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Positive symptoms associate with cortical thinning in the superior temporal gyrus via the ENIGMA-Schizophrenia consortium

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Abstract

Objective—Based on the role of the superior temporal gyrus (STG) in auditory processing, language comprehension and self-monitoring, this study aimed to investigate the relationship between STG cortical thickness and positive symptom severity in schizophrenia.

Method—This prospective meta-analysis includes data from 1,987 individuals with schizophrenia collected at seventeen centers around the world that contribute to the ENIGMA Schizophrenia Working Group. STG thickness measures were extracted from T1-weighted brain scans using FreeSurfer. The study performed a meta-analysis of effect sizes across sites generated by a model predicting left or right STG thickness with a positive symptom severity score (harmonized SAPS or PANSS positive scores), while controlling for age, sex, and site. Secondary models investigated relationships between antipsychotic medication, duration of illness, overall illness severity, handedness and STG thickness.

Results—Positive symptom severity was negatively related to STG thickness in both hemispheres (left: β_{std}=−0.052; p=0.021; right: β_{std}=−0.073; p=0.001) when statistically controlling for age, sex and site. This effect remained stable in models including duration of illness, antipsychotic medication or handedness.

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Declaration of interest

The authors of this manuscript have no financial conflicts of interest to disclose.

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Conclusion—Our findings further underline the important role of the STG in hallmark symptoms in schizophrenia. These findings can assist in advancing insight into symptom-relevant pathophysiological mechanisms in schizophrenia.

Keywords

schizophrenia; positive symptoms; superior temporal gyrus; cortical thickness; ENIGMA; FreeSurfer; MRI; SAPS; PANSS

Introduction

Schizophrenia is a heterogeneous disorder with a wide range of symptoms that vary over time and across patients. This large degree of variability hinders research on the underlying etiological factors and biological correlates. So, rather than investigating broad diagnostic categories, progress may also be made by studying distinct and continuous symptom dimensions of the disorder.

Positive symptoms in schizophrenia refer to disturbances of thought and perception that are very uncommon in a healthy person and might lead to unusual behaviors. Hallmark features include hallucinations, delusions, and thought disturbances [1], which can cause substantial distress and disruption of functioning in patients. Premorbid signs of positive symptoms, including neuromotor abnormalities during childhood and adolescence, have been found to be a significant risk factor for the development of schizophrenia [2]. Furthermore, duration of untreated psychosis is one of the strongest predictor for poor functional outcome [3,4], and while antipsychotic treatment tends to reduce positive symptoms severity, 20 – 30% of patients do not respond to pharmacotherapy [5]. Investigating the brain-based correlates of positive symptoms (such as cortical thickness) may increase our understanding of symptom-related pathophysiological processes in schizophrenia.

Cortical thickness deficits in patients with schizophrenia have been reported in a number of studies [6–8]. While deficits were observed across the entire cortex, temporal and frontal regions seemed to be most prominently affected [9–11]. Some studies suggest that deficits in temporal regions are associated with poor cognitive functioning [12], while deficits in frontal regions are associated with more severe negative symptoms [13,14]. However, little is known about the link between cortical thickness and positive symptom severity in schizophrenia.

The superior temporal gyrus (STG) includes key brain areas linked to auditory processing [15] and is part of a wider temporal-frontal-parietal network that is involved in language production, interpretation and self-monitoring [16,17]. Aberrant neural activity in the STG has been repeatedly associated with positive symptoms such as (mostly auditory) hallucinations and thought disturbances. A recent fMRI study [18] reported increased activity in the left medial *planum temporale* in patients with verbal auditory hallucinations, in line with findings from a related meta-analysis [19]. Another similar meta-analysis [20] differentiated between state- and trait-based studies (i.e. comparing periods of presence and absence of hallucinations within subjects vs comparing patients with hallucination to those without hallucination or to healthy controls). The authors observed converging evidence for

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the STG only in trait studies pointing to more permanent (and possibly structural) alteration in activity of the temporal cortex in hallucinating patients. In an fMRI study of verbal fluency, neural activity in bilateral superior temporal lobules was greater in patients with acute psychosis compared to patients in remission [21], further supporting the role of the STG in language disturbances and positive symptoms in schizophrenia.

In addition to these functional findings, numerous MRI studies also reported deficits in STG structure in patients with schizophrenia. A meta-analysis of volumetric alterations in schizophrenia found the left superior and medial temporal gyrus to be most consistently reduced in patients, although the link to symptoms was not investigated in that work [9]. Similar findings were reported in a volumetric meta-analysis [22], in which STG volume reductions were found to relate to various positive symptom dimensions such as hallucinations, thought disturbances and delusions. Related structural alterations such as cortical thinning and gray matter concentration reductions of the STG in patients have also been reported [10,11]. Interestingly, some studies investigated STG sub-regions and found that structural abnormalities in the STG of patients might be specific to the lateral aspect of the STG and the planum temporale, a region in which differences were even specific to patients with schizophrenia compared to those with bipolar disorder [23–25].

Building on the observed associations between neural activity and volume alterations in the STG [22] and aspects of positive symptoms, this study investigates the relationship between cortical thickness and positive symptoms. Few studies so far researched the link between STG thickness and positive symptoms. While non-significant correlations of thickness with positive symptoms have been reported in two small studies [26,27], a study by Padmanabhan et al. [28] observed that PANSS positive symptoms were negatively correlated with right temporal thinning, while Van Haren et al. [29] found a relationship between left STG cortical thinning and poor outcome (as measured through a factor score, which also included PANSS symptom ratings).

Aims of the Study

Given the consistent link between positive symptoms and the STG based on functional and structural imaging studies, but divergent findings regarding the size of the effect (which might relate to sample size differences between studies and potentially moderating confounders such as illness severity, duration of illness, or antipsychotic medication), we set out to examine the effect size of the association between cortical thickness in the STG and positive symptoms in schizophrenia, using data from almost 2,000 individuals with schizophrenia pooled together by the ENIGMA Schizophrenia Working Group. Analyses based on larger samples can help derive a more precise estimates of the underlying effect sizes and enable the examination of potential moderator effects. In light of prior structural imaging findings, we predicted that lower STG thickness was associated with higher positive symptom severity in schizophrenia.

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Material and Methods

Study samples

The current study includes a total of 1,987 individuals with schizophrenia from seventeen research groups around the world as part of the ENIGMA Schizophrenia Working Group. Schizophrenia diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM, editions III-R or IV) or the International Classification of Diseases (ICD, edition 10) criteria using either the Structured Clinical Interview for DSM Disorders (SCID), the Comprehensive Assessment of Symptoms and History (CASH), the Present State Examination (PSE), and/or a review of case files/medical records by trained clinicians. All individuals had positive symptom ratings and structural imaging data available. Mean sample size at each research site was 117 patients (range: 23–245). See Supplementary Information (SI) Table 1 for more details.

Each study sample was collected with participants' written informed consent approved by local Institutional Review Boards. No individual subject imaging or clinical data were shared among the ENIGMA institutions.

Positive symptom measures and score conversion

Positive symptom severity was assessed using the Scale for the Assessment of Positive Symptoms (SAPS) [30] and the Positive and Negative Syndrome Scale (PANSS) [31]. Positive symptom scores were calculated as follows:

1. Total SAPS (Composite) score = sum of SAPS items 1–6, 8–19, 21–24, and 26–33;
2. Global SAPS (Summary) score = sum of SAPS items 7, 20, 25, and 34 (which include hallucinations, delusions, bizarre behaviour, and thought disorder global rating scores, respectively); or
3. PANSS Positive = sum of PANSS items 1–7.

To harmonize scores, we decided to convert all positive scores (i.e. PANSS Positive and Total SAPS Composite scores) to Global SAPS (Summary) scores following recommendations by Andreasen et al. [32] and using the algorithms published in van Erp et al. [33]. For additional details see SI Section 1.1.

Image acquisition and processing

Based on i) well-replicated structural deficits in the STG in patients with schizophrenia, and ii) a link between functional and volumetric measures in the STG and positive symptom dimensions [9,19,22,28] we followed a region-of-interest (ROI) approach, focusing on cortical thickness in the STG. Left and right STG thickness values – based on the Desikan-Killiany atlas [34] - were obtained using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) from high-resolution T1-weighted structural brain scans. Details on study type (single site or multisite), scanner vendor/strength/sequence, acquisition parameters and FreeSurfer versions used are provided in SI Table 2. For quality control, histograms of STG thickness values were generated and outliers were visually inspected by overlaying their parcellation on the

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subjects' anatomical images. Only parcellations judged to be accurate upon visual inspection were subjected to statistical analyses (see SI Figure 1 for left and right STG thickness summarized by sample).

Statistical analyses

Within each sample, an association of positive symptoms with left and right STG thickness was analyzed using multiple linear regression analyses (R's linear model function *lm*) predicting mean STG thickness by global SAPS score. The main analysis included age and sex as covariates. In cases of multi-site studies (FBIRN, MCIC, UMCU and Osaka) binary dummy covariates were included in the model to account for n–1 sites. For samples where information was available, secondary models were run separately with each of the following covariates: 1) current antipsychotic medication (atypical/typical/both/none), 2) duration of illness, 3) illness severity (measured using PANSS Total score), and 4) handedness (right/left/ambidextrous). Analyses of individual subject data were performed by the site that contributed the sample, using code created within the ENIGMA collaboration.

Meta-analyses

From each sample, standardized regression coefficients were extracted from the main and secondary models as a measure of effect size for the left and right STG using the *lm.beta* function in the lm.beta R package [35]. A meta-analysis was conducted over these effect sizes using the *rma* function in the R package metafor [36]. We meta-analyzed the estimates across sites by weighting Fisher's r-to-z transformed effect size values by sample size in a random-effects model using the default REML estimator. The same procedure was used to investigate the effects of age, sex, illness severity and duration of illness on STG thickness. For analyses, in which both left and right STG were analyzed, the significance threshold was corrected for two tests (p=0.05/2=0.025).

Due to between-site differences in study characteristics such as antipsychotic medication, handedness and number of sites (single vs multi-site status; SI Table 1), we used moderator analyses to investigate between-sample differences. A moderator analysis was also used to investigate the potentially moderating effects of negative symptom severity on the association between positive symptoms and STG thickness.

Results

Demographics

Mean age (weighted by sample-size) across patient samples was 34 years (range: 28–43). Patients were on average 68% male (range: 55–76%). The weighted mean duration of illness across the patient groups was 10 years (range: 1–20). For samples where current antipsychotic type and dose information was available, the weighted percentage of patients on first-generation (typical), second-generation antipsychotics (atypical), both typical and atypical or no antipsychotic medication was 11%, 71%, 9% and 9%. Ninety percent of patients were right-handed (range: 68–95), while only 8% (range: 4–14) were left-handed and 2% (range: 0–25) were ambidextrous (Table 1 and SI Table 1).

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Meta-analysis

The weighted mean global SAPS scores across the samples was 5.91 (range: 3.19–8.72). Weighted mean STG thickness was 2.69 mm (range: 2.41–2.85) in the left hemisphere and 2.74 mm (range: 2.41–2.88) in the right hemisphere. Meta-analytical results showed that global SAPS scores were negatively associated with left (β_{std}=−0.052; p_{SAPS}=0.021; Figure 1A) and right STG thickness (β_{std}=−0.073; p_{SAPS}=0.001; Figure 1B) after accounting for age, sex and number of sites (if applicable) and after correcting for two tests. There was no indication of bias (Egger's p_{left}=0.464 and p_{right}=0.164; see SI Figure 2 for funnel plots) or effect size heterogeneity in either hemisphere (left: Q(16)=8.157; p=0.944; I^2=0.00%; right: Q(16)=11.928; p=0.749; I^2=0.00%). For detailed results, see SI Table 3, models A and B).

Effects of covariates and moderator analyses

We carried on investigating both within-sample and moderating between-sample effects of age, sex, illness severity and duration of illness, as well as antipsychotic medication, handedness and multi-site status based on samples in which this information was available (SI Table 1).

While a meta-analysis of within-sample effects indicated that left and right STG thickness decreased with age (left: β_{std}=−0.357; p<0.0001; right: β_{std}=−0.332; p<0.0001), this did not differ between males and females (left: β_{std}=−0.030; p=0.202; right: β_{std}=−0.036; p=0.142). The main association of global SAPS and left/right STG thickness remained significant after controlling for age and sex (see main model above and SI Table 3, models A–F).

Overall illness severity was not associated with left or right STG thickness (p_{left}=0.131; p_{right}=0.188; SI Table 3, models G and H) after accounting for age, sex and site (if applicable), but was positively correlated with global SAPS (weighted mean correlation = 0.76; p<0.001). Additionally, accounting for illness severity within each sample also reduced the main effect of SAPS on left and right STG thickness ($p_{SAPS\text{-}left}$=0.640; $p_{SAPS\text{-}right}$=0.902; SI Table 3, models I and J), although multicollinearity might be a problem (weighted VIF = 2.26) as positive symptom severity is part of total symptom severity.

Duration of illness (DOI) correlated negatively with left and right STG thickness (left: Fisher's z=−0.267; p<0.001; right: Fisher's z=−0.262; p<0.001) and positively with global SAPS score (Fisher's z=0.092; p=0.005) and age (Fisher's z=0.834; p<0.001). However, DOI was not significantly associated with left or right STG thickness when age was included in the regression models ($p_{DOI\text{-}left}$=0.424; $p_{DOI\text{-}right}$=0.280; SI Table 3, models K and L), while the global SAPS effect in the same model remained significant (after multiple correction) in the right hemisphere (left: β_{std}=−0.052; p_{SAPS}=0.038; right: β_{std}=−0.065; p_{SAPS}=0.009; SI Table 3, models M and N).

The main effect of SAPS on left and right STG thickness also remained significant, after additionally accounting for antipsychotic medication (left: β_{std}=−0.056; p_{SAPS}=0.022; right: β_{std}=−0.063; p_{SAPS}=0.011; SI Table 3, models O and P), handedness (left: β_{std}=−0.055; p_{SAPS}=0.019; right: β_{std}=−0.075; p_{SAPS}=0.001; SI Table 3, models Q and R), or negative symptom severity (left: β_{std}=−0.053; p_{SAPS}=0.022; right: β_{std}=−0.073; p_{SAPS}=0.001; SI

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Table 3, models W and X), which themselves did not moderate the global SAPS – STG thickness relationship between samples (left: p_{MED}=0.734; p_{HAND}=0.727; p_{SANS}=0.871; right: p_{MED}=0.735; p_{HAND}=0.576; p_{SANS}=0.946; SI Table 3, models S – X).

Discussion

Summary

The main finding of this study is that positive symptom severity, but not total symptom severity, is negatively associated with STG cortical thickness in schizophrenia. This finding is present in both hemispheres without indication of effect size heterogeneity. The finding remained stable after accounting for duration of illness, age, sex, and antipsychotic medication. This investigation has two major strengths. First, by conducting a meta-analytical approach within the ENIGMA consortium this study's sample size is 10 times greater than that of prior studies investigating the relationship between STG and positive symptoms. Second, the large sample size allowed the investigation of the potentially confounding effects of age, sex, illness severity, duration of illness, antipsychotic medication, and handedness on the relationship between STG thickness and positive symptom severity.

Cortical thickness in the superior temporal gyrus and positive symptoms

We found a negative correlation between positive symptoms and cortical thickness in the STG, which corroborates findings of previous studies [28,29,37]. Van Haren et al. [29] reported a link between STG thickness and *poor functional and symptomatic outcome* in a sample of 96 patients. Of note, their outcome variable was based on PANSS symptom ratings and other measures of global functioning and hence indexes a somewhat broader range of schizophrenia symptoms. Padmanabhan et al. [28] investigated directly PANSS positive symptoms effect on STG thickness in a cohort of 455 patients with schizophrenia, schizoaffective or bipolar disorder. The authors reported an inverse relationship between positive symptoms and temporal thinning, with strongest effects in the schizophrenia subgroup. Importantly, the samples in both studies included chronic patients with a mean duration of illness of 11 and 19 years, respectively. Therefore, it remains unclear whether effects also apply to first-episode patients or might be confounded by factors such as prolonged medication intake (although no correlation between *poor functional and symptomatic outcome* and medication intake was evident in van Haren et al. [29]). Strikingly, the majority of studies, which failed to identify an association between STG thickness and positive symptoms, were based on young, largely unmedicated, first-episode patients [38–40]. Two investigations, which did not find a correlation between positive symptom scores and thickness in the temporal (or any other cortical) regions, studied minimally medicated or medication-naïve, first-episode patients with a duration of illness less than one year [39,41]. Similarly, two more studies, which compared patients with a psychotic disorder versus high-risk or healthy control participants and failed to find differences in STG thickness, were based on young (mean age range across studies 21 – 24 years), first-episode patients [38,40].

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In our study, duration of illness related negatively to STG thickness and positively to global SAPS scores, but we could not identify duration of illness effects beyond age effects. Reassuringly, the fact that i) the association between STG thickness and positive symptoms remained stable after accounting for age effects, and ii) we did not find moderating effects of antipsychotic medication indicate that these are more etiological effects rather than secondary effects of due to contextual correlates of the disease status. In support, STG thinning was also observed in a smaller study by Ziermans et al. [37] in ultra-high risk participants, who later became psychotic, compared to healthy controls, indicating that STG thinning might precede disease onset and possibly medication or other downstream effects. Similar results were reported by Oertel-Knöchel et al. [27], who linked STG thinning to a *predisposition towards hallucinations* (but not to PANSS positive symptom scores itself) in patients and unaffected relatives, but not in controls. As put forward by the authors, this points towards a possible trait-like STG-symptom link – an argument, which is also supported by findings in Kühn and Gallinat's meta-analysis [20].

Studies based on patients with neurological (but not psychiatric) disorders found the STG to be involved in auditory processing [15] and – in conjunction with a wider temporal-frontal-parietal network – to have a role in language production, interpretation and self-monitoring [16,17]. Interestingly, psychosis-like symptoms such as illusions and hallucinations, have long been observed during electrical stimulation of the STG and in patients with epilepsy (for a review see [42]). Moreover, a recent meta-analysis found that repetitive transcranial magnetic stimulation applied to temporoparietal areas is an effective treatment of auditory verbal hallucinations [43]. These studies further support our own findings that the STG appears to be a central region involved in processes underlying positive symptoms and is less affected by confounders that are highly prevalent in schizophrenia patients.

Potential modulators

Illness severity was the only significant modulator observed on the current study, as positive symptoms no longer predicted STG thickness after accounting for illness severity (as well as age and sex). While this may indicate that some of the variance in thickness that is explained by positive symptoms may also depend on illness severity, we would also like to emphasize that it is conceptually and statistically challenging to disentangle the effects of illness severity and positive symptoms as they were highly correlated. Illness severity was not linked to STG thickness in two prior studies [11,44]. This divergence in findings may be due in part to different sample characteristics.

Limitations

The following limitations should be considered when interpreting our findings. First, we followed a hypothesis-driven approach, as only effects in the superior temporal gyrus were studied. Second, we cannot address directional effects due the cross-sectional design of the current study. Longitudinal, prospective studies should determine whether positive symptoms precede or follow the development of cortical thinning. Third, we employed a measure of global positive symptom severity and of global STG thickness. It is however possible, that effects were driven by either symptom sub-dimensions or STG sub-region specific features. Fourth, while we discovered no effect of current antipsychotic medication,

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it is still possible that cumulative medication use (i.e. taking into account the treatment duration) may have important confounding effects on brain structure [45].

Conclusion

We used data from several large cohorts from three continents collected within the ENIGMA consortium comprising almost 2,000 patients to study the association between cortical thickness in the superior temporal gyrus and positive symptoms. Positive symptom severity was significantly related to thickness in this region in both hemispheres, and remained stable after accounting for age, sex, antipsychotic medication and duration of illness. Illness severity had some modulating effects. These results may help to advance insight into symptom-relevant pathophysiological mechanisms in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significant Outcomes

- Our work is based on data from the ENIGMA Schizophrenia Working group, a global alliance of scientists spread across many countries collectively analysing brain imaging data in schizophrenia.
- Using a meta-analytical approach, we found that in schizophrenia positive symptoms were inversely related to cortical thickness in the superior temporal gyrus.
- Compared to previous studies, we were able to increase our sample size by a magnitude of 10 and to investigate potentially influencing, but small effects of age, gender, illness severity, and their complex interdependencies.

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Limitations

- We followed a hypothesis-driven approach, as only effects in the superior temporal gyrus were studied.
- We cannot address causal effects due the cross-sectional design of the current study.
- We employed a measure of global positive symptom severity. It is however possible, that effects were driven by subdimension-specific features.

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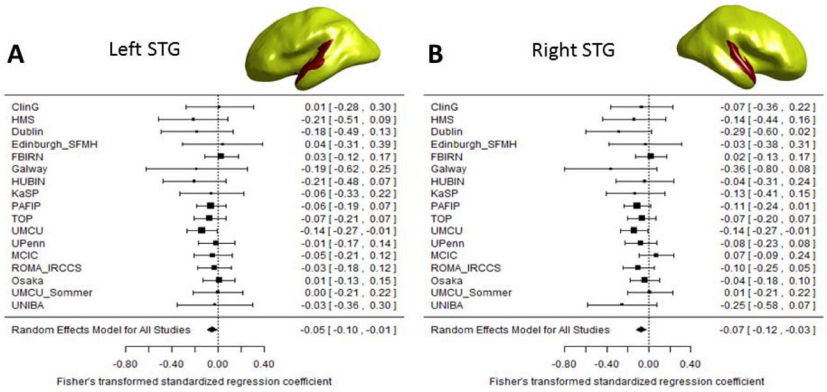

Figure 1.

Forest plot of association between global SAPS and cortical thickness in the A) left and B) right superior temporal gyrus across all 17 study sites, controlling for age, sex and number of sites (if applicable). Fisher's transformed standardized regression coefficients are denoted by black boxes. Black lines indicate 95% confidence intervals. The combined estimate for all sites is represented by a black diamond with the outer edges of the diamond indicating the confidence interval limits.

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Table 1

Demographics. Mean are weighted by study sample size.

	estimate	range	data available for N number of studies
% males	68	55–76	17
Mean age in years	34	28–43	17
Mean SAPS Global	5.91	3.19–8.72	17
Mean duration of illness in years	10	1–20	13
Mean illness severity (PANSS Total)	70.44	49.81–90.22	11
Antipsychotic medication			*13*
%Atypical	71	39–91	
%Typical	11	0–45	
%Both A & T	9	0–24	
%None	9	0–53	
Handedness			*14*
%Right	90	68–95	
%Left	8	2–14	
%Ambidextrous	2	0–25	
Cortical thickness			*17*
Mean left superior temporal gyrus	2.69	2.41–2.85	
Mean right superior temporal gyrus	2.74	2.41–2.88	