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Cortical Gray Matter Loss, Augmented Vulnerability to Speech-on-Speech Masking, and Delusion in People With Schizophrenia

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People with schizophrenia exhibit impairments in target-speech recognition (TSR) against multiple-talker-induced informational speech masking. Up to date, the underlying neural mechanisms and its relationships with psychotic symptoms remain largely unknown. This study aimed to investigate whether the schizophrenia-associated TSR impairment contribute to certain psychotic symptoms by sharing underlying alternations in cortical gray-matter volume (GMV) with the psychotic symptoms. Participants with schizophrenia (N D 34) and their matched healthy controls (N D 29) were tested for TSR against a two-talker-speech masker. Psychotic symptoms of participants with schizophrenia were evaluated using the Positive and Negative Syndrome Scale. The regional GMV across various cortical regions was assessed using the voxel-based morphometry. The results of partial-correlation and mediation analyses showed that in participants with schizophrenia, the TSR was negatively correlated with the delusion severity, but positively with the GMV in the bilateral superior/middle temporal cortex, bilateral insular, left medial orbital frontal gyrus, left Rolandic operculum, left mid-cingulate cortex, left posterior fusiform, and left cerebellum. Moreover, the association between GMV and delusion was based on the mediating role played by the TSR performance. Thus, in peopl

INTRODUCTION

I par nts n sp B an t ou t proB ss s av n Bons r as Br t Ba B araBt r st Bs n p op w t sB op r n a It as n su st t at nv st at on o t r at ons p tw n Bts o p rB ptua Bo n t v proB ss s an t p Ba s pto s o sB op r n a s portant or un rstan n t natur o t s sor r nB par n tor B an s satt n uro o Ba v n p op w t sB op r n a ar assoBat w t B rta n ps B ot Bs pto s r . Bt n t nBapa t o a quat proB ss n u t p nputs at t p rB ptua v , t s o portanB to now w t r Bts o p rB ptua Bo n t v proB ss s an B rta n s pto s n p op w t sB op r n a s ar t sa or s ar un r n n ura su strat s assoBat w t pa r n tor proB ss n

r vous stu s av s own t at n a v rs st n n nv ron nts w t u t p ta rs, ot p op w t rst p so sB op r n a an p op w t B ron B sB op r n a x t a uB ar r Bu t n tar t sp B r Bo n t on a a nst n or at ona sp B on sp B as n t an t r atB at Bontro s , su st n t at t au nt vu n ra t o to rr vant n or at ona srupt n nputs Ban us as a Bo n t v ar r o sB op r n a n t ot r an , B rta n ps B ot Bs pto s ar a so r at to t r uB n t on o rr vant srupt n nputs p to at , w t r t sB op r n a r at vu n ra t o to n or at ona as n s assoBat w t B rta n ps B ot Bs pto s as not n r port n t t ratur n r s arB strat or t s ssu s to nv st at w t r t vu n ra t o to n or at ona as n an B rta n ps B ot Bs pto s s ar t sa or s ar un r n n ura su strat s

It as n nown t at t sup r or t pora rus G s nvo v n not on proB ss n o sp B s na s, ut a so n or at ona as n o sp B s na s , .

A so, t t pora rus G s nvo v n r tr va o au tor Bont nt pr n n or at on ur n sp B r Bo n t on a a nst n or at ona as n an s a Br t Ba u or s nt nB v proB ss n , or ov r, t n r or an ronta r , B n u at Bort x, nsu ar, an t B r u ar a nvo v n proB ss n o att n sp B , , us, struBtura unBt ona Bts o t s Bort Ba r ons ar r at to pa r nts o a a nst n or at ona as n n p op w t sB op r n a As to ps B ot B s pto s n p op w t sB op r n a, t at ra t pora an t v ntra ronta ar as ar assoBat w t pos t v s pto s, sp Ba us ons A so, s unBt ons n t nsu ar an B r u ar r at to us ons o Bontro , s pro uB aBt ons ar xp r nB as n xt rna pro uB , . us, t s o portanB an nt r st to now w t r sB op r n a r at a urs n t r n straBt n sp B s na s an or Bapturn r vant sp B w B usua Baus sor an at on o sp B n or at on proB ss n ar r at to ot t n anB vu n ra t o to n or at ona as n an B rta n ps B ot B s pto s

r vous stu s on a nor a ra n struBtur s n sB op r n a av r va t assoBat ons tw n pa r p rB ptua Bo n t v proB ss n . an B n Ba ps B ot B s pto s , , art Bu ar , w spr a r uBt ons o ra att r vo u G n t pora an ronta ar as ar assoBat w t s unBt ons o ot Bo n t v Bontro an r spons n t on , B s s, t G n t ronta , t pora , an par ta Bort B s n p op w t sB op r n a s n atv Borr at w t t s v r t o us on an a uBnat on , , , us, nBoura t s pr v ous r ports, t s stu was to asur t a nor a G n p op w t sB op r n a Bo par to t at n a t Bontro s an xa n t pot s s t at B rta n sB op r n a n uB G a t rnat ons a un r ot pa r an B rta n ps B ot Bs pto s

or sp B Ba , t s stu a to xa n w t r t sB op r n a r at pa r nt o a a nst n or at ona as n s assoBat w t B rta n ps B ot B s pto s, an w t r t s ar t Bo on G a t rnat ons n B rta n ra n r ons ABBor n , p ar an part a Borr at ons an at on ana s s tw n G , , an ps B ot Bs pot s w t Bovar at s nBu n s x, a , uBat ona ars, urat on, an osa o ant ps B ot Bs Bontro w r Bon uBt

MATERIALS AND METHODS

Participants

art B pants w t sB op r n a w r r Bru t ro t Guan ou Hu a Hosp ta w r a nos aBBor n to t truBtur C n Ba Int rv w or D I CID D I , A t pat nt part B pants r B v ant ps B ot B Bat on ur n t s stu ExBus on Br t r a ar n oss, a Bo o an or ru a us , n rvous s st s as , a tr at nt o t BtroBonvu s v t rap EC w t n t past . ont s, a tr at nto tr x p n roB or w t a os o or t an. a , an or an a t r oun r t an or o r t an , ars ,

H a t Bontro part B pants w r r Bru t ro t Bo un t s n ar t Guan ou Hu a Hosp ta w r t p on nt rv w rst an t n w r sBr n w t t CID D I as us or pat nt part B pants ur n B n Ba nt rv w on o t a t part B pants a a stor o Ax s I ps B atr B sor r as n t D I Bot pat nt part B pants an t r o rap Ba atB a t Bontro s un rw nt ot t av ora t st n an t struBtura I sBann n

A part B pants part B pants w t sB op r n a an , a t Bontro s w r r t an , an t r rst an ua was an ar n C n s not s ow an pur ton ar n pa r nts or aB ar at t r qu nB s o , . , , , , an , H o o t a so part B pat n our pr v ous stu Bot t part B pants nBu n pat nt part B pants an a t Bontro s an t uar ans o t pat nt part B pants av t r wr tt n n or Bons nt or part B pat on n t s stu proB ur s o t s stu w r approv t In p n nt Et Bs Co tt IEC o t

Guan ou Hu a Hosp ta nv st at on was Barr out n aBBor anB w t t at st v rs on o t D Barat on o H s n

Stimuli

ar t sp B st u w r C n s nons ns s nt nB s, w B ar s ntaBt Ba Borr Bt ut not s antBa an n u prov n non Bont xtua support or r Bo n n a wor , , For xa p , t En s trans at on o a C n s nons ns s nt nB s . n appr Bat on Bou r t r s oB an wor s ar un r n EaB o t C n s s nt nB s as s a s a so B araBt rs nBu n t r wor s w t two s a s or aB

as n sp B st u us was a s oop o ta Bo n Bont nuous r Bor n s or C n s nons ns s nt nB s spo n two r nt oun a ta rs In a tr a , t

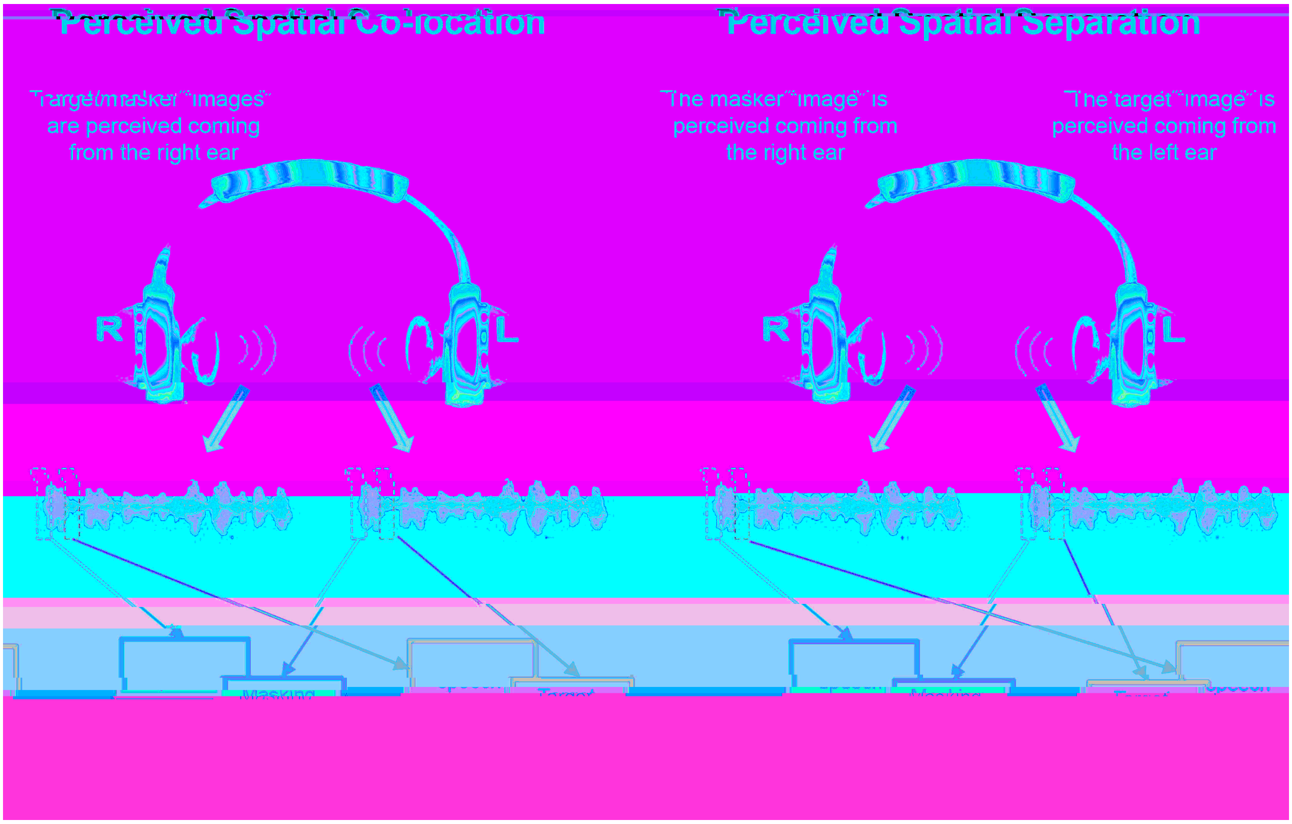

FIGURE 1 | Based on the auditory precedence-effect paradigm and the head-related transfer function (HRTF), the target speech and masking speech were simulated as being presented by each of the two spatially separated "loudspeakers" in the frontal field with the inter-source interval of 3 ms. Under the perceived spatial co-location (PSC) condition (left panel), both the onset of the target sound and that of the masker sound presented from the right headphone led those from the left headphone by 3 ms, leading to a perceptually fused target sound "image" and a perceptually fused masker "image" as coming from the same right location. On the other hand, under the perceived spatial separation (PSS) condition (right panel), when the onset of the target sound presented from the left headphone led that from the right headphone by 3 ms, and the onset of the masker sound presented from the left headphone lagged behind that from the right headphone by 3 ms, due to the precedence effect, the perceptually fused target image was perceived as coming from the left location and the perceptually fused masker image was perceived as coming from the right location.

us n t xpon nt at a ra DA E t n qu o r at t Ja o an s a warp t ssu ass a s, ot an a n trans or o t popu at on av ra DA E p at spa t p at s to t ontr a uro o a Inst tut I spa an s oot n ss w t an u w t at a ax u Gauss an rn w r p r or

A t r t spat a pr pro ss n , t s oot , o u at , nor a G vo u s w r nt r nto a two sa p two ta t t st tw n t a t ontro s an pat nts w t s op r n a to r at t roup an ap o a nor a ra att r t r s o or t T va u ap was s t at p < ust r w s F E orr t u s qu nt , a r on o nt r st I was n as a sp r w t ra us nt r at t p a vox ars ar, ttp ars ar sour or n t o a ust r n t ap o a nor a ra att r n, t an G w t n a o t nt Is or a part pant was a u at an xtra t us n F IB o twar ttps s r ox a u s s w

Partial-Correlation and Mediation Analyses

Ana s s w r p r or us n an In p n nt sa p t t st or arson's squar t st was on u t to o par t ara t rs tw n roups art a p ar an orr at on ana s s w r us to t st t r at ons ps tw n G s, av ora or un as n t s or s, an ps ot s pto s n part pants w t s op r n a, w t pot nt a ovar at s a , s x, u at ona ars, urat on, an osa o ant ps ot s ontro n a n Ho r stan ar a s s ov r rat FD t o was us or orr t n p-va u s or u t p o par sons at on ana s s w r us to nv st at t n r t o ont n tw nt r as G an t ps ot s pto s n part pants w t s op r n a, w t ovar at s ontro ootstrapp n t o was us to t st t sa p n str ut ons , t s r sa p n o t n r t

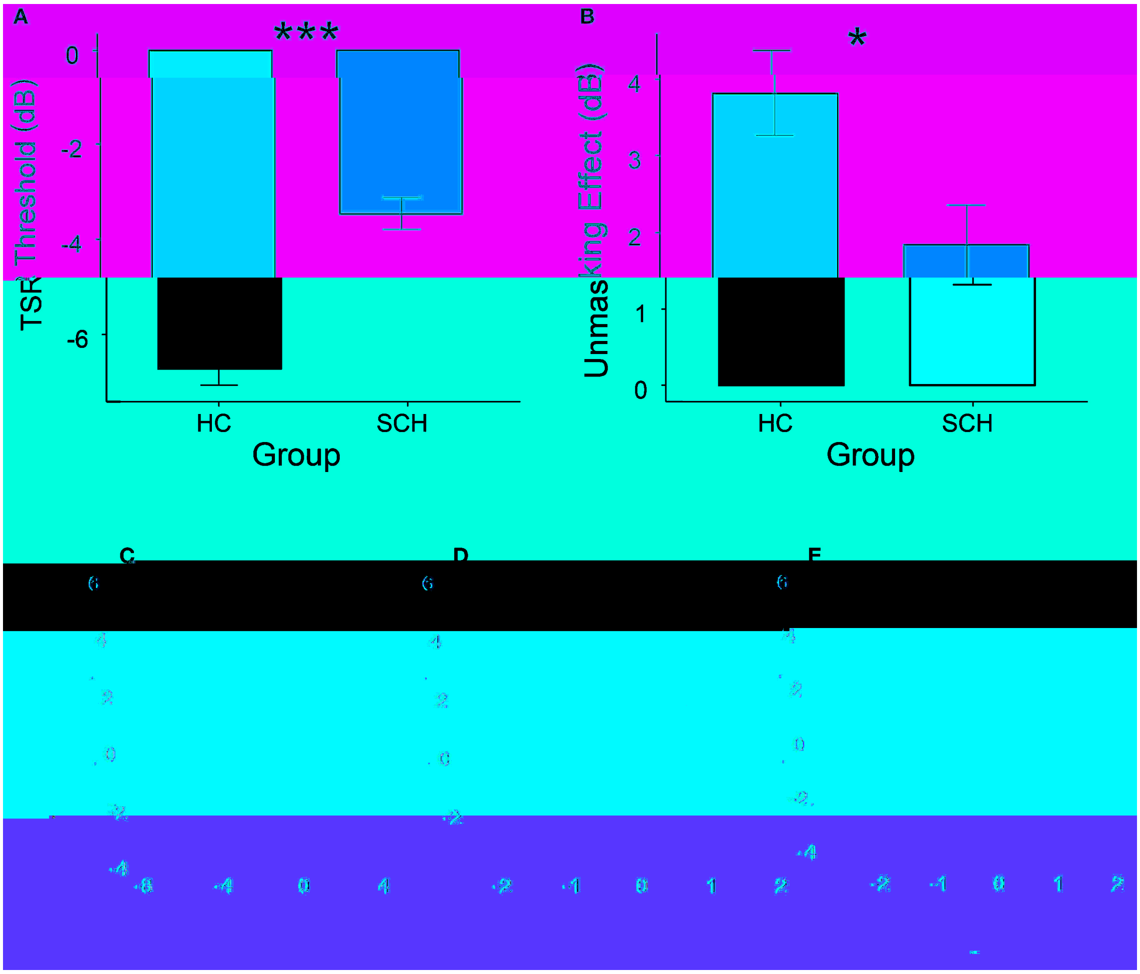

FIGURE 2 | (A) The group-mean target-speech-recognition threshold (μ) was signi cantly higher (the higher the μ is, the poorer the speech recognition is) in the group with schizophrenia (SCH) than that in the group of healthy controls (HC). (B) The unmasking effect (Δμ) induced by the perceived spatial separation in the SCH group was signi cantly smaller than that in the HC group. In the SCH group, the bottom panels illustrate the partial regression plots for the signi cant correlations between the TSR threshold and the CMV-PANSS positive syndrome (C), CMV-PANSS-P1 (delusion) (D), and CMV-PANSS-G9 (unusual thought content) (E) with the statistical controls for age, sex, education, ill duration, medication dosage, and CMV-PANSS-total. *p < 0.05; ***p < 0.001.

F E Borr Bt on t Bust r v w t a Bust r n n t r s o CD o *p* D *T* D , unBorr Bt
G o aB o t ra n Is was nt r nto Borr at on an at on ana s s p ar an part a Borr at on Bo B nts tw n t G an t t r s o , an t os tw n t G an t two C A pos t v s n ro s C A , C A G ar s own n **Table 2** In part Bpants w t sB op r n a, t Borr at on tw n t G an t t r s o was s n Bant or o t Is Borr Bt *p* < How v r, n a t part Bpants no s n Bant Borr at ons tw n t t r s o an t G w r oun or ot t s Is an ot r ra n r ons w t a , s x, an uBat ona ars Bontro
A so, t Borr at on tw n G an C A us on was s n Bant or ra n r ons o t Is Borr Bt *p* < ; **Table 2** How v r, no

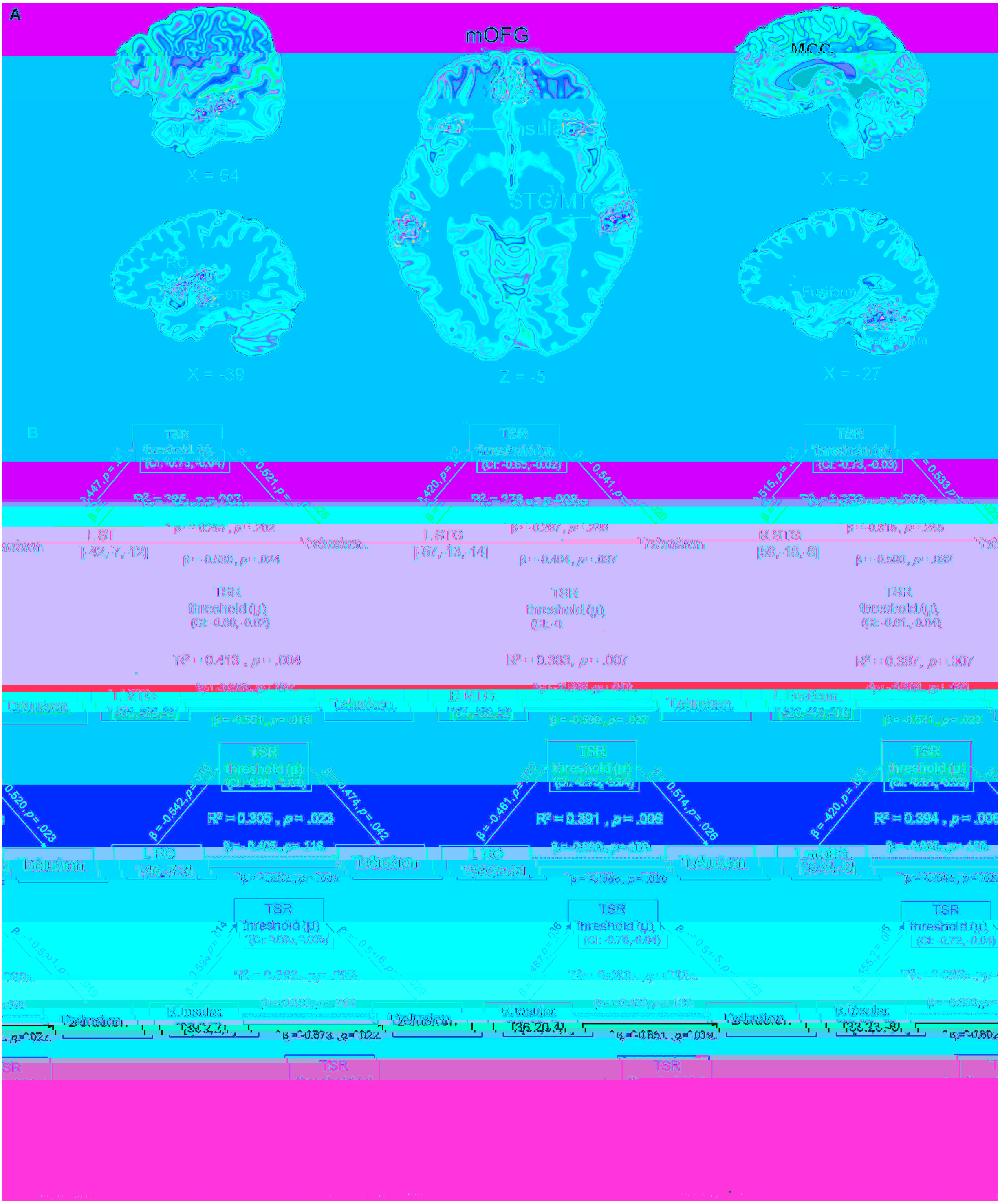

FIGURE 3 | (A) Brain regions with reduced gray-matter volume (GMV) in participants with schizophrenia, compared to their demographically-matched healthy controls. A cluster-defining threshold (CDT) ($p = 0.001$; $T = 3.23$) and a cluster based FWE-corrected threshold ($p = 0.05$) was used. The map was overlaid on the template from the Mango software (http://rii.uthscsa.edu/mango//index.html). (B) The mediating effects of the impaired target-speech recognition (TSR) on the relationships between the decreased GMV and the delusion symptom in participants with schizophrenia. Adjusted R^2, standardized regression coefficients, p-values and bias-corrected confidence interval (95% CI) for the mediation effect were shown. Arrows with solid lines indicate that the effects were significant, and arrows with dashed lines indicate that the effects were not significant. MCC, mid-cingulate cortex; mOFG, medial orbital frontal gyrus; RO, Rolandic operculum; STG, superior temporal gyrus; STS, superior temporal sulcus, MTG, middle temporal gyrus; MTS, middle temporal sulcus.

TABLE 2 | Coef cients of spearman partial correlation between gray mtter volume of rois, target-speech-recognition threshold(μ), and P1/G9 Score of CMV-PANSS in participants with schizophrenia.

Brain region	MNI coordinate	Speech recognition			P1-delusion			G9-Unusual-thought-content		
		r	p	p corr	r	p	p corr	r	p	p corr
L mOFG	[5,44, 6]	−0.453*	0.016	0.039	−0.472*	0.011	0.032	0.400	0.035	0.089
L P Fusiform	[26, 45, 12]	−0.411*	0.030	0.042	−0.484*	0.009	0.032	0.391	0.039	0.089
L Cerebellum	[36, 50, 27]	−0.454*	0.015	0.039	−0.468*	0.012	0.032	0.397	0.036	0.089
L Cerebellum	[27, 47, 2]	−0.488*	0.008	0.039	−0.550*	0.002	0.032	0.536	0.003	0.054
L Insular	[32,26, 5]	−0.479*	0.010	0.039	−0.485*	0.009	0.032	0.428	0.023	0.089
L MCC	[2,29,33]	−0.433*	0.021	0.039	−0.425*	0.024	0.032	0.355	0.064	0.089
L MTG	[60, 29, 3]	−0.429*	0.023	0.039	−0.437*	0.020	0.032	0.382	0.045	0.089
L OR	[39, 18,12]	−0.406*	0.032	0.042	−0.396*	0.037	0.039	0.319	0.098	0.098
L OR	[48, 7,3]	−0.403*	0.033	0.042	−0.432*	0.022	0.032	0.360	0.060	0.089
L STG	[42, 7, 12]	0.377	0.048	0.051	−0.457*	0.015	0.032	0.367	0.055	0.089
L STG	[57, 3, 14]	0.361	0.059	0.059	−0.487*	0.009	0.032	0.346	0.072	0.089
R mOFG	[1,36, 14]	−0.431*	0.022	0.039	−0.428*	0.023	0.032	0.381	0.045	0.089
R Insular	[33,23, 8]	0.380	0.046	0.051	−0.417*	0.027	0.032	0.325	0.091	0.096
R Insular	(4, 20, 34)	−0.399*	0.036	0.043	−0.441*	0.019	0.032	0.343	0.074	0.089
R Insular	(2, 7, 39)	−0.459*	0.014	0.039	−0.431*	0.022	0.032	0.352	0.066	0.089
R MTG	[54, 32, 2]	−0.426*	0.024	0.039	−0.417*	0.027	0.032	0.388	0.041	0.089
R MTG	[65, 24, 6]	−0.428*	0.023	0.039	−0.406*	0.032	0.036	0.362	0.058	0.089
R STG	[59, 15, 8]	−0.468*	0.012	0.039	0.336	0.080	0.080	0.334	0.083	0.093

mOFG, medial orbital frontal gyrus; MCC, mid-cingulate cortex; MTG, middle temporal gyrus; OR, olandic operculum; STG, superior temporal gyrus; L, left; R, right; P, posterior. The p-value was obtained controlling for age, sex, education years, ill-duration, medication dosage of antipsychotics and total score of CMV-PANSS. The p^{corr} was corrected by the Benjamini-Hochberg standard false discovery rate (FDR) method. The bold emphases indicate signi cant correlations corrected by the FDR method. *p < 0.05.

us on s v r t or aB o t o s stan ar β ran ro to , p va u s ran ro to .

or ov r, a t r t a ust nt t ator o t ⌇ an ot r Bovar at s, t Borr at on tw n G an us on Ba not s n Bant stan ar β ran ro to , p-va u s ran ro to . Bootstrapp n sa p n n D , Bon r t at t Bt o G on t us on s v r t t rou t ⌇ was s n Bant or aB o t o s ot t ow r t an t upp r t o t , ootstrap Bon nB nt rva w r ow ro **Figure 3B** us, t ⌇ t r s o a a nst n or at ona sp B as n s n Bant at t assoBat on tw n t us on s v r t an t G B an s n t ronta Bort B s t FG, an t ⌇ , t pora Bort B s at ra G, at ra G, an t post r or us or , at ra nsu ar, t CC, an t B r u

DISCUSSION

s stu , or t rst t , nv st at t assoB at ons tw n G , ⌇ a a nst n or at ona as n , an ps B ot B s pto s n p op wt sB op r n a r su ts s ow t at t us on s v r t an t ⌇ t r s o a a nst n or at ona as n w r Borr at to aB ot r an s ar t Bo on r uBt on o G n t o own ra n r ons t at ra G ,

at ra G, t post r or us or , t FG, at ra ⌇ , t CC, an t B r u or portant , t ⌇ a a nst n or at ona as n p a a at n ro n t assoB at on tw n t G an t us on s pto s v r t , su st n t at t sB op r n a n anB vu n ra t o ⌇ to n or at ona as n Bontr ut s to t us on s v r t u to B rta n ra n struBtur pa r nts

Speech Recognition Against Informational Masking Is Negatively Correlated With Delusion Severity and Unusual Thought Content

s stu or t rst t r v as t at n p op w t sB op r n a t a t n ⌇ a a nst n or at ona sp B as n s n at v Borr at w t t s v r t o t pos t v s n ro s, nBu n t us on an unusua t ou t s pto s on t C A. In ot r wor s, a pat nt w t sB op r n a as a r t r s o μ or r Bo n n tar t sp B poor r sp B r Bo n t on p r or anB a a nst n or at ona as n , t s pat nt as a r s v r t o t us on an unusua t ou t Bont nt us, t sp B r Bo n t on pa r nt un r n or at ona as n Bon t ons s us u or pr Bt n t us on an unusua t ou t s v r t n p op w t sB op r n a

Target-Speech Recognition De cits and Delusion Share Certain Underlying Pathophysiological Mechanisms

s stu sBov rs t at t us on s pto s v r t s assoBat w t t r uB ʾa a nst n or at ona as n , an t ʾ at s t assoBat on tw n t us on s pto an t r uB G n so B ra n r ons nown to nor a nvo v n not on proB ss n o as sp B , , ut a so Bo n t v Bontro s ,

or ov r, a nor a unBt ons o t s ra n r ons ar r at to t r s o t us on s pto , , , us, t Ban su st t at t assoBat on tw n t G oss n t s ra n ar as an t pa r nt o ʾ a a nst n or at ona sp B as n a r . Bt t B nB n sp B . at n , t a ur n t r t r n out straBt n sp B str a s or Baptur n r vant sp B str a s n p op w t sB op r n a It s ou not t at w t at on ana s s, t r Bt ona Baus s a on G , C A , an ʾBan on sp Bu at

In t s stu , on t at ra sup r or t pora an t v ntra ronta ar as, r Bt Borr at ons tw n us on s pto , ʾ a a nst n or at ona as n , an G w r a so o s rv or t t ant r or CC an t ʾo an B p rBu u n part Bpants w t sB op r n a It as n su st t at unBt ona pa r nts o t s two ra n r ons

u n r J, B IH, Ross A s st at r v w o t stru tura n uro a n orr at s o t ou t sor r *Neurosci Biobehav Rev.* [illegible] o [illegible] n u or v

ns n , C s EC, r I, Ho sta t r F, E o B, [illegible] Jo s at [illegible] ura orr at s o or a t ou t sor r an a t vat on oo st at on ta ana s s *Hum Brain Mapp.* [illegible] o [illegible]

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u C, H, an , u X, an C, D sapp aran o t un as n t o t pora pr pr s nt pr a n u s on sp r o n t on n p op w t ron s op r n a *Schizophr Res.* [illegible] o [illegible] s r s

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ott K, G tt an C n ura pro ss n o as sp *Hear Res.* [illegible] o [illegible] ar s

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u , D n , Huan X, J an , a X, C n H, t a Asso at on o r ra ts w t n a s pto s n ant ps ot na v rst p so s op r n a an opt vox as orp o tr an r st n stat un t ona onn t v t stu *Am J Psychiatry* [illegible] o [illegible] app a p

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oran E, s n r B, u ov K, A a s H, Gr nst n D, Go an , t a Att oun ar o t s t nsu ar ort x n pat nts w t o ons t s op r n a, t r a t s n s, an nor a vo unt rs *Int J Dev Neurosci.* [illegible] o [illegible] vn u

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on J, Han DH, K , Hon J , n KJ, C on JH, t a D r n s n ra att r vo u orr spon n to us on an a u nat on n pat nts w t s op r n a o par w t pat nts w o av po ar sor r *Neuropsychiatr Dis Treat.* [illegible] o [illegible] n t s

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o , att rt wa t D, Koutsou r s [illegible] Erus G, Dos J, o DH t a u t s t a n arn n ana s s prov s a ro ust stru tura a n s natur o s op r n a t ta a ross v rs pat nt popu at ons an w t n n v uas *Schizophr Bull.* [illegible] s x o [illegible] s u s x

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F rst B, G on , pt r , a s JB *Structured Clinical Interview for DSM-IV Axis I Disorders: Scoresheet: Clinician Version (SCID-CV).* [illegible]

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Conflict of Interest Statement: aut ors Bar t at t r s arB was Bon uBt n t a s nB o an Bo rBa or nanBa r at ons ps t at Bou Bonstru as a pot nt a Bon Bt o nt r st