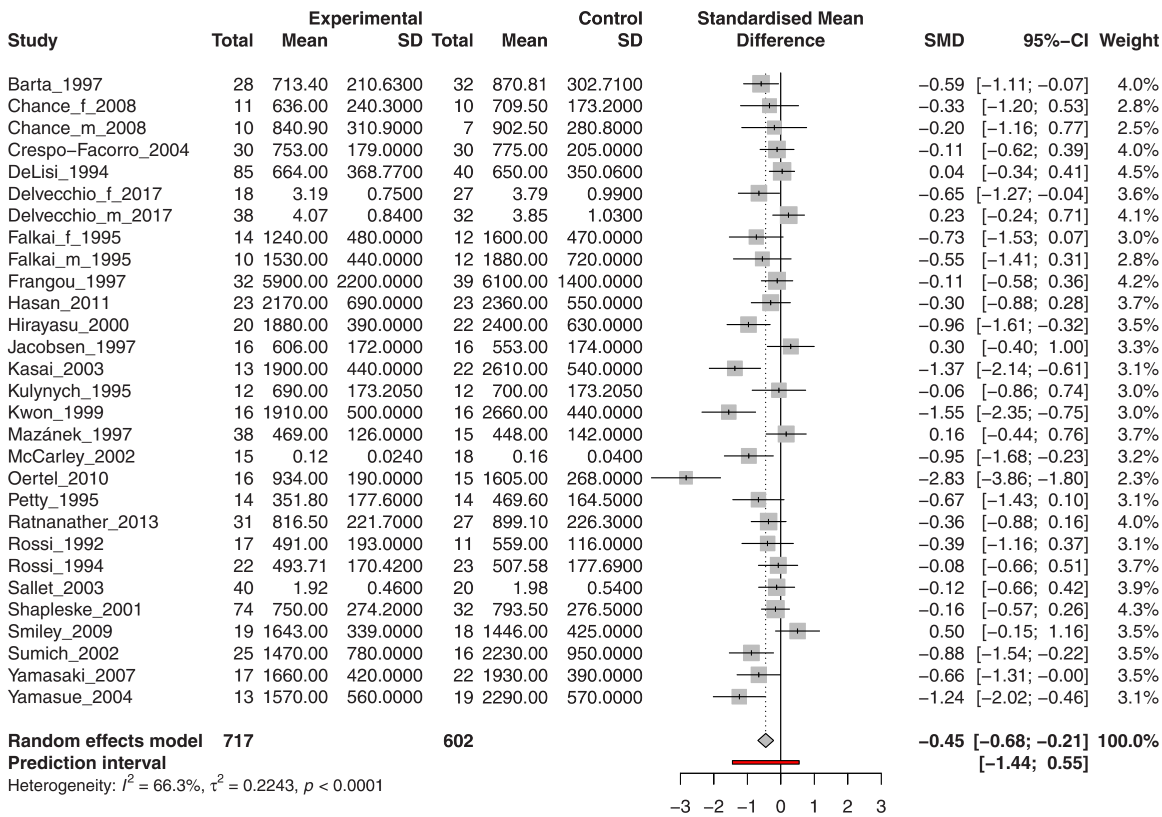

Fig. 4. Forest plot for the left planum temporale analysis.

significant funnel plot asymmetry, as presented in Fig. 5 ($t(27) = -3.62$; $p = 0.0012$), indicating potential publication bias among the integrated studies for this analysis.

Similar to the left PT analysis, the random-effects model for the right PT included $k = 26$ studies with an overall of 29 samples and $n = 1319$ participants (717 schizophrenia patients and 602 controls) resulting in a SMD of 0.07 [95 % CI: −0.10;0.24] (95 % prediction interval: −0.55;0.69). The model did not reach significance ($p = 0.409$), therefore the size of the right PT in patients with schizophrenia is not significantly larger compared to the non-patient group. The results are shown in Fig. 6. Heterogeneity and inconsistency between the studies can be interpreted as high with an I^2 index of 47.2 % [95 % CI: 18.4 %;65.8 %], $\tau^2 = 0.0864$ [95 % CI: 0.02;0.2747], and $Q(28) = 53$, $p = 0.0029$.

Compatible to the frequentist analysis, Robust Bayesian meta-analysis showed moderate evidence for the null hypothesis ($BF_{10} = 0.117$), indicating comparable size of the right PT in patients with schizophrenia and unaffected controls. As the results of the frequentist and the Bayes analyses were in line, we did not perform additional robustness checks. Bias analyses showed moderate evidence against publication bias ($BF_{10} = 0.278$). The review for small study bias revealed no evidence of funnel plot asymmetry for the right PT analysis ($t(27) = -0.11$; $p = 0.9132$) (see Fig. 7).

3.4. Analyses of further moderator variables

Further multiple meta-regressions were performed (for AI, left PT and right PT) including the additional predictors age, sex ratio, classification system, unit of measurement, year, and medication. Predictors showed low R^2 scores again and all models failed to reach significance (see Table 2).

3.5. Risk of bias assessment

The Risk of Bias assessment (Wells et al., 2000) of the individual articles is shown in detail in Fig. 8. Twelve articles had high quality with a total score between seven and nine stars (Barta et al., 1997; Crespo-Facorro et al., 2004; DeLisi et al., 1994; Delvecchio et al., 2017; Falkai et al., 1995; Jacobsen et al., 1997; Kwon et al., 1999; Oertel et al.,

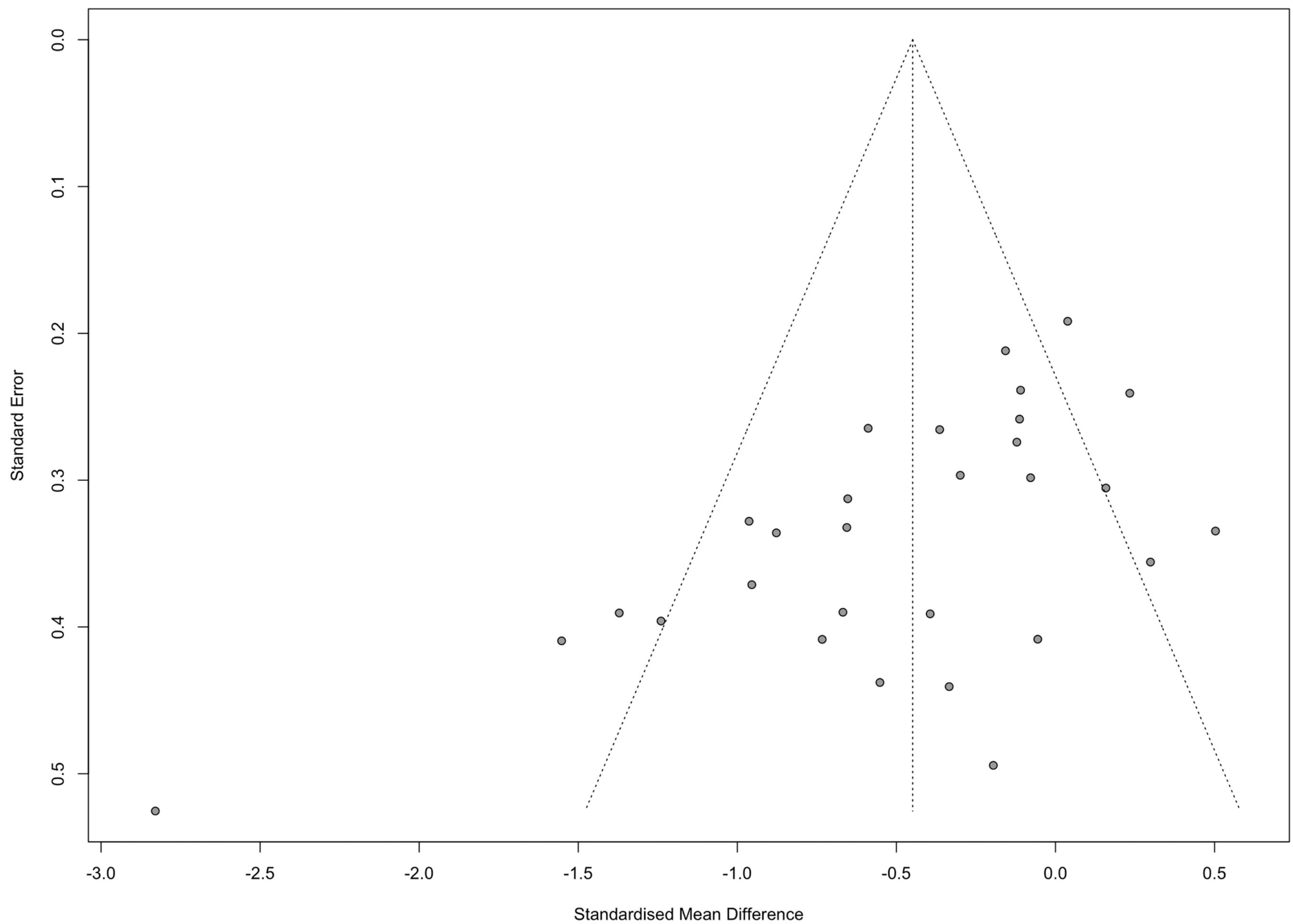

Fig. 5. Funnel plot for the left planum temporale analysis.

2010; Petty et al., 1995; Shapleske et al., 2001; Sumich et al., 2002; Yamasaki et al., 2007), 14 studies showed moderate quality with a sum score between four and six stars (Frangou et al., 1997; Hasan et al., 2011; Hirayasu et al., 2000; Kasai et al., 2003; Kleinschmidt et al., 1994; Kulynych et al., 1995; Mazánek et al., 1997; McCarley et al., 2002; Park et al., 2004; Rossi et al., 1992, 1994; Sallet et al., 2003; Smiley et al., 2009; Yamasue et al., 2004), and two showed low quality with a score between zero to three (Chance et al., 2008; Ratnanather et al., 2013). This indicates that the majority of articles reached a moderate to high quality and potential bias is relatively low.

3.6. Sensitivity analyses

When only studies of high quality ($n = 12$) were included in the frequentist analyses, the results for the asymmetry index (SMD= 0.38 [95 % CI: 0.03;0.73], (95 % prediction interval: −0.98; 1.74), $p = 0.033$)), and the left PT (SMD= −0.56 [95 % CI: −0.99;-0.13], (95 % prediction interval: −1.93;0.82), $p = 0.0145$)) were consistent with the result interpretations of the overall analyses reported earlier. In contrast, no significant effect was found when only high-quality studies were included in the right PT analysis (SMD= −0.02 [95 % CI: −0.37;0.34], (95 % prediction interval: −1.14;1.11), $p = 0.9273$)). The results did not differ from the overall analyses when studies with high and medium quality were included either.

4. Discussion

This meta-analysis aimed to quantitatively summarize the existing literature on the relationship between structural PT asymmetries in patients with schizophrenia compared to controls, and to further examine the influence of moderating factors, such as positive and negative symptoms. Three frequentist and additional Bayesian analyses were conducted to investigate the relationship between schizophrenia and the asymmetry indices of the PT, as well as the size of the left and right PT.

Our first hypothesis, that patients with schizophrenia show increased atypical structural asymmetries in the PT compared to controls, was confirmed. Frequentist analyses revealed significantly weaker leftward PT asymmetry in patients with schizophrenia compared to controls. In an exploratory analysis, we found a significantly smaller left PT size in schizophrenia patients compared to controls. The findings of the right PT analysis did not reach significance. Since the PT is closely linked to language, such an atypical asymmetry could lead to disturbances in language processing and therefore might explain the development of schizophrenia associated symptoms such as auditory hallucinations (Hugdahl et al., 2007). Furthermore, these findings overlap with results from a previous meta-analysis (Sommer et al., 2001) which also highlight a strong relationship between atypical hemispheric asymmetries and schizophrenia.

The results of the Robust Bayesian meta-analyses, when using a prior of zero, similarly supported the frequentist findings in the left and right PT analyses. However, regarding the asymmetry index, the Bayesian analysis provided anecdotal evidence towards the null hypothesis, suggesting that the significant result of the frequentist meta-analysis may not be robust. When applying wider priors, the results of Bayesian analyses approached the result found by the frequentist

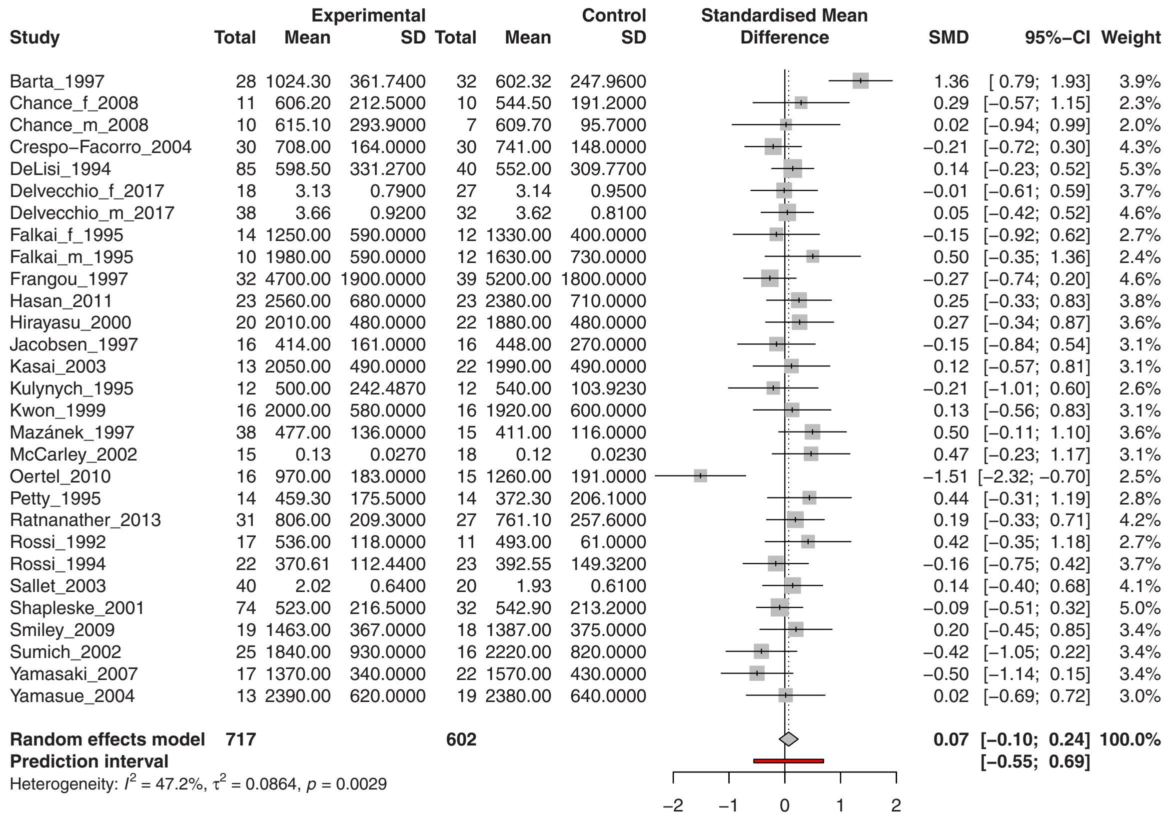

Fig. 6. Forest plot for the right planum temporale analysis.

analysis in favor of the alternative hypothesis.

As some articles have emphasized the relevance of symptom severity on changes in brain structures(Angrilli et al., 2009; Sommer et al., 2001), the possible role of the severity of positive and negative symptoms on PT asymmetry was also examined (Hypotheses 2 and 3 respectively). Due to the low ($n = 9$) number of studies that collected and reported complete data on symptomatology (Crespo-Facorro et al., 2004; Delvecchio et al., 2017; Hasan et al., 2011; Kleinschmidt et al., 1994; Oertel et al., 2010; Sallet et al., 2003; Shapleske et al., 2001; Yamasaki et al., 2007; Yamasue et al., 2004), the performed regression analyses were statistically underpowered. This could explain why it did not yield statistically significant effects. It should be mentioned that three articles (Chance et al., 2008; Falkai et al., 1995; Smiley et al., 2009) were based on post-mortem investigations and therefore could not provide information about current symptom severity. With these limitations in mind, the present results currently do not support a link between (positive/negative) symptom severity and PT asymmetry in schizophrenia.

Similarly, our findings regarding age, sex ratio, classification system, unit of measurement, year, and medication as moderator variables do not support clear links with PT asymmetry in patients with schizophrenia.

In the Risk of Bias assessment, the majority of studies ($n = 26$) were rated as moderate to high quality, with only two studies categorized as low quality. This distribution, favoring high-quality studies, might serve as an explanation for the results of the sensitivity analysis: When the two low-quality studies were excluded, the effects remained unchanged. This can be attributed to the strong influence of the large number of high-quality studies on the overall outcome.

4.1. Limitations and future directions

A major conceptual limitation of the present meta-analysis is that PT asymmetries may not represent the only relevant form of structural asymmetry within the temporal lobe or in other regions potentially implicated in schizophrenia. Research shows that auditory hallucinations are also linked to alterations over the left superior temporal and left temporoparietal as well as right prefrontal regions (Gaser et al., 2004). These alterations are at times reflected in grey matter volume reductions in the left superior (transverse) temporal gyrus, the left middle frontal gyrus, and the right cuneus (Neckelmann et al., 2006). This substantial loss of grey matter volume may contribute to spontaneous neuronal activity, leading to speech-perception experiences in the absence of external auditory input and thereby contributing to hallucinations (Neckelmann et al., 2006).

More specifically, structural atypicalities in Heschl's gyrus, a brain area located closely to the PT, were reported in primary (Gaser et al., 2004; Nenadic et al., 2010), as well as meta-analytic investigations (Modinos et al., 2013) on schizophrenia patients. These structural brain changes have frequently been associated with the occurrence of strong auditory hallucinations: For instance, patients experiencing auditory hallucinations showed reduced cortical thickness in the left Heschl's gyrus (Mørch-Johnsen et al., 2017). These findings highlight the importance of investigating brain regions adjacent to the PT, which are functionally interconnected with the PT, as they may also exhibit asymmetrical structures relevant for understanding structural alterations associated with the symptomatology of schizophrenia.

Future research should aim for a brain-wide perspective including asymmetries in adjacent areas, as soon as enough primary studies have been published to allow conducting robust meta-analytical models and to adopt a more network-oriented, interregional perspective on brain asymmetries in schizophrenia (van Tol et al., 2014). Moreover, it could be valuable to incorporate specific schizophrenia symptoms, such as hallucinations, directly into key search terms to capture broader, brain-wide differences rather than limiting investigations to specific brain areas.

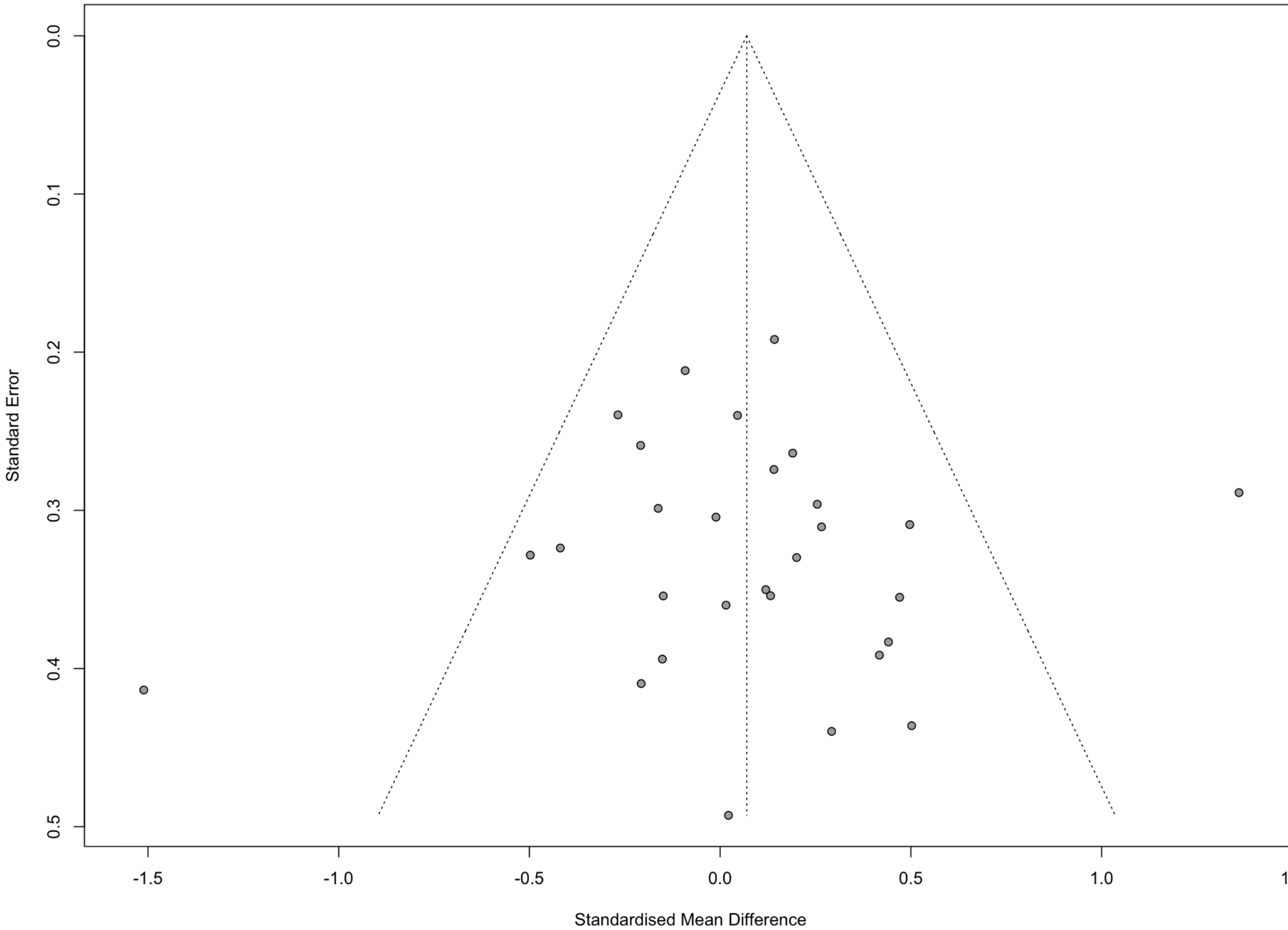

Fig. 7. Funnel plot for the right planum temporale analysis.

In addition to the conceptual limitations, several methodological limitations should also be taken into account: As previously mentioned, the various analyses are based on differing numbers of usable studies drawn from the overall pool of 28 studies. Due to incomplete data on the AI, left and/or right PT in some articles, only 16 studies could be included in the AI analysis, 26 studies were available for the (exploratory) left PT analysis and 26 for the (exploratory) right PT analysis. Consequently, none of the analyses incorporated all 28 studies which represents a limitation of the study. It seems important to note that the absence of asymmetry indices in several studies reduced the statistical power for testing the primary hypothesis (H1) of this study. Moreover, we did not perform a comparison of the left and right PT with group interaction tests of schizophrenia patients and controls by PT size. The results of the left and right PT analyses can therefore only be interpreted independently and not in relation or comparison to each other.

While integrating frequentist and Bayesian approaches can offer a more comprehensive understanding of statistical inference, this integration can also be criticized. One key criticism lies in the foundational differences between the two approaches: Frequentist results rely strongly on sample size, whereas Bayesian analyses are dependent on the choice of prior distributions and the incorporation of prior knowledge. While frequentist statistics emphasize objectivity through sampling theory, Bayesian methods rely on subjectivity via prior assumptions. Moreover, the requirement for prior knowledge in Bayesian analysis can be particularly problematic when such knowledge is uncertain. In such cases, analysts may face the issue of competing priors, where different priors lead to different posterior conclusions. This can challenge objectivity or reproducibility of the results (Goligher and Harhay, 2024). Future research should focus on developing frameworks and guidelines for combining Bayesian and frequentist methods ensuring methodological coherence and to improve transparency in the handling of priors.

Additionally, and due to the significant funnel plot asymmetry of the left PT analysis, it seems possible that the results might be biased. Nevertheless, it can be speculated whether this funnel plot asymmetry can also be attributed to methodological deficits, since a significant funnel plot asymmetry was only found for the left PT, although the left and right PT analyses were based on the same studies.

The high heterogeneity scores and the potential moderating influences of positive and negative symptoms could not be explained by the moderator analyses. However, the low number of included studies has to be considered. While, to our knowledge, there are no established guidelines regarding the minimum number of articles required for such analyses, the limited number of studies reporting complete data on symptomatology has reduced the representativeness and statistical power of the associated analyses. Despite the non-significant results of the moderator analyses, a previous meta-analysis underlines that schizophrenia-related symptoms and especially the severity of auditory-verbal hallucinations might explain the degree of language lateralization (Sommer et al., 2001) and should therefore be further examined in future research.

All data were acquired using MRI, and the studies showed no variation in this regard, so the influence of the specific neuroimaging technique could not be considered in further analyses. In the future, it could be relevant to examine the link between PT and schizophrenia by means of other neuroscientific methods (such as CT or DTI). Moreover,

Risk of Bias Assessment following the Newcastle - Ottawa Scale

Study	Selection				Comparability	Exposure			Total (9/9)
	Adequate case definition	Representa-tiveness of cases	Selection of controls	Definition of controls	Of cases and controls on the basis of design/analysis	Ascertain-ment of exposure	Same for cases and controls	Non-response rate	
Barta et al.	*	*	*	*	**	*	*	-	(8/9)
Chance et al.	-	-	-	*	-	*	-	-	(2/9)
Crespo-Facorro et al.	*	*	*	*	**	*	*	-	(8/9)
De Lisi et al.	*	*	*	*	**	*	*	-	(8/9)
Delvecchio et al.	*	*	*	*	**	*	*	-	(8/9)
Falkai et al.	*	*	*	*	**	*	*	-	(8/9)
Frangou et al.	*	*	*	*	-	*	*	-	(6/9)
Hasan et al.	*	*	*	-	-	*	-	-	(4/9)
Hirayasu et al.	*	-	*	*	-	*	*	-	(5/9)
Jacobsen et al.	*	*	*	*	**	*	*	-	(8/9)
Kasai et al.	*	-	*	*	-	*	*	-	(5/9)
Kleinschmidt et al.	*	*	*	*	*	*	-	-	(6/9)
Kulynych et al.	*	-	*	*	*	*	-	-	(5/9)
Kwon et al.	*	*	*	*	**	*	*	-	(8/9)
Mazánek et al.	*	*	*	-	-	*	*	-	(5/9)
McCareley et al.	*	-	*	*	-	*	*	-	(5/9)
Oertel et al.	*	*	*	*	**	*	*	-	(8/9)
Park et al.	*	-	-	*	**	*	*	-	(6/9)
Petty et al.	*	*	-	*	**	*	*	-	(7/9)
Ratnanather et al.	*	-	-	-	-	*	-	-	(2/9)
Rossi et al. (I)	*	*	*	-	**	*	-	-	(6/9)
Rossi et al. (II)	*	-	*	-	**	*	-	-	(5/9)
Sallet et al.	*	-	*	-	**	*	*	-	(6/9)
Shapleske et al.	*	*	*	*	**	*	-	-	(7/9)
Smiley et al.	*	*	*	-	*	*	*	-	(6/9)
Sumich et al.	*	*	*	*	**	*	*	-	(8/9)
Yamasaki et al.	*	*	*	*	**	*	-	-	(7/9)
Yamasue et al.	*	*	-	*	**	*	-	-	(6/9)

Fig. 8. Risk of Bias Assessment following the Newcastle-Ottawa Scale (Wells et al., 2000). Notes. "*" denotes the fulfillment of criteria; "-" denotes unclear information about the criteria or not fulfilling the criteria.

the measurements in which the sizes of the PT were reported were summarized to comparable units (mm^2 or mm^3). No comparisons of these two units of measurement were considered, as the number of articles was also insufficient for robust analyses. Literature has emphasized methodological differences between cortical surface area or volume when it comes to hemispheric asymmetries (Hasan et al., 2011; Oertel et al., 2010). Since we did not differentiate between these two measures, future investigations should take these different measures of brain structure into account.

Sex was examined using sex ratios because only four articles reported data separately for sex which is not sufficient for robust analyses. Future research should integrate sex-stratified data to allow for a more precise understanding of the impact of sex. Furthermore, the results of the regression analysis of medication intake could not provide any explanation for the high heterogeneity scores, which can likely be ascribed to the fact that in almost all samples, patients received antipsychotic medication and thus a comprehensive comparison between medication and non-medication was not possible. Future research should include comparisons between schizophrenia patients with no antipsychotic medication and patients who receive such medication, given that long-term antipsychotic medication seems to influence certain brain structures (Ho et al., 2011). Since the included articles did not sufficiently give information on the duration of the disorder (e.g., first-episode/chronic), the state of the disorder (e.g., acute episode/remission) and the specific class or dose of the antipsychotic medication these aspects could not be integrated in the analyses and could be meaningful to integrate in future examinations. Moreover, future research could explore other schizophrenia-associated symptoms, such as formal thought disorder, that were beyond the scope of the present study.

Additionally, the included data were exclusively comprised of sources from peer-reviewed journals, thus any grey literature was not considered. For future research, authors should provide openly shared data from pre-registered studies, thereby enhancing transparency and enabling comprehensive multi-level meta-analyses.

5. Conclusion

This meta-analysis provides evidence for reduced leftward PT asymmetry and a reduced size

of the left PT in schizophrenia patients compared to unaffected controls. These findings could

be linked to language processing disturbances in schizophrenia. The impact of symptom

severity and antipsychotic medication on PT asymmetries remains unclear. It also remains

unclear if schizophrenia is favored by structural PT asymmetry, or if schizophrenia-related

symptoms might influence the neuroplasticity in this area. Nevertheless, the

present insights highlight the potential relevance of atypical hemispheric asymmetries in understanding the neurobiological underpinnings of schizophrenia.

Author contributions

Concept and design: J.B., S.O. and M.P.P., Data acquisition and literature search: J.B. and S.O., Data extraction: J.B. and S.O., Analysis and Interpretation of the data: J.B., S.O., Further analyses and R Code for OSF: S.M., Writing original draft: J.B., Revision of the manuscript: J.B., S.O., M.P.P., J.P., S.M.

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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.neubiorev.2025.106536.

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