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Unraveling consistently altered brain activations of language deficits in schizophrenia: evidence from ALE meta-analysis

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BACKGROUND: Language deficits are commonly observed in patients with schizophrenia, significantly impacting their quality of life. Current medicine has little curing effects on language deficits in patients with schizophrenia. Therefore, it is crucial to investigate the underlying pathology of these deficits and unravel the potential intervention targets.
METHODS: We systematically reviewed fMRI publications on language processing in schizophrenia and summarized the evidence quantitatively with activation likelihood estimation algorithms following PRISMA guidelines. A total of 82 experiments involving 1538 schizophrenia patients and 1413 healthy controls were included in the current study.
RESULTS: Our findings revealed that the left middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) were consistently related to language deficits in schizophrenia across all modalities and all contrasts. Subsequent analysis revealed increased activation in the left MFG related to language deficits in schizophrenia. Subgroup analyses uncovered modality-specific alterations. Specifically, reduced activation in bilateral MFG in language comprehension, and increased activation in left IFG in language production in schizophrenia. Further evidence in comparison analysis also uncovered greater alteration in right MFG related to comprehension than production, while greater alterations in left IFG and others related to production than comprehension in schizophrenia. Moreover, we found that age modulates the altered activation patterns in schizophrenia, while positive or negative symptoms, or sex, did not show significant correlations with these patterns.
CONCLUSIONS: In summary, our study highlights convergent altered activation patterns in specific brain regions and identifies several heterogeneous sources (e.g., language modality, age) contributing to language deficits in schizophrenia.

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INTRODUCTION

Cognitive deficits are common in patients with schizophrenia (SZ) [1–4]. While numerous antipsychotic medications have been developed to address positive symptoms, few options are proposed to improve cognitive impairments in SZ patients [5]. The lack of treatment options for cognitive deficits in schizophrenia diminishes the potential for improved quality of life in the affected individuals. It is imperative to unveil the brain mechanisms underlying cognitive impairments and try to facilitate the development of better treatment strategies. Previous studies have inspected the dysfunctional brain activations associated with deficits in working memory, executive function, and other cognitive functions in SZ patients [6, 7]. However, although language constitutes a crucial higher-order function and an important component in daily life, few quantitative studies have examined the consistently altered brain activations related to language deficits in schizophrenia. Therefore, it is important to identify the convergently altered brain activation patterns related to language deficits in SZ, which might help capture the potential intervention targets to improve language deficits in SZ patients.

Language is defined as "a system of shared symbolic representations of the world, the self and abstract concepts that support thought and communication", consisting of five components including phonology, prosodics, syntax and morphology, semantics, and pragmatics [8]. SZ patients often exhibit language deficits in several perspectives including illogical statements [9, 10], reduced use of clausal embedding [11], difficulty in understanding ironic meanings [12] and metaphors [13, 14], and impaired verbal fluency [15, 16]. Many neuroimaging studies have been performed to detect the altered structural and functional brain networks associated with language deficits in SZ [17–20]. However, discrepancies in altered brain activations have been observed across different studies, even if the same task paradigm was adopted. For example, several studies exploring language production deficits in schizophrenia adopted a verbal fluency paradigm [21, 22]. These studies commonly reported altered brain activity during verbal fluency task performance in the bilateral inferior frontal gyrus and anterior cingulate cortex in SZ patients compared to healthy controls. However, one of them reported altered brain activity in the lingual gyrus [21], while another one

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revealed altered brain activity in the supramarginal gyrus [22]. The discrepancy in altered brain activations may relate to differing sample sizes, data processing procedures, or inter-subject variance to some degree [15, 16, 21], which impedes efforts to summarize evidence across studies. Several qualitative reviews summarized the altered brain pathways related to language deficits in SZ [17, 18]. Li et al. pointed out loss of left hemisphere lateralization in the temporal and frontal lobes during language task performance in SZ patients, which was aligned with findings demonstrating decreased gray matter density in these brain regions [17]. Bhati also emphasized the interhemispheric abnormality and the altered brain activity related to receptive language in SZ, and indicated the potential deficits in Broca's region related to expressive language in SZ [18]. However, these reviews failed to provide quantitative evidence on the specified brain alterations. Another review summarized extensive brain coordinates, including temporal, frontal, parietal lobes, and other brain regions, in which altered brain activity was reported by a small group of studies related to sentence-level language comprehension in SZ [19]. Despite the efforts to quantitatively summarize the evidence, this review only provided some quantitative descriptions regarding the evidence pool but was not able to resolve the discrepancy among different studies. A quantitative review uncovered that formal thought disorder was associated with consistent alterations in the superior temporal gyrus and left posterior middle temporal gyrus, revealing thought disorder was intricately involved with language network, but it did not address the language deficits in SZ directly [23], which is the focus of our current study. Consequently, it is imperative for us to summarize the neural evidence quantitatively to uncover the neural underpinnings related to language deficits in schizophrenia.

As mentioned above, the altered brain activations related to language deficits in SZ patients involve diverse brain regions [17–19]. Disentangling what kinds of factors might contribute to the heterogeneity of neural profiles related to language deficit in SZ patients and dissociating the specific profiles of language deficits under different contexts could shed light on the understanding of the brain mechanism of language deficit in SZ patients. First of all, different language modalities (comprehension or production) engage different brain regions [24, 25]. Language comprehension involves extracting semantics from syllables, words, sentences, and discourse, while language production involves word, sentence, and speech generation [26]. Language comprehension may engage the posterior temporal cortex, anterior temporal lobe, inferior frontal cortex, and inferior parietal lobule, while language production may engage the left inferior frontal gyrus, left superior temporal gyrus, operculum, insula, and lateral pre-motor cortex [25]. However, there appears to be no convergent evidence disclosing whether different language modality deficits would relate to different profiles of altered activations in schizophrenia. Moreover, as there is no consensus about whether increased or decreased activation of brain regions in language networks is related to SZ language deficits [17], the current study aimed to examine the convergently increased and decreased brain activations related to language-modality-specific deficits in SZ separately. Meanwhile, whether the cognitive deficits would fluctuate during the progress of the lifespan disease is still a hitting issue [27]. Understanding whether patients of different ages would display similar or different dysfunctional brain patterns related to language deficits in SZ could offer us further insights into the development of dysfunctional profiles across the lifespan.

Collectively, this study hopes to inspect the convergently altered brain activations related to language deficits and then explore how the potential imperative factors (e.g., language modality, age, sex, negative or positive symptoms, auditory hallucinations) regulate language deficits in SZ. We hypothesized that 1) there were consistent brain regions involved in language deficits in SZ patients; 2) there were different brain profiles in language comprehension and language production deficits in SZ patients; 3) age effects may contribute to different dysfunctional brain profiles related to language deficits in SZ patients. It is expected that the new findings might introduce a new avenue for fully understanding the neural mechanism associated with language deficit in SZ.

MATERIALS AND METHODS

Literature search and selection

We conducted a systematic search and selection of relevant papers according to the PRISMA guidelines [28]. To identify relevant papers in English related to fMRI studies of language processing, including phonology, prosodics, syntax and morphology, semantics and pragmatics [8], in schizophrenia, we used the following keyword combinations: ("fMRI or functional magnetic resonance imaging" & "schizophrenia" & "language or speech or semantic or reading or word or sentence or verbal fluency or comprehension") to search PubMed and Web of Science by March 2025. After combining all the reference lists from different sources, we removed duplicates and included studies that met the following criteria: 1) an fMRI study was conducted, 2) participants performed language processing under an fMRI scan, 3) there was at least one group contrast between SZ patients, which include schizophreniform disorder and schizophrenia disorder diagnosed according to Diagnostic and Statistical Manual of Mental Disorders or International Statistical Classification of Diseases and Related Health Problems, and healthy controls or group effect of brain activations related to language processing, 4) peak coordinates of the between-group differences or the group effects of brain activation were reported, 5) whole brain-wide analysis instead of ROI analysis was performed, 6) the peak coordinates were presented in Talairach space or MNI space (all peak coordinates presented in Talairach space were converted to MNI space by an icbm2tal algorithm [29]). Finally, we included a total of 82 published papers for the current study. The flow of literature search and selection is shown in Fig. 1. The peak coordinates of significant between-group contrasts related to language processing in patients with schizophrenia, number of patients and healthy controls, the demographic information (e.g., age, diagnosis, symptoms, receiving drug status, etc.), task paradigms, contrast type, etc. were extracted from the included study.

Activation likelihood estimation analysis

ALE is a method for dealing with spatial uncertainty and inter-subject variability that models the activation likelihood around a peak coordinate by a Gaussian kernel, the parameters of which are weighted by sample size, enabling studies with larger sample sizes to have smaller Gaussian distributions and indicating more reliable activation [30–32]. Integration of likelihood from individual studies is conducted by a non-additive method, choosing the closest peak coordinate's maximum probability to obtain an ALE map [33]. Of note, the sample size of each study would be used as a weight to take account of the sample size effects [33], giving studies with small sample size very limited weight of evidence, while giving studies with large sample size large weight of evidence. The ALE map is then compared to a null distribution that is created by a non-linear histogram integration algorithm. This step confirms whether there is a high probability that the brain nodes would be convergently activated by a particular process across studies [21]. We used cluster-level family-wise error correction (FWE cluster-level $p < 0.05$, voxel-level cluster forming threshold $p = 0.001$) with 1000 permutations for thresholding the results. To avoid results being dominated by a few experiments, we only conducted analyses involving 17 or more experiments, as suggested by a previous study [34]. Additionally, the significant clusters revealed by ALE should have at least two contributing experiments. The contribution of each experiment to a significant cluster was

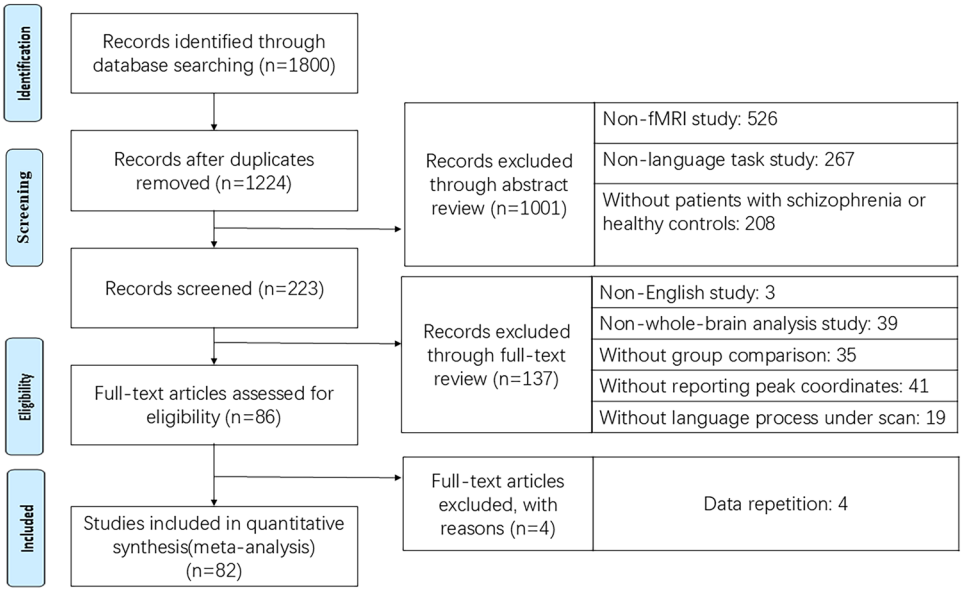

Fig. 1 Study selection flow. A total of 1800 papers were screened after the initial search. After removing duplicates, studies that did not include fMRI scans, language process tasks, or did not include both patients with schizophrenia and healthy controls were excluded by reviewing abstracts. The remaining studies were assessed via full-text article, removing studies that were not reported in English, did not perform whole-brain-wise analysis, contain group comparison, report peak coordinates, or involve language process during fRMI scans. Some studies including results published in another included article were also removed. Finally, a total of 82 studies met the inclusion criteria and were included for analysis.

calculated [34]. It is required that the contribution of the most dominant experiment should not exceed 50% and the contribution of the two most dominant experiments should not exceed 80% [34]. Since ALE algorithms are unable to process the statistical images from original studies, they cannot directly assess the directionality of brain activity. To address this, we extracted peak coordinates that indicated increased or decreased activity in patients relative to healthy controls from each experiment. These were then pooled into two separate contrast sets: increased and decreased contrasts. This approach allowed us to investigate the directionality of altered brain activity in patients with schizophrenia using the ALE method. Theoretically, there were 3 (all modalities, language comprehension, language production) × 3 (all contrasts, increased contrast in patients, decreased contrast in patients) ALE analyses.

To calculate the age-group-specific alterations, we divided studies into two age groups according to each experiment's average age of SZ patients. Only one experiment included SZ patients whose age was under 18. The average age of all experiments' SZ patients was around 34. Based on this finding, we classified experiments with patients' average age younger than 35 into one group, while experiments with patients' average age equal to or older than 35 into another group. To provide contrast-specific altered brain profiles for each age group, we constrained the analysis to contrast-specific datasets. Thus, there were 3 (all modalities, language comprehension, language production) × 2 (increased contrast in patients, decreased contrast in patients) × 2 (age < 35, age >= 35) ALE analyses.

After removing 5 analyses that did not have 17 or more experiments, 16 ALE analyses were performed with GingerALE (version 3.0.2).

Comparison and conjunction analysis

The separate ALE maps were calculated by the aforementioned ALE analysis. To compare the modality-divergent and modality-common alterations in SZ patients, we used the corrected ALE maps (FWE cluster-level $p < 0.05$, initial cluster forming threshold $p < 0.001$) to perform comparison and conjunction analyses for two corresponding modalities, i.e., comprehension and production ALE maps across all contrasts having survived clusters after correction, following previous studies [35, 36]. Specifically, two comparison images were generated by subtracting one ALE image from the other. To assess the statistical significance of these comparisons, we pooled data from two separate datasets and randomly divided them into two groups, each matching the size of the original datasets. ALE images were then computed for each simulated dataset, and the corresponding comparison images were created by subtracting one ALE image from the other. This permutation process was repeated 10,000 times to generate a null distribution of comparison values, allowing us to determine the statistical significance of the actual comparison results. For conjunction analysis, the voxel-wise minimum of the two original ALE images was used. Significant clusters were defined by a threshold of $p < 0.05$ and a minimum cluster size of 100 mm^3. Meanwhile, comparison and conjunction analyses were not performed for other corresponding pairs without completely corrected clusters, i.e., there was a corrected cluster of comprehension modality in decreased contrasts, but no cluster survived the correction in the ALE analysis for production modality in decreased contrasts. In addition, comparison and conjunction analyses were not performed for age groups since no paired age groups had completely corrected clusters.

Leave-one-experiment-out analysis (LOEO)

To ensure that the findings of one experiment did not dominantly contribute to the significant clusters in the ALE analysis, we conducted LOEO for each ALE analysis with significant clusters to quantify the contribution of each experiment, excluding the significant clusters having more than 50% contribution from a single experiment, or having more than 80% contribution from two experiments. The significant voxels of an ALE analysis should also be found in more than 80% of the folds of the LOEO analyses.

Analyses for covariate effects

To assess the potential effects of positive or negative symptoms on the findings of convergent clusters, per-voxel probabilities

were extracted to perform rank correlation analyses to examine the relationship between positive/negative symptom scores and the per-voxel probabilities across the included studies [37]. The Scale for the Assessment of Positive Symptoms (SAPS) or Scale for the Assessment of Negative Symptoms (SANS) scores were converted to Positive and Negative Syndrome Scale (PANSS) scores based on the conversion criteria introduced in a study [38] before conducting the correlation analyses. In addition, the percentage of female participants in the combined set of SZ and healthy groups was extracted as the sex ratio, which was correlated with the per-voxel probabilities to examine whether the sex ratio contributed significantly to the brain profiles related to language deficits in SZ.

To investigate the potential effect of auditory hallucinations, we conducted the ALE analyses separately for patients with auditory hallucinations.

RESULTS

Study selection

Figure 1 shows the study selection flow, which resulted in 82 experiments included for analysis (1538 SZ patients and 1413 healthy controls, 679 foci). The full list of the included experiments is displayed in Table S1. The meta-analysis for language comprehension included 57 experiments (1133 patients, 985 controls, 425 foci), while language production included 26 experiments (420 patients, 443 controls, 254 foci). Sub-analyses were also conducted for sub-contrasts, including increased contrasts for all modalities (51 experiments, 948 patients, 890 controls, 266 foci), decreased contrasts for all modalities (63 experiments, 1121 patients, 973 controls, 387 foci), increased contrasts for language comprehension (33 experiments, 635 patients, 537 controls, 153 foci), decreased contrasts for language comprehension (47 experiments, 942 patients, 799 controls, 262 foci), increased contrasts for language production (18 experiments, 313 patients, 353 controls, 113 foci), and decreased contrasts for language production (17 experiments, 194 patients, 189 controls, 125 foci). The experiment information for different age groups is detailed in Table S2 in the supplementary materials.

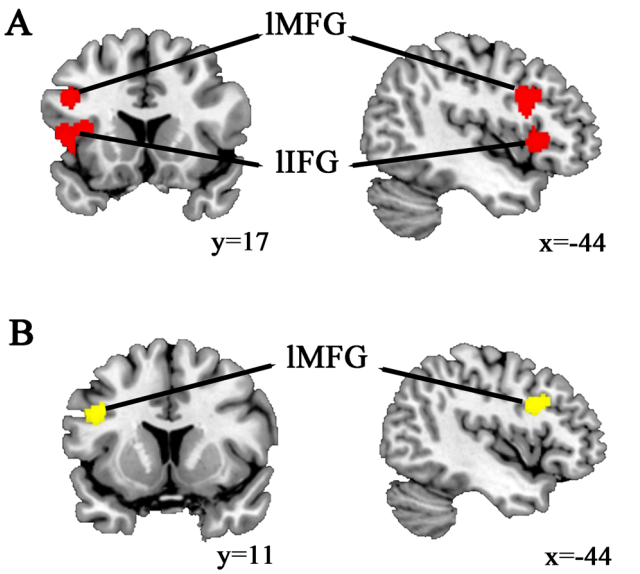

Fig. 2 Convergently altered brain regions related to language deficits across all modalities. A the brain regions (the left MFG and the left IFG) with altered brain activations related to language processing across all modalities and all contrasts in patients with schizophrenia compared to healthy controls; **B** the increased activations in the left MFG were convergently found in patients with schizophrenia across all modalities. Denotes: lMFG: left middle frontal gyrus; lIFG: left inferior frontal gyrus.

Main results of ALE analysis

As presented in Fig. 2 and Table 1, the main analysis revealed that the left middle frontal gyrus (MFG) and left inferior frontal gyrus (IFG) were consistently related to language deficits in SZ patients across all modalities and all contrasts. Further analysis revealed that increased activation in the left MFG was consistently found in deficient language processing across all modalities in SZ patients (Fig. 2B). Meta-linear regression analyses revealed that positive or negative symptoms in SZ patients had no significant correlation with the contribution sizes (positive symptoms: $rho = -0.04$, $p = 0.75$; negative symptoms: $rho = -0.10$, $p = 0.48$). In addition, the sex ratio also did not contribute significantly to the altered brain profiles related to language deficits in SZ ($rho = 0.18$, $p = 0.11$). Eighteen experiments included patients with auditory hallucinations, but ALE analyses with these patients did not reveal any convergent findings.

Modality and age-specific altered brain profiles in SZ patients

Sub-group analysis revealed that bilateral MFG were consistently related to language comprehension deficits in SZ patients across all contrasts (Fig. 3A & Table 1), left IFG was consistently related to language production deficits in SZ patients across all contrasts (Fig. 3C & Table 1). Further comparison analysis uncovered that the right MFG had greater alterations in language comprehension deficits than in language production deficits (Fig. 3B & Table 1), while the left IFG, insula, and MFG had greater alterations in language production deficits than in language comprehension deficits in SZ patients (Fig. 3D & Table 1). Of note, the left MFG, having greater alterations in language production deficits, was different from the left MFG indicated in language comprehension deficits across all contrasts (Fig. 3E), which suggests that different sub-components of a brain region might hold different language functions related to deficits across all contrasts in SZ patients. No common brain regions were found related to both language comprehension and production deficits in SZ patients.

Further analysis showed that there were consistently decreased activations in the right MFG related to language comprehension (Fig. 4A), increased activations in the left IFG related to language production (Fig. 4B) in SZ patients when compared to healthy controls.

Age effects were also found in this study (Fig. 5). Increased activations in the left MFG across all language modalities were also observed in patients older than 35 years old (Fig. 5A), while decreased activations in the right MFG related to language comprehension were found in patients younger than 35 years old (Fig. 5B). This suggests that age may influence altered brain patterns related to language processing in schizophrenia.

DISCUSSION

The present study reports consistent alterations in brain activation related to language processing in SZ patients when compared to healthy controls. Left MFG and IFG were consistently related to language deficits across all modalities and contrasts. The increased activation in the left MFG was convergently observed in language processes in SZ patients compared to healthy controls across all modalities. The following analyses revealed language-modality-specific alterations in SZ patients. Specifically, bilateral MFG was consistently related to language comprehension deficits, and left IFG was consistently related to language production deficits in SZ patients across all contrasts. Further analyses uncovered convergently reduced activation in the right MFG was engaged in language comprehension in SZ patients, while the increased activation in left IFG was engaged in language production in SZ patients. What's more, it was found that ages

Table 1. The significant clusters of ALE analysis.

Type	Age range	Modality	Contrast	Cluster Names	x	y	z	cluster size (2*2*2 mm)	Remark
Main analysis	All	All	All	lIFG	−42	15	5	266	extending to Ins
				lMFG	−44	12	29	385	extending to IFG
	All	All	Increase	lMFG	−44	13	29	161	extending to IFG
Sub-group analysis	All	Comprehension	All	lMFG	−44	11	28	182	extending to IFG
				rMFG	43	43	18	107	
	All	Production	All	lIFG	−45	20	2	129	extending to Ins
Comparison analysis	All	Comprehension > Production	All	rMFG	42	42	21	66	
	All	Comprehension < Production	All	lIFG	−45	20	2	113	extending to Ins
				lIns	−37	15	12	37	
				lMFG	−44	20	31	21	
Sub-group analysis	All	Comprehension	Decrease	rMFG	43	44	17	123	
	All	Production	Increase	lIFG	−40	12	8	202	extending to Ins
Age-effects	>=35	All	Increase	lMFG	−44	14	30	137	extending to IFG
	<35	Comprehension	Decrease	rMFG	43	46	13	149	

Denotes: *lMFG* left middle frontal gyrus; *lIFG* left inferior frontal gyrus; *rMFG* right middle frontal gyrus; *lIns* left insula.

were involved in different profiles of altered brain activations in SZ patients. Meanwhile, the positive or negative symptoms did not significantly influence the brain patterns related to language deficits in schizophrenia.

Language deficits are pervasive in SZ patients [11, 17, 39]. However, it is difficult to predict what kind of language deficits an SZ patient would have or how is the severity of the language symptoms experienced in the SZ patients. The patients display heterogeneous language symptoms, including reading, syntax understanding, generation of appropriate language responses, illogical communication, and so on [40–42]. Despite the heterogeneity of language symptoms in SZ patients, whether common brain circuits are engaged in language deficits in SZ patients has not been well understood. Our current study filled this research gap, collecting evidence from all the fMRI studies related to language processing in SZ patients from the past two decades to reveal the convergently altered brain patterns of language deficits in SZ patients. Left MFG and IFG were consistently related to language deficits across all modalities and contrasts. Among these two brain regions, the increased activation in the left MFG was consistently found across all language modality deficits in SZ patients, suggesting that increased activations in the left MFG were consistently involved in language deficiency in SZ patients no matter of what language deficits an SZ patient has. The left MFG is an important brain region in semantic access and working memory [43, 44], both of which are important for language comprehension, language production and second language learning. Thus, altered activation in left MFG would make versatile language abilities vulnerable. These findings make the left MFG an ideal target for intervention to improve the language abilities in SZ patients.

Discovering language-modality-specific alterations in SZ patients is also an interesting finding. Language comprehension and language production involve correlated but different distributed brain networks [24, 45–47]. Our study found that different brain regions are related to language comprehension and production deficits in SZ patients, respectively. Namely, the bilateral MFG, important for syntactic processing, semantic maintenance, prosody understanding, and so on [24, 48], were found convergently engaged in language comprehension deficit in SZ patients, while the left IFG (extending to insula), a typical brain region, including Broca's region, related to language production [24, 48], was found to be convergently altered in language production in SZ patients. Comparison analysis uncovered that the right MFG had greater alterations in language comprehension deficits than in language production deficits, while the left IFG, insula, and MFG had greater alterations in language production deficits than in language comprehension deficits in SZ patients. This suggests that different language modality deficits involve distinct brain pathways, such that different treatment targets for neuromodulation may be necessary to address these deficits. Furthermore, increased activations were found in the left IFG related to language production, while decreased activations were found in the right MFG related to language comprehension in schizophrenia. The differences in brain activations and brain deactivations are related to different molecular activities (e.g., GABA and glutamate) [49–51], understanding these mechanisms is crucial for identifying potential treatment strategies for language deficits in schizophrenia. These results collectively suggest that different strategies should be taken to tackle different language modality deficits in SZ patients through behavioral, neuromodulation, or drug therapy.

What's more, our study revealed age-related effects on convergent patterns of activations related to language processing in schizophrenia. Older patients were more convergently related to altered activations in the left hemisphere, while younger patients were more convergently related to altered activations in the right hemisphere. The difference in brain alteration between

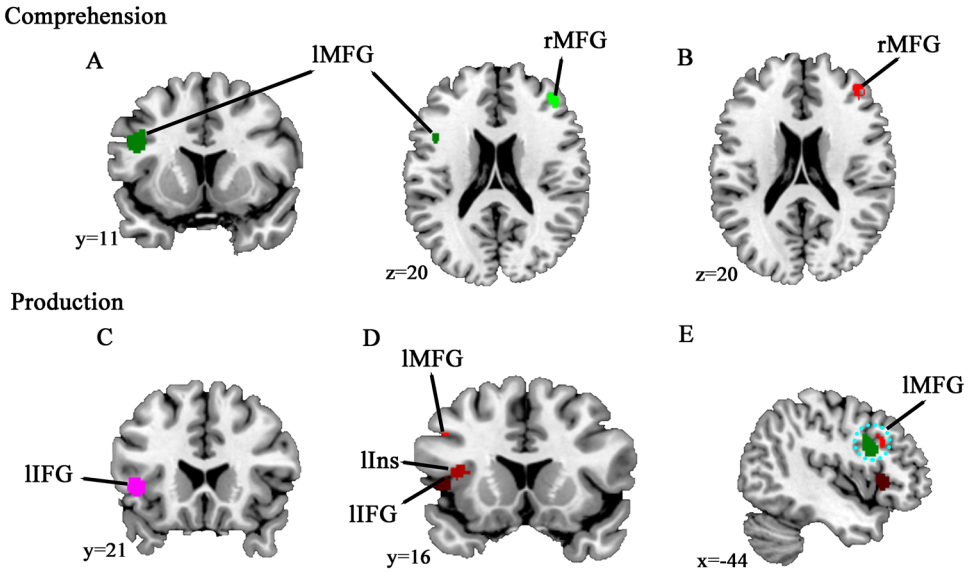

Fig. 3 Modality-specific altered brain regions in schizophrenia across all contrasts. A Bilateral MFG convergently related to language comprehension in schizophrenia; **B** comparison analysis showed right MFG had greater alteration in language comprehension than that in language production in schizophrenia; **C** left IFG convergently related to language production in schizophrenia; **D** comparison analysis revealed left MFG, Ins, and IFG had greater alteration in language production than that in language comprehension in schizophrenia; **E** the lMFG (red), which had greater alteration in language production, is separate from the lMFG (green) convergently found related to language comprehension. Denotes: lMFG: left middle frontal gyrus; lIFG: left inferior frontal gyrus; rMFG: right middle frontal gyrus; lIns: left insula.

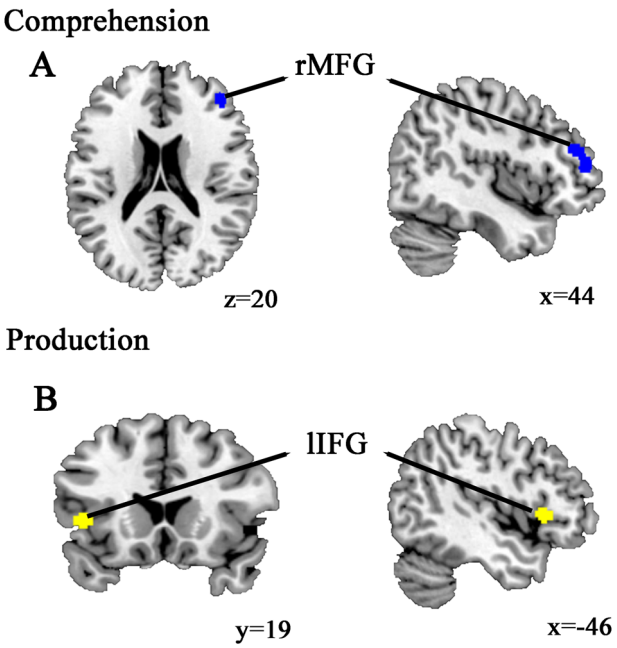

Fig. 4 Modality and contrast-specific altered brain regions in schizophrenia. A The convergently decreased activations in the right MFG related to language comprehension in schizophrenia; **B** The convergently increased activations in the left IFG related to language production in schizophrenia. Denotes: lIFG: left inferior frontal gyrus; rMFG: right middle frontal gyrus.

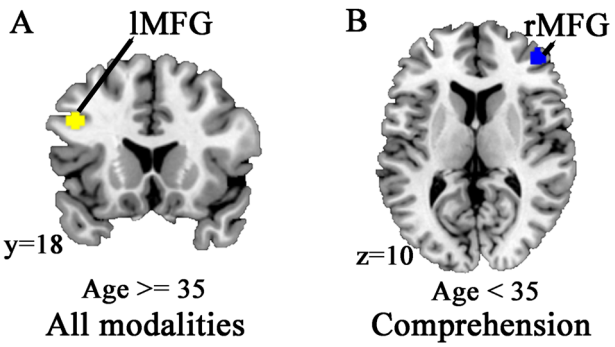

Fig. 5 Age effects on the altered brain patterns related to language processing in schizophrenia. A The convergently increased activations in the left MFG across all language tasks in patients equal to or older than 35; **B** The convergently decreased activations in the right MFG related to language comprehension in patients younger than 35. Denotes: lMFG: left middle frontal gyrus; rMFG: right middle frontal gyrus.

different age groups may be attributed to fluctuating brain states along with the fluctuation of cognitive deficits across the life span of SZ patients [27]. We found that only younger patients displayed convergently altered brain activations related to language comprehension. These results are consistent with previous studies suggesting age effects on the heterogeneity of cognitive deficits in schizophrenia [4, 52]. However, due to the limited amount of published literature, our study could not demonstrate the age effect on language production. The effects of age and duration of disease are highly correlated in SZ patients [53], disentangling these effects would require detailed information about the duration of the disease in each experiment. However, many studies did not report on patients' durations of disease. Nevertheless, attention is required when addressing the language deficit in SZ patients of different ages or duration of disease.

Of note, negative symptoms were reported to correlate with cognitive deficits, while positive symptoms had a moderate correlation with cognitive deficits in SZ patients [54–56]. In our current study, the severity of negative symptoms or positive symptoms did not correlate with the profiles of altered activations related to language deficits in SZ patients. Such findings indicate that the severity of positive or negative symptoms might not influence the neural underpinnings of language deficits in SZ patients, suggesting the language deficit is pervasive in SZ patients across different severity levels. Another analysis of ours

did not find convergently altered brain activations related to language deficits in SZ patients with auditory hallucinations. However, further analysis is needed to demonstrate this finding since the current result might be restricted by limited experiments recruiting patients with auditory hallucinations, while the auditory hallucinations might involve many brain regions in the language network [57].

Developing treatments to ameliorate language deficits and other cognitive deficits in schizophrenia would be a key to improving their quality of life [5]. In particular, identifying dysfunctional brain regions related to language deficits in schizophrenia would encourage researchers to develop efficient intervention approaches to improve symptoms. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are emerging neuromodulatory methods to treat negative symptoms in schizophrenia. Some studies have reported using TMS to stimulate brain regions, including the dorsolateral prefrontal cortex (DLPFC) and the parietotemporal cortex, to improve language performance in SZ patients [58–60]. However, we argue that some parts of these language pathways are not always dysfunctional in patients with heterogeneous language deficits. Especially, many of these studies did not choose target regions based on scientific estimation of the involved brain regions, which could hinder the development of efficient measures to address language and other cognitive deficits in schizophrenia. Importantly, the present study identified the left MFG as consistently altered in various language processing conditions in SZ patients compared to healthy controls, and other language modality deficit-specific brain regions. As such, targeting left MFG or other brain regions identified by our study, according to patients' behavioral display of language deficits, as tailored treatment targets, may have the potential to improve the treatment effects on language deficits. However, it is crucial to give careful attention to designing subtly tailored strategies for addressing deficits in different language modalities with different durations of disease in SZ patients.

Despite the valuable insights gained from uncovering altered brain activations and the diverse sources of language deficits in SZ, our study has some limitations that warrant further discussion. Firstly, there were fewer included papers related to language production than to language comprehension, which may bias the results for language modality-specific altered brain activations. Yet, we used several correction methods to avoid biased results revealed by limited research papers. Secondly, our current study only included fMRI studies. Given that many EEG studies reported some important findings regarding language deficits in SZ patients, it would be important to develop a way to integrate our current results and EEG findings. Thirdly, we cannot disentangle the medication effects from our current findings. Many experiments included in our study recruited SZ patients who took medication therapies, but most of these experiments did not report the detailed dosage of the drug taken by the patients, making us unable to examine whether medication therapies would influence our current findings. Fourthly, the ALE analysis cannot make use of the original signed statistical maps from each experiment, making it less powerful in addressing the consistent findings related to increased contrasts or decreased contrasts. However, as a robust and popular coordinate-based meta-analysis approach, ALE is reliable in revealing consistent findings regarding the spatial distribution of brain profile patterns.

In conclusion, our study revealed increased brain activation in the left MFG related to language processing in SZ patients under different contexts. We addressed language-modality-specific dysfunctional brain regions, the convergence of incremental or decremental brain activations, and age effects related to the altered brain patterns regarding language processing in schizophrenia. Our current study did not find that the severity of negative or positive symptoms contributes to the profiles of altered brain activations related to language deficits in SZ patients, nor the convergent brain activations found in SZ patients with auditory hallucinations. Collectively, our results point out the potential brain targets for treating language deficits by neuromodulation (e.g., TMS or tDCS) in schizophrenia, while encouraging researchers to consider multiple factors that might contribute to the heterogeneity of the distributed network related to language deficit in schizophrenia.

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AUTHOR CONTRIBUTIONS

YuH: Conceptualization, Investigation, Methodology, Data analysis, Writing- Original Draft, Writing-Review & Editing; **YaH**: Conceptualization, Investigation, Methodology, Writing-Review & Editing; **YZ**: Methodology, Writing-Review & Editing; **RG**: Methodology, Writing-Review & Editing; **FG**: Writing-Review & Editing; **ZY**: Conceptualization, Writing-Review & Editing, Supervision & Fund Application.

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COMPETING INTERESTS

The authors declare no competing interests.

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