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Short communication

Correlation between abnormal N-acetyl-aspartate levels in posterior cingulate cortex and persistent auditory verbal hallucinations in Chinese patients with chronic schizophrenia

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ABSTRACT

The aim of this study was to investigate the relationship between persistent auditory verbal hallucinations (pAVHs) and N-acetyl-aspartate (NAA) levels in posterior cingulate cortex (PCC). 117 schizophrenia (SCZ) patients (61 pAVHs and 56 non-AVHs) and 66 healthy controls were included. The P3 item of the Positive and Negative Syndrome Scale and the Auditory Hallucinations subscale of the Psychotic Symptom Rating Scale were used to assess the severity of pAVHs. NAA levels were significantly lower in the AVHs group, and were negatively correlated with pAVHs. Therefore, increasing the NAA levels in PCC may be helpful in treating pAVHs.

1. Introduction

Auditory verbal hallucinations (AVHs), which manifest as illusory misperceptions of sounds in the absence of objective external stimuli (Barber et al., 2021), are one of the positive symptoms of Schizophrenia (SCZ) and affect approximately 60% or more of SCZ individuals (Alderson-Day et al., 2015). Although antipsychotics largely improve the extent and frequency of AVHs (Sommer et al., 2012), about 25% or more of AVHs are still resistant to conventional antipsychotics (Liu et al., 2015). Therefore, AVHs that persist for at least 1 year after treatment with two different mechanisms of action of antipsychotics are referred to as persistent AVHs (pAVHs). While pAVHs are often associated with poor treatment outcomes, high disability, and suicide (Hjorthøj et al., 2017).

AVHs often involve frontotemporal network brain regions that process auditory information and language function (Zmigrod et al., 2016). The cingulate gyrus, which has direct or indirect fiber connections to the prefrontal cortex, is closely associated with cognitive function, self-control, and emotion regulation (Basil et al., 2018). The posterior cingulate cortex (PCC) receives output from the amygdala, orbitofrontal gyrus, and medial prefrontal cortex (mPFC), and transmits nerve impulses to the anterior cingulate cortex (ACC) and striatum, which is an

Abbreviations: AVHs, Auditory verbal hallucinations; SCZ, Schizophrenia; PCC, Posterior cingulate cortex; mPFC, Medial prefrontal cortex; ^{1}H-MRS, Proton magnetic resonance spectroscopy; NAA, N-acetyl-aspartate; NAAG, N-acetyl-aspartate glutamate; tNAA, Total NAA; HC, Health controls; PANSS, Positive and Negative Syndrome Scale; PSYRATS-H, Auditory hallucinations subscale from the Psychotic Symptom Rating Scale; MRI, Magnetic Resonance Imaging; ANOVA, Analysis of variance; ANCOVA, Univariate analysis of covariance; CPZ, Chlorpromazine; PANSS-T, PANSS total score; PANSS-P, PANSS positive score; PANSS-N, PANSS negative score; PANSS-G, PANSS general psychopathology score; FWHM, Full width half maximum; SNR, Signal to noise ratio; CRLB, Cramer–Rao Lower Bound; GM, Grey matter; WM, White matte; CSF, Cerebrospinal fluid.

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important site of contact and may be related to the occurrence of AVHs (Hau et al., 2019).

Proton magnetic resonance spectroscopy (^{1}H-MRS) has often allowed the identification of changes in steady-state metabolites levels in the human brain in many studies (Li et al., 2020). N-acetyl-aspartate (NAA) is a reliable indicator of neuronal vitality and activity and has the largest MRS spectral peak, making it an easily measured marker of neuronal metabolism (Psomiades et al., 2018b). However, only one ^{1}H-MRS study has focused on PCC in SCZ patients (Shimizu et al., 2007). Therefore, the relationship between pAVHs and NAA levels in PCC of SCZ patients deserves further exploration.

Given the relationship between PCC and mPFC and the results of our previous study (Wang et al., 2022), we hypothesized that NAA levels of PCC in the AVHs group might be different from those in the non-AVHs and healthy controls (HC) groups. Therefore, the purpose of this study was to examine the variations of NAA levels in PCC in SCZ patients with AVHs and to further explore the association its association with the severity of pAVHs.

2. Materials and methods

2.1. Subjects

A total of 117 SCZ patients (61 pAVHs and 56 non-AVHs) and 66 HCs were recruited for this study. The inclusion criteria for subjects in this study are detailed in the supplementary material. The sample for this study was drawn from the same sample pool as our previous study (Wang et al., 2022).

2.2. Clinical symptom assessment

The Positive and Negative Syndrome Scale (PANSS) was applied to evaluate the severity of the patients' current psychotic symptoms (Kay et al., 1987), while the severity of pAVHs was assessed using the Auditory Hallucinations subscale from the Psychotic Symptom Rating Scale (PSYRATS-H) (Haddock et al., 1999) and the P3 item of the PANSS (Benetti et al., 2015). SCZ patients were divided into two subgroups based on whether they scored ≥ 4 (moderate degree or more) on the P3 item of the PANSS (Kubera et al., 2014).

2.3. MRS data acquisition

Acquisition of MRI data using a 3.0 T Siemens Skyra, Germany MRI scanner with a 16-channel head coil at the MRI Centre of Hunan Children's Hospital. The conversion of antipsychotic medication, scanning parameters for MRI, analysis of MRI data and quality control are detailed in the supplementary material.

2.4. Statistical analysis

Statistical analysis was carried out using SPSS 26. Analysis of variance (ANOVA)/univariate analysis of covariance (ANCOVA), chi-square tests, or Mann-Whitney U tests were used to conduct between-group comparisons of variables when appropriate. Age, gender, and education level were used as covariates in the ANCOVA. Bonferroni correction was used for ANCOVA ($p < 0.05/21 = 0.002$) and multiple comparisons ($p < 0.05/4 = 0.013$). The execution of post hoc tests for multiple comparisons using the Bonferroni correction must ensure that the differences between variables in the above analysis are significant. Partial correlation analysis with age, gender, education level, and Chlorpromazine (CPZ) equivalent dose as covariates was performed to detect the association between the severity of AVHs and the levels of NAA (Bonferroni correction $p < 0.05/2 = 0.025$). All tests were two-tailed and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Sociodemographic and clinical data

The sociodemographic and clinical data characteristics of the subjects in this study are shown in Table 1. The HC group had significantly higher education level than the AVH and non-AVHs groups (results of post hoc analysis for AVH vs non-AVHs, $p = 0.17$; for AVHs vs HC, $p < 0.001$; for non-AVHs vs HC, $p = 0.001$).

In terms of clinical symptoms, the non-AVHs group had significantly lower negative symptom (PANSS-N) score ($p = 0.04$), and P3 item (P3) score, total PANSS (PANSS-T) score, positive symptom (PANSS-P) score (all $p < 0.001$) than the corresponding scores for the AVHs group. Compared to the AVHs group, SCZ patients in the non-AVHs group had an older age of onset and a shorter duration of illness.

3.2. Quality of ^{1}H-MRS Spectra

No differences were found among the three groups for grey matter (GM), white matte (WM), cerebrospinal fluid (CSF), signal to noise ratio (SRNR), and full width half maximum (FWHM) ($p > 0.05$) (Table 2). Cramer–Rao Lower Bound (CRLB) values for NAA were $< 20\%$ in all three groups.

3.3. The levels of NAA in the PCC

NAA levels were significantly different among the three groups ($F = 6.94$, $p = 0.001$) (results of post hoc analysis for AVH vs non-AVHs, $p = 0.006$; for AVHs vs HC, $p = 0.002$; for non-AVHs vs HC, $p = 1.00$) (Table 2). It should be noted that when comparing NAA levels between the two patient groups using ANCOVA, the covariate adds the CPZ equivalent dose to the original.

3.4. Correlation of levels of NAA with the severity of AVHs

Bonferroni-corrected results showed that the NAA levels were negatively correlated with the severity of AVHs (P3: $r = -0.39$, $p = 0.003$; PSYRATS-H: $r = -0.40$, $p = 0.002$).

4. Discussion

To the best of our knowledge, this is the first study of a relatively large sample to examine differences in NAA levels in PCC among three groups of participants: AVHs, non-AVHs and the HC groups. In addition, this study included SCZ patients with moderate intensity and higher pAVHs, a population that is representative of treatment resistant SCZ, which will likely contribute to clinical practitioners' understanding of the pathogenesis and treatment of pAVHs in this population.

In the current study, NAA levels were found to be higher in both the non-AVHs and HC groups than in the AVHs group, while there was no difference between NAA levels in the non-AVHs and HC groups. Furthermore, there was a negative correlation between NAA levels and the severity of pAVHs in the AVHs group. These findings are consistent with previous findings. For example, our previous study found that totle NAA (tNAA = N-acetyl-aspartate glutamate (NAAG) + NAA) levels in mPFC were lower in the AVHs group than in both the non-AVHs and HC groups, and that the severity of AVHs was negatively correlated with tNAA levels in the AVHs group (Wang et al., 2022). However, Psomiades, M. et al. (Psomiades et al., 2018a) found lower NAA levels in dorsolateral PFC in non-AVHs group than in AVHs group, and that the severity of AVHs was positively correlated with NAA levels. The reasons for inconsistent study results may depend on the heterogeneity of the clinical sample, sample size, and different study parameters, such as different MRI scan parameters and voxel location and size.

NAA is a neuro-metabolite that reflects the density, function, or viability of neurons, and is also an important neuro-material involved in

Table 1
Demographic and clinical characteristics of patients and healthy controls groups.

Characteristics	HC (n = 66)	Patients (n = 117)		Significance			
		AVHs (n = 61)	non-AVHs (n = 56)	3 groups	HC vs non-AVHs	HC vs AVHs	AVHs vs non-AVHs
					p value		
Gender (M/F), n	30/36	35/26	34/22	χ^2= 3.24 (0.20)	0.09	0.18	0.71
Age(y), (M±SD)	26.70 ± 6.07	25.44 ± 5.80	26.95 ± 5.93	F= 1.11 (0.33)	1.00	0.70	0.52
Education (y), (M±SD)	14.73 ± 2.36	11.89 ± 3.21	12.94 ± 2.81	F= 16.37 (< 0.001)* *	0.001 * *	< 0.001 * *	0.17
Smoker/non-smoker, n	9/57	12/49	13/43	χ^2= 1.91 (0.39)	0.17	0.36	0.64
Drinker/non-drinker, n	2/64	0/61	1/55	χ^2= 1.82 (0.40)	0.66	0.17	0.30
Age at disease onset(y), (M±SD)	–	18.26 ± 5.01	21.48 ± 4.72	–	–	–	U= 1016.5 (< 0.001)* *
Illness duration (y), (M±SD)	–	7.61 ± 4.90	5.75 ± 4.00	–	–	–	U= 1267 (0.03)*
PANSS-P, (M±SD)	–	16.53 ± 4.33	10.45 ± 4.02	–	–	–	U= 475.3 (< 0.001)* *
PANSS-N, (M±SD)	–	15.48 ± 5.42	14.20 ± 7.44	–	–	–	U= 1308.5 (0.04)
PANSS-G, (M±SD)	–	27.73 ± 6.60	27.13 ± 8.81	–	–	–	U= 1452 (0.21)
P3 hallucination item of PANSS, (M±SD)	–	4.93 ± 0.75	1.00 ± 0.00	–	–	–	U= 0.000 (< 0.001)* *
PANSS-T, (M±SD)	–	60.08 ± 12.64	51.77 ± 18.07	–	–	–	U= 995.5 (< 0.001)* *
PSYRATS-H, (M±SD)	–	28.62 ± 5.41	–	–	–	–	–
CPZ equivalent (mg/d), (M±SD)	–	704.21 ± 342.30	607.16 ± 344.46	–	–	–	U= 1385.5 (0.08)

Note: M: mean; SD: standard deviation; n: number; M/F: male/female; pAVH: persistent auditory verbal hallucinations; non-AVH: without auditory verbal hallucinations; HC: health control; PANSS: Positive and Negative Symptoms Scale; PANSS-T: PANSS total score; PANSS-P: PANSS positive score; PANSS-N: PANSS negative score; PANSS-G: PANSS general psychopathology score; PSYRATS-H: the Psychotic Symptom Rating Scale auditory hallucinations subscale; CPZ: chlorpromazine. * : p < 0.05 ; * *: p < 0.01.

Table 2
MRS data of patients and healthy controls groups.

Variable	M±SD			F (p value)[a]	HC vs non-AVHs[a]	HC vs AVHs[a]	AVHs vs non-AVHs[b]
	HC	AVHs	non-AVHs				
NAA[c]	7.47 ± 0.98	6.82 ± 0.85	7.33 ± 0.96	6.94, (0.001)*	1.00	0.002	0.006
NAA//tCr[c]	1.16 ± 0.13	1.12 ± 0.11	1.17 ± 0.12	2.87, (0.06)	0.92	0.56	0.03
SNR[d]	25.64 ± 4.69	23.79 ± 5.13	24.77 ± 4.69	2.31 (0.10)	0.97	0.10	0.83
FWHM, (ppm)[d]	0.066 ± 0.03	0.055 ± 0.03	0.062 ± 0.03	1.76 (0.17)	1.00	0.20	0.68
CRLB (%)[d]	4.83 ± 1.57	5.16 ± 1.47	4.88 ± 1.49	0.87 (0.42)	1.00	0.66	0.91
GM[d]	0.64 ± 0.05	0.64 ± 0.05	0.63 ± 0.06	1.33(0.27)	0.83	1.00	0.33
WM[d]	0.27 ± 0.03	0.27 ± 0.03	0.27 ± 0.32	0.89(0.89)	1.00	1.00	0.56
CSF[d]	0.10 ± 0.06	0.09 ± 0.06	0.10 ± 0.07	0.31(0.73)	1.00	1.00	1.00

Note: M: mean; SD: standard deviation; ANOVA: one-way analysis of variance; AVHs: persistent auditory verbal hallucinations; non-AVHs: without auditory verbal hallucinations; HC: health control; NAA: N-acetyl-aspartate; tCr: total creatine; FWHM: full width half maximum; ppm: parts-per-million; SNR: signal to noise ratio; CRLB: Cramer–Rao lower Bound; %: percent; GM: grey matter; WM: white matte; CSF: cerebrospinal fluid. *: means survival under Bonferroni correction.

[a] The levels of metabolites were compared among the three groups using ANCOVA, with age, gender, and education level as covariates.

[b] The ANCOVA was used to compare the levels of metabolites between the two patient groups with age, gender, education level, PANSS-P score, PANSS-N score, and CPZ equivalent dose as covariates.

[c] Metabolite levels are in institutional units (IU).

[d] One-way analysis of variance (ANOVA).

the maintenance of axon-myelin integrity (Eric et al., 2016; Kossowski et al., 2019). Therefore, NAA abnormalities may reflect neuronal dysfunction. Studies have found that reduced NAA might be associated with neuronal degeneration or loss of dendritic pathology (Kantarci et al., 2002).

AVHs of SCZ patients are associated with increased frontal excitability and abnormal frontotemporal liaison (Mallikarjun et al., 2018). Previous studies have found that AVHs are closely associated with NAA levels in frontal regions (Wang et al., 2022). Meanwhile, the PCC receives output from the amygdala, orbitofrontal gyrus, and mPFC, and transmits nerve impulses to the ACC and striatum, which is an important site of contact and may be related to the occurrence of AVHs (Hau et al., 2019). The results of the present study found that the NAA levels of PCC in the AVHs group were significantly correlated with the severity of AVHs. Based on this theory, we speculate that the metabolic alterations in PCC may be caused by the transmission of pAVHs to PCC through the frontotemporal/fringe lobe neural network when they occur, suggesting that PCC may be a link in the transmission pathway of this neural network.

Several limitations in our study should be acknowledged. Firstly, it was a cross-sectional survey, which limited the elucidation of the causality. Secondly, all patients in this study were taking antipsychotics,

which may have a certain influence on the study results.

5. Conclusion

In conclusion, this study found significantly lower NAA levels in the AVHs group compared to the non-AVHs and HC groups. No differences in NAA levels were found between the non-AVHs and HC groups. Also, NAA levels in PCC in the AVHs group were negatively correlated with pAVHs. Therefore, improving NAA levels in PCC of SCZ patients with pAVHs may help in the treatment of pAVHs.

Ethics approval and consent to participate

The Ethics Committee of the Second Xiangya Hospital of Central South University (No. S006, 2018) supported this study. All subjects signed a written informed consent form.

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Conflict of interest

All authors declare that they have no conflict of interest in this study.

Data availability statement

Original data for this study were requested from the corresponding author where reasonable.

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Author contributions

All authors were involved in the preparation of the article and approved the final manuscript for publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2022.103416.

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