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Research article

The predictive value of baseline NAA/Cr for treatment response of first-episode schizophrenia: A ^{1}H MRS study

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HIGHLIGHTS

- We conducted a ^{1}H MRS study on schizophrenia and healthy controls.
- Schizophrenia patients had lower NAA/Cr than controls.
- Non-hallucination patients had even lower NAA/Cr than hallucination patients.
- Baseline NAA/Cr correlated with PANSS score reduction.
- Baseline NAA/Cr had predictive value for the treatment response.

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ABSTRACT

The study focused on the predictive value of baseline metabolite ratios in bilateral hippocampus of first-episode schizophrenia by using proton magnetic resonance spectroscopy (^{1}H MRS). ^{1}H MRS data were acquired from 23 hallucination and 17 non-hallucination first-episode schizophrenia patients compared with 17 healthy participants. Clinical characteristics of patients were rated using the Positive and Negative Syndrome Scale (PANSS) before and after 3-month treatment. The schizophrenia patients showed lower NAA/Cr ratio than healthy participants respectively ($p = 0.024$; $p = 0.001$), and non-hallucination patients had even lower NAA/Cr ratio than hallucination patients ($p = 0.033$). After 3-month treatment, hallucination patients had greater improvement in negative symptoms than non-hallucination patients ($p = 0.018$). The reduction of PANSS total score and negative factor score was positively correlated with the left NAA/Cr in both group patients ($p < 0.05$). Given that the bilateral hippocampal baseline NAA/Cr had predictive value for the whole treatment response, and the left hippocampal NAA/Cr can predict the prognosis of negative symptoms during acute phase medication in first-episode schizophrenia.

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1. Introduction

Auditory verbal hallucinations (AVHs), or perceptions of external speech in the absence of any stimulus, are often "voices" heard conversing with or commenting on a patient with schizophrenia (SZ), and appears in 70–75% of the affected individuals [18]. However, in clinical practice, a number of first-episode SZ patients, whose major positive symptoms are delusions, have no experience of hallucinations, especially AVHs. To our knowledge, there are few reports about the difference in medication effectiveness between these two kinds of SZ.

Previous documents reveal many predictors of outcome in SZ, including age, gender, negative symptoms, cognitive performance [30], adverse life events, and duration of untreated psychosis [14]. However most of these associations were established retrospectively in chronic SZ, which has made it difficult to predict outcome from the first psychotic episode or drug-naïve state.

Neuroimaging techniques provide evidence that SZ is linked to abnormal structural and neurometabolic integrity of cortical and subcortical areas [7,26]. The best replicated findings were observed for the hippocampus [1,26], and the alterations of its structure, function and metabolite in SZ have consistently been reported [6]. Recent reports reveal the hippocampus is involved in conscious-

Abbreviations: AVH, auditory verbal hallucination; SZ, schizophrenia; ^{1}HMRS, proton magnetic resonance spectroscopy; NAA, Nacetylaspartate; Cr, creatine; Cho, choline; MI, myo-inositol; PANSS, positive and negative syndrome scale.

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

Characteristics	Patients		Healthy participants	Statistic value	*p*
	Hallucination SZ	Non-hallucination SZ			
Gender: male/female (n)	12/11	6/11	7/10	$x^2 = 1.20$	0.548
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)		
Age in years	23.17 (5.19)	26.76 (7.92)	26.94 (6.11)	$F(2,54) = 2.29$	0.111
Years in education	12.35 (1.58)	12.88 (1.73)	12.47 (1.91)	$F(2,54) = 0.49$	0.616
Illness duration, months	5.11 (3.43)	5.65 (3.41)		$F(1, 38) = 2.41$	0.626
Symptoms (PANSS) before medication					
Negative	22.61 (3.01)	23.88 (3.28)		$F(1,38) = 1.62$	0.210
Disorganization	18.13 (2.56)	18.06 (3.45)		$F(1,38) = 0.01$	0.940
Positive	25.22 (2.70)	21.94 (2.61)		$F(1,38) = 14.83$	0.000
Excitement	9.96 (3.08)	9.35 (2.12)		$F(1,38) = 0.48$	0.492
Distress	15.43 (2.39)	16.24 (2.54)		$F(1,38) = 1.04$	0.314
Total score	91.34 (6.14)	89.74 (8.00)		$F(1,38) = 0.71$	0.406
Medication level (chlorpromazine equivalents) (mg/d)	444.78 (73.29)	442.94 (54.63)		$F(1,38) = 0.01$	0.931
Specific medication (mg/d)[#]	n/mean dosage (S.D.)	n/mean dosage (S.D.)			
Olanzapine	18/18.89 (2.74)	11/19.09 (2.02)			
Risperidone	2/5.75 (2.47)	5/6.40 (1.08)			
Quetiapine	3/766.67 (28.87)	1/750.00			
Body mass index (range)[*]	16.53–23.53	18.52–23.88	18.20–23.88		
Body mass index (Mean (S.E.M))[*]	20.68 (0.42)	20.82 (0.45)	20.70 (0.46)	$F(2,54) = 0.03$	0.973

[*] The Body mass index dot plot of each study group was presented in Supplementary Fig. S1. SZ, schizophrenia; PANSS, positive and negative syndrome scale.
[#] Specific antipsychotic dosage of each patient was listed in Supplementary Table S1and Fig. S2.

ness perception of hallucination and relate to symptom severity and antipsychotic dosage [3,34]. Hippocampus, in a position to integrate stimulus-related and spatial or nonspatial contextual information processed in posterior association cortices (parietal and temporal), might be a sensitive structure in cognitive processing in SZ [19]. Moreover, there is evidence for a specific defect of hippocampal interneurons in SZ [10]. As an imaging tool, brain magnetic resonance spectroscopy (MRS) can predict outcome in psychosis disorders [32]. This technique assesses the concentration of various brain metabolites in vivo and gives more detailed information about the integrity of the region of interest at the cellular and metabolic levels [28]. N-acetylaspartate (NAA) is suggested to be a marker of neuronal integrity and indicator for the number of viable neurons [12,28]. The highest concentrations of NAA can be found in pyramidal glutamatergic neurons in rats [16]. Previous reports suggest that dysfunctions of glutamate and other excitatory neurotransmitters have been implicated in the psychopathology of schizophrenia [13], and the reductions in NAA are consistent with glutamate-related excitotoxicity [2]. Choline (Cho) arising from cell membrane phospholipids marks cellular density and membrane turnover [5]. As part of a second messenger system triggering the release of Ca^{2+} in mitochondria and endoplasmatic reticulum, Myo-inositol (MI) can also be regarded as a marker of astroglial activity [9].

In present study, we focused on the baseline metabolite ratios in bilateral hippocampus. We hypothesized that the baseline metabolite ratios may have predictive value of medication outcome, and aimed to explore whether there were differences between hallucination and non-hallucination patients of first-episode SZ.

2. Methods

2.1. Participants

The study involved 40 SZ patients and 17 healthy participants. All participants were right-handed. The healthy volunteers were recruited from medical staff or community people and did not take placebo. They were physically healthy, neither suffering from any neuropsychiatric disorders, nor having any history of head injury or alcohol/substance abuse. All patients were diagnosed as paranoid SZ at the acute first-episode according to the criteria of the International Classification of Diseases-10 [33] and had never accepted any antipsychotic medication before ^{1}H MRS performing. All patients were excluded from suffering any form of systemic and inflammatory disease (i.e., hyperthyroidism, cardiac disease, obesity, rheumatoid arthritis, systemic lupus erythematosus, etc.). Patients underwent a structure interview of Structured Clinical Interview for Positive and Negative Syndrome Scale and rated with the Positive and Negative Syndrome Scale (PANSS) by a senior psychiatrist [11]; Sub-scores for positive, negative, disorganization, excitement and depressive symptoms were created according to a five-factor model of PANSS [31]. According to the hallucination syndrome and PANSS hallucination score (P3), we divided these 40 patients into two groups. Patients who received P3 score of 3 or more than 3 ('mild', 'moderate' or 'extreme' hallucinations) were grouped into the hallucination sub-group ($n = 23$), while patients with a score of less than 3 ('absence' or 'minimal/dubious' hallucinations) were grouped into the non-hallucination sub-group ($n = 17$) [11]. The PANSS total and factor scores between these two subgroups had no significant difference before treatment. After ^{1}H MRS acquisition, all patients were medicated with atypical antipsychotics. No difference was found in antipsychotic dosages (Chlorpromazine equivalent) between hallucination and non-hallucination groups. After 3-month follow-up, all patients were assessed with PANSS by the same psychiatrist. The patient and control groups were age, gender and body mass index matched (Table 1).

All participants provided written informed consent to participate in the study. The study was approved by the local ethic committee.

2.2. Magnetic resonance spectroscopy: data acquisition and processing

Brain MRI and ^{1}H MRS were performed on a clinical 3.0T MR system using a standard eight-channel head coil (Signa HDx, GE Medical System, Milwaukee, WI, USA). The Routine axial T1-weighted fluid attenuation inversion recovery (TR = 500 ms, TE = 15 ms) and fast spin echo T2-weighted MR images (TR = 2800 ms, TE = 105 ms) were obtained to screen for any struc-

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