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Decoupling of brain temperature and glutamate in recent-onset of schizophrenia: a 7 Tesla ^{1}H-MRS study

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Abstract

Background—Converging evidence suggests that cerebral metabolic and cellular homeostasis is altered in patients with recent-onset of schizophrenia. As a possible marker of metabolic changes that might link to altered neurotransmission, we used proton magnetic resonance spectroscopy (^{1}H-MRS) to estimate brain temperature, and we evaluated its relationship to a relevant metabolite, glutamate, within this study population.

Methods—Twenty patients with recent-onset (≤24 months after first psychotic symptoms) of schizophrenia and 20 healthy controls were studied using ^{1}H-MRS at 7 Tesla. We measured levels of *N*-acetylaspartate (NAA) and glutamate, and estimated brain temperature in a non-invasive manner.

Results—Healthy controls showed a significant negative correlation between glutamate and brain temperature in the anterior cingulate cortex. In contrast, the physiological correlation between glutamate and brain temperature was lost in patients with recent-onset of schizophrenia.

Conclusions—This study supports the hypothesized, disrupted relationship between brain metabolism and neurotransmission in patients with recent-onset of schizophrenia. The findings include mechanistic implications that are to be followed up in both preclinical and clinical studies.

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Keywords

anterior cingulate cortex; proton magnetic resonance spectroscopy; brain temperature; schizophrenia; glutamate; imaging

Introduction

Schizophrenia (SZ) is a devastating brain disorder with complex, enigmatic pathology (1–3). Converging evidence suggests that seemingly diverse biological systems are altered in this disease. Involvement of oxidative stress and inflammation has been suggested by epidemiological studies and studies of tissues from patients (4–10), while altered glutamatergic neurotransmission has also been implicated in the underlying pathophysiology (11–15). These varied biological systems may be unified by the hypothesis of dysfunctional homeostatic regulation, with possible links to impaired cellular metabolism and dysfunctional neural networks (16).

Proton magnetic resonance spectroscopy (^{1}H-MRS) may be a powerful approach to address this question, as this methodology allows us to estimate the levels of neurotransmitters and metabolites in the brains of living subjects, while also examining the effects of other clinical factors such as stage of illness and medication exposure (13–15). *N*-acetylasparatate (NAA) and glutamate are biochemically linked through reactions of the tricarboxylic acid (TCA) cycle. NAA is proposed to function as a physiological reservoir for glutamate in the healthy brain, among other roles such as acting as an osmolyte and as an acetate donor in myelination (17, 18).

Brain metabolites in health and disease are influenced by the effect of local cerebral energetics on enzymatically-driven, multi-step pathways. Brain temperature (BT) reflects the balance between heat produced by neural activity/metabolism and dissipation of this heat through blood flow (19–21). In preclinical studies, presynaptic BT gradients reportedly influence the release of neurotransmitters and neurotransmitter removal from the synapse (22, 23). In clinical investigations, an altered relationship between lateral ventricle temperature and cerebral blood flow, as well as the presence of higher occipital-frontal temperature gradient have been observed in SZ (24, 25). Thus, BT may be a useful and underused measure to study dysfunctional, metabolic homeostasis in SZ.

^{1}H-MRS allows the non-invasive and quantitative estimation of human BT *in vivo* (26–29). ^{1}H-MRS thermometry takes advantage of the linear dependence of the chemical shift of water on temperature and estimates temperature within a voxel based on the chemical shift differences between the water peak and NAA peak, the latter serving as a reference (26, 27). The precision of this method relies on the accuracy of resonance frequency determination, which is improved at higher magnetic field strength, such as 7 Tesla (7T), compared to that of lower magnetic field strengths (1.5T or 3T) (30, 31). Moreover, ^{1}H-MRS can be used to examine the relationship between BT and co-localized, physiologically-linked brain metabolites, such as glutamate.

Since brain energy homeostasis affects biochemical cycling of glutamate pools and likely influences glutamate-related circuitry (32), in the present study we used 7T ^{1}H-MRS to estimate glutamate, NAA, and BT in the anterior cingulate cortex (ACC). We then compared the relationship between glutamate and BT between healthy controls and patients with recent-onset of SZ, the latter defined as within 24 months of first psychotic symptoms. The ACC was selected based on evidence that altered neurotransmission in the ACC may be linked to cognitive deficits and negative symptoms in patients with SZ (33, 34).

Methods and Materials

Participants

Twenty patients diagnosed with recent-onset of SZ and twenty healthy controls were enrolled in this study. Patients were recruited from the Johns Hopkins Medical Institutions (outpatient psychiatric clinics), while controls were recruited from flyers in the Greater Baltimore area. All patients were clinically stable at the time of participation. Diagnosis was established and confirmed with the use of the Structured Clinical Interview for DSM-IV (SCID) (35), administered to all participants. Recent-onset was assessed using the SCID and was defined as within 24 months of the first psychotic symptoms. Psychopathology was assessed and quantified by clinical psychiatrists using the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) (36). Chlorpromazine (CP) equivalent dose was calculated (37). Participants were excluded for: (a) age below 18 years old or above 30 years old, (b) history of structural brain injury and/or history of traumatic brain injury with loss of consciousness, (c) any unstable medical condition, (d) history of vertigo, seizure disorder, or middle-ear disorder, (e) contraindication to magnetic resonance imaging (such as metal in the body or claustrophobia), (f) cannabis use in the past four months, (g) short acting benzodiazepine use in the past two weeks, (h) long acting benzodiazepine use in the past four weeks, or (i) pyrexia. All subjects provided written informed consent. The study was approved by a Johns Hopkins Institutional Review Board.

Neuropsychological Assessment

Participants completed a battery of neuropsychological tests (Table S1) to assess performance in domains of processing speed, attention/working memory, verbal memory, visual memory, ideational fluency, and executive function as previously described (38). Factor scores were calculated for each domain after controlling for age, sex, race, and premorbid ability using the Calibrated Neuropsychological Normative System (CNNS) (39, 40). Premorbid ability was estimated using the Hopkins Adult Reading Test (41). Composite neuropsychological performance, defined as the average of all domain scores, was calculated for each participant.

Magnetic resonance imaging (MRI) and spectroscopy acquisition

All scans were performed between noon and 2 pm. Participants were asked to wait 20 min in a standardized room prior to measurement of oral temperature, ensuring acclimatization. Core Body Temperature (CBT) was measured using a digital thermometer that was placed sublingually (42).

All investigations were performed on a 7T whole-body magnetic resonance scanner (Philips, Cleveland, USA) equipped with a birdcage transmit head coil in combination with a 32-channel receive coil (both Nova Medical Inc., Burlington, USA). Head movement was minimized with the use of foam padding. A T_1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (225 slices, 0.8 mm isotropic voxels, repetition time (TR) = 4.3 ms, echo time (TE) = 1.93 ms, flip angle = 7°, field of view = 220 × 220 × 180 mm^3, 276 × 274 acquisition matrix, SENSE factor 4) was obtained for anatomical reference and tissue classification. The spectroscopic voxel (30 × 30 × 30 mm^3) was positioned in the ACC, immediately superior and parallel to the genu of the corpus callosum (Figure 1A).

Spectra were acquired using a STimulated Echo Acquisition Mode sequence (STEAM; TR = 3000 ms, TE = 15 ms, mixing time (TM) = 25 ms, 64 averages with water suppression and two averages without water suppression). Water suppression was achieved using variable pulse powers and optimized relaxation delays (VAPOR) presaturation pulses.

STEAM spectra were analyzed using LCModel version 6.3 (43). The basis set was simulated using VeSPA density matrix simulation program (44), and consisted of 20 metabolites, including glutamate, NAA, creatine (Cr), and phosphocreatine (PCr) with spin systems taken from literature (45) (Figure 1B). The default macromolecule spectra along with the spline baseline from LCModel were used to fit the baseline with an added constraint of 0.2 ppm knot spacing for the baseline. There were no metabolite concentration uncertainties provided by LCModel that exceeded a Cramer-Rao Lower Bound (CRLB) of 2% for glutamate or NAA. Signal-to-noise values were high and full-width half maximum measures were low in all acquired spectra (mean ± standard deviation = 97.0 ± 17.7 and 11.9 ±2.6 Hz, respectively). Glutamate and NAA values from all participants were therefore considered high quality and were then normalized to the value of total creatine (Cr+PCr = tCr) for further analyses. Glutamate/tCr and NAA/tCr are here forward referred to as ‘glutamate ratio’ and ‘NAA ratio’ respectively. Fractional tissue composition of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in the ^{1}H-MRS voxel were calculated using the ‘Gannet’ program (46).

For *in vivo* ^{1}H-MRS thermometry a semi-localized by adiabatic refocusing sequence (sLASER; TR = 3000 ms, TE = 120 ms, 2048 points, 16 averages) was used without water suppression. BT was estimated using the water chemical shift relative to NAA, which was measured using the program ‘csx3’ (47). The water-NAA chemical shift differences were used to calculate BT using the formula given by $BT(Celsius)=282.0-92.2(\delta_{water}-\delta_{NAA})$ (28).

Statistical analysis

All statistical analyses were performed using Stata 13.1 software (STATA, College Station, Texas, USA). We first tested the homogeneity of the sample by using χ^2 test or Fisher’s exact test for dichotomous variables and t-test for continuous variables. Differences between groups were tested using two sample t-tests, with the exception of testing differences in BT and CBT where a paired t-test was employed. Pearson’s correlation or Spearman’s correlation analysis was used depending on the normality of the data. Normality of the data was judged by the skewness and kurtosis normality test. Partial correlation analysis was performed when accounting for CP equivalent dose. Results are presented as mean ±

Standard Deviation (SD). The threshold for statistical significance in all analyses was set as $P < 0.05$, with further correction for multiple comparisons when noted.

Results

Study participants and neuropsychological performance

20 patients and 20 healthy controls completed 7T ^{1}H-MRS acquisition. There were no differences between patients and controls in age, gender, race, and years of education (Table 1). Among patients, the duration of illness ranged from 1–24 months (median 12 months). Six patients and two healthy control participants were smokers. Four patients were not taking antipsychotic medication at the time of participation. Two patients were taking typical antipsychotic medication, and the other 14 patients were taking second-generation antipsychotic medication, the latter of which included two patients taking clozapine). The range of CP equivalents within the study population was 0–400. While the majority of patients were prescribed antipsychotic monotherapy, three patients were prescribed a selective serotonin reuptake inhibitor medication and one was taking lithium.

Patients with recent-onset of SZ had lower composite neuropsychological scores ($P < 0.001$) and lower scores in the domains of processing speed, attention/working memory, and ideational fluency compared to controls ($P < 0.008$, Table 1).

7T ^{1}H-MRS: basic characterization and relationship with neuropsychological performance

There were no differences between patients with recent-onset of SZ and controls in segmentation fractions (white matter, grey matter, cerebrospinal fluid) or in CRLB values, a marker of data quality, for glutamate and NAA (Table S2). The ratio of tCr to water in the voxel was not different between patients with SZ and controls ($P = 0.36$), and there was no correlation found between the ratio of tCr to water and BT, supporting use of tCr for normalization of the glutamate and NAA spectra in this study population. There was no correlation between BT and white matter, grey matter, or cerebrospinal fluid when assessed across the whole study population or within either cohort (patients, controls).

We observed no difference in glutamate or NAA ratios between patients with recent-onset of SZ and controls (glutamate ratio: SZ 1.29 ± 0.10, Control 1.33 ± 0.14, $P = 0.30$; NAA ratio: SZ 1.29 ± 0.07, Control 1.32 ± 0.07, $P = 0.15$). There was also no difference in glutamate or NAA measures relative to water between patients with recent-onset of SZ and controls before or after correction for CSF within the voxel ($glutamate_{uncorrected}$: SZ 7.56 ± 1.18, Control 7.56 ± 1.34, $P = 0.16$; $NAA_{uncorrected}$: SZ 7.56 ± 1.34, Control 8.33 ± 2.45, $P = 0.23$; $glutamate_{CSF\_corrected}$: SZ 8.38 ± 1.24, Control 9.03 ± 1.94, $P = 0.22$; $NAA_{CSF\_corrected}$: SZ 8.38 ± 1.42, Control 9.09 ± 2.55, $P = 0.29$. Using data from the total study population and controlling for cohort, glutamate ratio did not correlate with neurocognitive performance in any cognitive domain. There was also no correlation between glutamate ratio and neuropsychological performance within the control group. Within the patients, glutamate ratio showed a negative correlation with executive function ($r = -0.620$, $P = 0.004$) (Table 2), but no correlation with other domains of neuropsychological

performance. Among patients, glutamate ratio was not correlated with total score on the SAPS (r = 0.37, $P = 0.10$) or SANS (r = −0.16, $P = 0.50$).

Brain temperature (BT)

BT, as measured by ^{1}H-MRS, was higher than CBT in both patients with recent-onset of SZ ($P < 0.001$) and healthy controls ($P < 0.001$), consistent with previous reports (19, 48). Patients with SZ and controls did not differ in BT or CBT (Table S3). There was no correlation found between BT or CBT and sex or age. While ΔT, defined as ΔT=BT-CBT, is higher in some patient populations with robust excitotoxicity, oxidative stress, or inflammatory processes (49–52), in our study population ΔT in controls (0.68 ± 0.72 °C) did not differ from that of patients with recent-onset of SZ (0.84 ± 0.50 °C) ($P = 0.43$). CBT and BT values were not correlated within controls (r = 0.182, $P = 0.443$) or within the patients (r = 0.231, $P = 0.327$).

A negative correlation was found between glutamate ratio and BT in controls (r = −0.527, $P = 0.017$) (Figure 2, Table S4A), but was not found in patients with recent-onset of SZ (r = 0.294, $P = 0.209$), even after correction for CP equivalent dose (r = 0.301, $P = 0.210$) or after exclusion of those four patients who were not taking antipsychotic medication (r = 0.206, $P = 0.445$). The difference in the correlation coefficients between the two cohorts (controls, patients) was significant (Fisher's z = −2.5916, $P = 0.0096$). No correlation was observed in either cohort between a) NAA ratio and BT or b) CBT and either metabolite ratio (glutamate, NAA) (Table S4A). Secondary analyses exploring the relationship between BT, CBT, and other metabolites measured using the LCModel revealed a negative correlation between BT and the combined measure of glutamate and glutamine relative to tCr in controls (r = −0.568, $P = 0.009$) (Table S4A), but this relationship was not found in patients with recent-onset of SZ (r = 0.362, $P = 0.117$), and there were no significant correlations between BT and glutamine/tCr in either cohort. BT did not correlate with neurocognitive performance, or with clinical characteristics (total score on the SAPS or SANS, CP equivalent dose) (Table S4B).

Discussion

Here we report a negative relationship between BT and glutamate ratio in the ACC of the healthy subjects. Interestingly, the correlation between these variables is not observed in patients with recent-onset of SZ. Our results also support the promise of this technique in exploring further the relationship between local BT and metabolite pools.

Physiological fluctuations in BT are increasingly recognized as mechanistically related to co-localized cell function (53). There is accumulating evidence indicating that diverse cellular machinery underlying neurotransmitter release and synaptic transmission are sensitive to local temperature (54, 55). Furthermore both dopamine release and its removal from the synapse dynamically change over the range of physiologic BT (22, 23). Nonetheless, such preclinical knowledge has not translated to clinical studies yet. Though more human studies are needed, the present data suggest that, in health, the total glutamate pool in the ACC may diminish with increased BT, whereas such physiological correlation is lost in patients with recent-onset of SZ. Related, integrative studies with both preclinical and

clinical components are expected to elucidate further the pathophysiological relationship of these measures relevant to SZ.

This study benefits from several technical and methodological strengths: we used a high-field strength scanner at 7T, allowing for better signal-to-noise ratio, and increased spectral resolution. These methodological characteristics allow precise BT measurement and improved ability to quantify glutamate and NAA compared with lower field strengths (31). In our study, we followed strict exclusion criteria, including recent cannabis and benzodiazepine use that could potentially affect the final results (56). Furthermore, we obtained past medical history and systematically assessed neuropsychological performance and symptoms across the population in order to probe the relationship between BT and clinical characteristics.

We also acknowledge the limitations of the present study. First, even with the use of the vendor-supplied macromolecule (MM) basis set in the LCModel, macromolecular resonances may still effect estimations of glutamate concentrations (57). Nevertheless there is no reason to expect any systematic differences in MM resonances between cohorts, and therefore this factor is unlikely to alter the conclusions of this study. Second, the sample size was relatively small. Larger sample size is needed to examine further the relationship between clinical characteristics such as smoking status or medication use and these findings within and between cohorts. Third, spatial coverage was limited to the ACC and we focused on glutamate while other brain regions and other brain metabolites are also relevant to pathophysiology of this disease. Finally, the cross-sectional study design supports descriptive, but not causal interpretations.

Ota *et al.* recently estimated BT in chronic SZ using diffusion-weighted imaging with 3T MRI (24). In this intriguing study, BT was measured inside the lateral ventricle and then tested for correlation with cerebral blood flow in several brain regions (24). A separate study of patients with SZ also examined BT using 3T ^{1}H-MRS, but without references to metabolite concentrations (25). In contrast, as far as we are aware, this study is the first application of ^{1}H-MRS-based BT measurement in psychiatric research at 7T, with the higher magnetic field strength allowing more precise BT measurement due to separation of the NAA peak from that of NAAG. We also uniquely examined the relationship between BT and glutamate in the same brain region, to which measurement of co-localized blood flow (58) could be added in further studies.

Together, the present study highlights the potential utility of ^{1}H-MRS to evaluate altered relationships between BT and metabolite pools that may be affected in parallel in SZ. Loss of these physiological relationships may reflect SZ-associated imbalance between glutamatergic signaling and metabolic cascades. Our findings include mechanistic implications that should be pursued in both preclinical and clinical studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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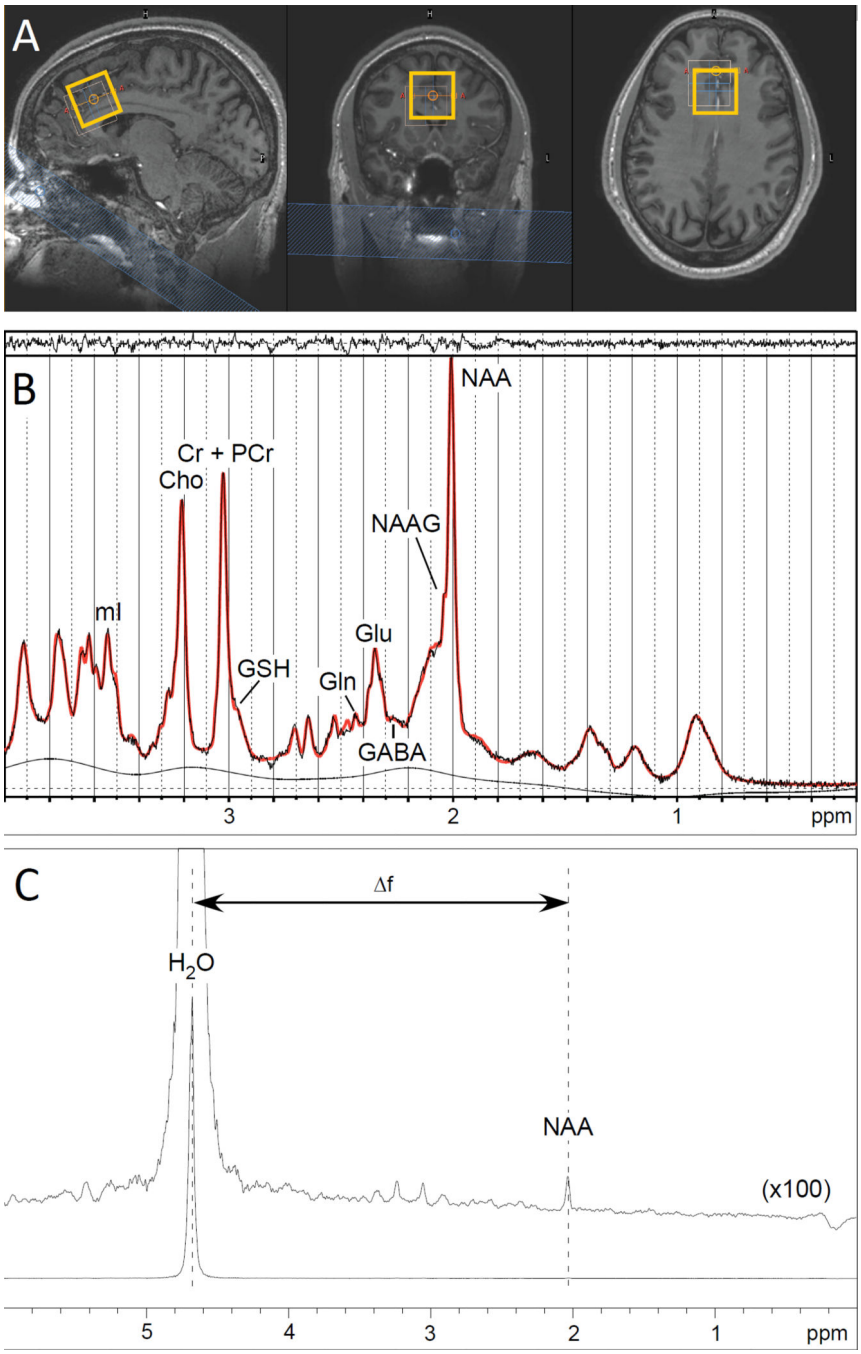

Figure 1. 7T Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

A. Voxel placement. From left to right: sagittal view, coronal view, and axial view of voxel placement in the anterior cingulate cortex (ACC). The thin line shows the chemical shift displacement effect of water relative to NAA (bold line).

B. Representative ^{1}H-MRS spectrum. An example of a spectrum (black line) acquired from voxel placement in the ACC, with LCModel-fitted spectrum (bold red line). Above the spectrum the residual signal after fitting is displayed. The baseline is displayed below the spectrum.

C. Representative spectrum from ^{1}H-MRS thermometry. An example of a spectrum acquired from voxel placement in the ACC using a semi-localized by adiabatic refocusing sequence (sLASER).

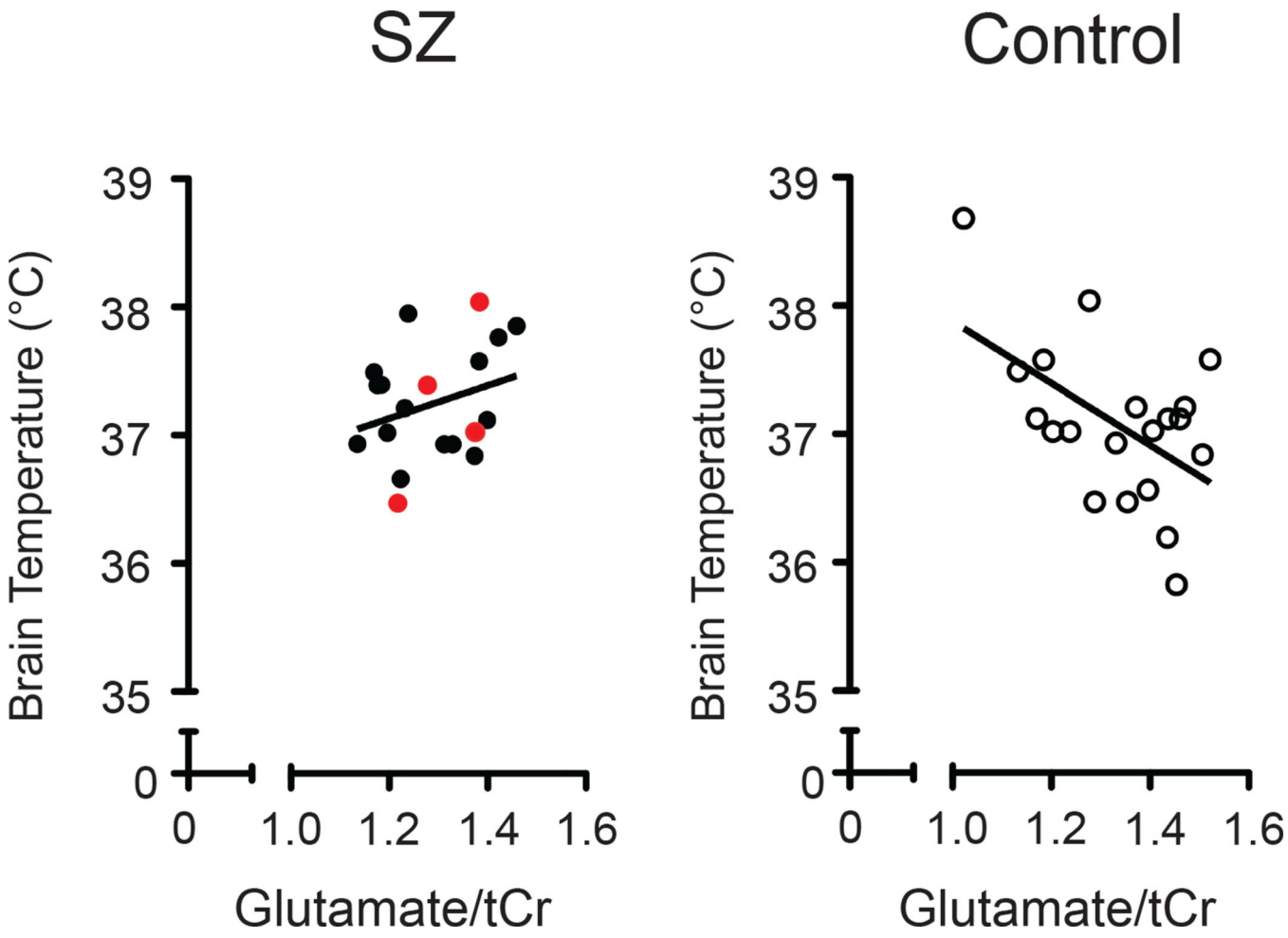

Figure 2. Correlations between brain temperature and glutamate in patients with recent-onset of schizophrenia (SZ) and healthy controls in anterior cingulate cortex

Glutamate values are normalized to total creatine (tCr). Data points from the patient group are indicated with closed circles and those from controls are marked with open circles. The four patients who were not taking antipsychotic medication have data points shown in red. For each group, the solid line represents the linear regression fit. Pearson's correlation coefficient in SZ (r = 0.294, $P = 0.209$) and controls (r = −0.527, $P = 0.017$). Degrees Celsius, °C.

Table 1

Clinical and demographic characteristics

Characteristics	SZ (N=20)	Control (N=20)	*P*
Age (Years)	24.25 ± 4.22	23.10 ± 2.99	0.326
Gender (Male/Female)	13/7	13/7	1.000[a]
Race (African American/Caucasian/Asian)	16/4/0	14/4/2	0.606[b]
Years of Education (Years)	12.83 ± 2.20	13.60 ± 1.96	0.246
Smoking (Yes/No)	6/14	2/18	0.235[b]
CP Equivalent Dose (mg)	188.00 ± 130.59	NA	
Neuropsychological Performance[c]			
Composite	88.19 ± 10.64	100.92 ± 9.10	<0.001*
Processing Speed	86.70 ± 15.84	101.65 ± 16.99	0.007*
Attention/Working Memory	85.60 ± 17.48	104.53 ± 16.86	0.001*
Verbal Memory	84.60 ±14.12	96.70 ± 15.80	0.015
Visual Memory	85.25 ± 16.59	96.45 ± 14.99	0.031
Ideational Fluency	92.85 ± 14.57	107.85 ± 12.23	0.001*
Executive Function	94.15 ± 18.65	98.85 ± 14.02	0.373
SAPS	13.55 ± 16.53	NA	
SANS	17.85 ± 11.99	NA	

Data are displayed as mean ± standard deviation with significance (*P* values) from two sample t-tests unless otherwise specified.

[a] $\chi 2$ test

[b] Fisher's exact test

[c] The threshold for significance in comparisons within each of the six cognitive domains was set as $P < 0.0083$, accounting for multiple comparisons. The threshold for significance in all other comparisons displayed was set as $P < 0.05$.

* Indicates significance.

Not applicable, NA.

Table 2

Relationship between glutamate and neuropsychological performance in the anterior cingulate cortex within patients with recent-onset of SZ.

Clinical Characteristics	Correlation Coefficient[a]	*P*[b]
Neuropsychological performance		
Processing Speed	0.093	0.695
Attention/Working Memory	0.190	0.422
Verbal Memory	0.220	0.351
Visual Memory	0.102	0.669
Ideational Fluency	0.135	0.570
Executive Function	−0.620	0.004*

[a]Pearson's correlation analysis was applied to data from 20 patients with recent-onset of SZ.

[b]The threshold for significance in comparisons within each of the six cognitive domains was set as $P < 0.0083$, accounting for multiple comparisons.

*Indicates significance.