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Age-related changes in anterior cingulate cortex glutamate in schizophrenia: A ^{1}H MRS Study at 7 Tesla

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Abstract

The extent of age-related changes in glutamate and other neurometabolites in the anterior cingulate cortex (ACC) in individuals with schizophrenia remain unclear. Magnetic resonance spectroscopy (MRS) at 7 Tesla, which yields precise measurements of various metabolites and can distinguish glutamate from glutamine, was used to determine levels of ACC glutamate and other

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metabolites in 24 individuals with schizophrenia and 24 matched controls. Multiple regression analysis revealed that ACC glutamate decreased with age in patients but not controls. No changes were detected in levels of glutamine, N-acetylaspartate, myo-inositol, GABA, glutathione or other metabolites. These results suggest that age may be an important modifier of ACC glutamate in schizophrenia.

Keywords

schizophrenia; glutamate; anterior cingulate cortex; magnetic resonance spectroscopy; 7T

1. INTRODUCTION

Imaging, post-mortem pathology, and genetics studies of schizophrenia have shown disruption of the glutamatergic system, yet the specifics remain unclear (Wijtenburg et al 2015). The components of the glutamate system have considerable potential as biomarkers of disease progression, though much is unknown, including the brain regions where measurement may yield the most useful information. The anterior cingulate cortex (ACC) is a region of particular interest in schizophrenia because of its involvement in emotion, attention, and cognition (Benes 2009, Reid et al 2010) and anatomic evidence for disruption in schizophrenia (Roberts et al 2015, Fornito et al 2009). Glutamatergic dysfunction may be modulated by hypofunction of the N-methyl-D-aspartate receptor (NMDAR), leading to increased glutamate release in the ACC, neurodegeneration, and subsequent decreased ACC glutamate levels (Plitman et al 2014). In humans, NMDAR antagonists lead to increased glutamate release and psychotic symptoms (Stone et al 2012; Moghaddam and Javitt 2012). Chronic NMDAR antagonist administered to rats leads to patterns of neurodegeneration similar to those found in schizophrenia, including in the ACC (Olney and Farber 1995).

Severity of symptoms in schizophrenia often decreases with advancing age, and the role of the glutamatergic system in these changes is not understood (Jeste et al 2011). Investigations of glutamate changes using magnetic resonance spectroscopy (MRS), which non-invasively quantifies steady-state concentrations of metabolites in specific brain regions, have reached inconsistent findings. This inconsistency is likely due to a combination of variation in voxel location, different methods of data acquisition and analysis (Wijtenburg et al 2015, Rowland et al 2013, Chang et al 2007), and differences in patient populations including age, disease duration, medication use, and included/excluded co-morbidities. A meta-analysis of studies using MRS at field strengths of 1.5 to 4T revealed lower levels of glutamate in the medial prefrontal region in older patients (Marsman et al 2013). Separating glutamate and glutamine at lower field strengths has proved challenging, despite promising new approaches (Zhang and Shen 2015, Ramadan et al 2013). Studies have shown improved precision of glutamate measurement, distinguishing it from glutamine, at 7T compared to lower field strengths (Mekle et al 2009, Pradhan et al 2015, Tkáč et al 2009). In the current study, therefore, the enhanced spectral sensitivity and resolution of 7T MRS was used to explore differences in ACC glutamate with age in patients with schizophrenia and healthy control subjects.

2. METHODS

2.1 Study Population

27 patients and 27 matched controls were recruited from Johns Hopkins clinics and the surrounding community. Inclusion criteria was diagnosis of schizophrenia or schizoaffective disorder. Exclusion criteria included intellectual disability, history of another central nervous system disorder, history of head injury resulting in loss of consciousness > 20 minutes, alcohol or substance dependence in past 6 months, recent marijuana use, abnormal movements sufficiently severe to interfere with MRI quality, and any contraindication for 7T MRI. All patients were clinically stable on antipsychotic medicines, including aripiprazole, clozapine, fluphenazine, haloperidol, risperidone, quetiapine, olanzapine, and ziprasidone. Four patients were also on low dose benzodiazepines at bedtime.

Controls, recruited from the local community, were matched for age, sex, and education level, and screened to ensure that neither they nor any first degree relative had a history of psychotic illness. The study was approved by the Johns Hopkins Medicine Institutional Review Board, and informed consent was obtained from all participants.

On the day of imaging, all subjects were assessed with the “Mini” Psychiatric Interview, the Montreal Cognitive Assessment (MOCA), the Edinburg Handedness Inventory, the Hopkins Adult Reading Test to estimate premorbid IQ, the Hamilton Depression Rating Scale, the Brief Psychiatric Rating Scale, and an MRI safety screening questionnaire. Data from three patients and three controls were excluded due to difficulties with data collection or processing or late discovery of an exclusion criterion. Data from 24 patients and 24 controls were included in the analysis.

2.2 MRI and MRS Acquisition

Scanning was performed at the F.M. Kirby Center for Functional Brain Imaging on a 7T whole-body scanner (‘Achieva’, Philips Healthcare LLC, Cleveland, OH) equipped with a 32-channel receive head coil (Nova Medical, Wilmington, MA). A high resolution T1-weighted MPRAGE structural image was used for voxel placement and tissue segmentation. MRS data were acquired using a stimulated echo acquisition mode (STEAM) sequence with TE 14ms, TR 3s, TE 28ms and 112 averages (scan time 5min 36s). VAPOR water suppression was used, along with a separate non-water suppressed acquisition for eddy-current correction and quantitation purposes. A $30 \times 20 \times 12$ mm^3 (7.2 mL) voxel was placed in the dorsal ACC, positioned just superior to the genu of the corpus callosum (Fig 1a).

2.3 Spectroscopy Data Processing

The ‘LCModel’ program (Provencher 1993) was used to analyze the spectra with a custom basis set that included 22 metabolites (simulated using chemical shifts and coupling constants from the literature) (Govindaraju et al 2000) (Fig 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. Glutamate (Glu), glutamine (Gln), N-acetyl aspartate (NAA), N-acetylaspartylglutamic acid (NAAG), myo-inositol (mI), GABA,

glutathione (GSH), total creatine (tCr), and total choline (tCh) were quantified relative to the ACC water signal. Only metabolites with Cramer-Rao lower bounds (CRLB) 20% or lower were included in the final analysis, except for NAAG (inclusion at CRLB of 50% or lower). Consequently, 4 NAAG concentrations were excluded from the final analysis.

2.4 Partial Voluming Correction

Metabolite concentrations were corrected for voxel tissue fraction. A voxel mask was created using the in-house program 'SVMask'. The T1-weighted images were segmented using FSL5.0 (Zhang et al 2001) to determine the voxel fractions of white matter, gray matter, and CSF. Corrected metabolite concentrations were calculated by normalizing the metabolite levels by the total tissue fraction for each participant.

2.5 Statistical Analysis

Students' t-test, Fisher's exact test, and multiple regression analyses were performed using Small Stata 14.1 for Mac. Current chlorpromazine (CPZ) equivalents were used as a proxy for lifetime antipsychotic exposure, and patients were divided into high and low CPZ groups by median CPZ equivalents (Andreasen et al 2010).

3. RESULTS

Demographic information is presented in Table 1. There were no significant differences in levels of ACC glutamate, the ratio of glutamate/glutamine, or any other metabolite studied (Table 2) when comparing all patients to all controls. ACC glutamate inversely correlated with age for patients and not for controls, independent of smoking status (Fig 2). For participants under age 40, there was a significant difference in ACC glutamate between patients ($M = 9.72$, $sd = 0.30$) and controls ($M = 8.84$, $sd = 0.18$); $t(25) = -2.47$, $p = 0.021$). For participants over age 40, the lower level of ACC glutamate in patients ($M= 8.38$, $sd = 0.64$) compared to controls ($M = 9.29$, $sd = 0.23$) did not reach statistical significance ($t(11.34) = 1.35$, $p = 0.20$). ACC glutamate/glutamine was not correlated with age for patients or controls. There were no significant relationships between other metabolites and age or smoking status for patients or controls (Supplementary Table). There were no significant differences in ACC glutamate levels between patients with high and low antipsychotic dosages. Excluding patients who were on antipsychotics for less than five years did not affect the results. There were no significant correlations between metabolite levels and MOCA score or between age and MOCA score.

4. DISCUSSION

Using 7T, we demonstrate an age-dependent difference in ACC glutamate between patients and controls. ACC glutamate was higher in younger patients than younger controls, and decreased with age in patients but not controls. This finding is consistent with a meta-analysis of MRS studies at 4T and below in the medial prefrontal cortex (Marsman et al 2013). No difference was found in ACC glutamate when comparing all patients and all controls without controlling for age, consistent with other MRS and postmortem studies of

the glutamatergic system (Wood et al 2007, Reid et al 2010, Kraguljac et al 2012, Barksdale et al 2014).

Decreased ACC glutamate with age may reflect an interaction between aging and disease, longer disease duration, or chronic medication use. The temporal changes in glutamate are consistent with a glutamatergic excitotoxicity hypothesis; increased glutamatergic activity may occur early in the disease, leading to neurodegeneration and decreased ACC glutamate later in the course. There have been discrepancies in the literature on the effect of smoking on ACC glutamate (Durazzo et al 2015, Mennecke et al 2014, Gallinat and Schubert 2007). Co-varying for smoking had no effect on our results.

MRS quantifies all glutamate within the localized voxel, including both ‘metabolic’ and ‘neuronal’ glutamate. The implications of changes in this entire pool of glutamate on neuronal function are not clear (Wijtenburg et al 2015). Given the close metabolic relationship of glutamate and NAA (two biosynthetic steps through aspartate), changes in glutamate levels that are not accompanied by NAA are notable. Similarly, glutamate and glutamine are metabolically coupled, as synaptic glutamate is taken up by astrocytes and converted to glutamine (Wijtenburg et al 2015). Our finding of an age-related decrease of glutamate in schizophrenia, without associated changes in NAA or glutamine, could indicate an age related glutamate specific process, such as dysfunction of Glu-Gln cycling or uncoupling of ACC glutamate and NAA (Coughlin et al 2015), perhaps in a specific neuronal subtype.

The study is limited by a modest sample size. Gender in particular may be an important modifier of ACC glutamate that we could not assess given the inclusion of few women. Another important limitation is the universal treatment of patients with antipsychotic medications. Several MRS studies have shown decreased glutamate or glutamine+glutamate in brain, including in the dorsolateral prefrontal cortex, associative striatum, and medial prefrontal cortex, after the use of antipsychotic medications (Poels et al 2014, de la Fuente-Sandoval et al 2013, Kegeles et al 2012). However, this finding is not consistent, as changes in glutamate in the ACC or thalamus were not detected in other studies when examining antipsychotic treatment over 30 or 80 months (Théberge et al 2007, Aoyama et al 2011, Wijtenburg 2015 et al). We did not find an effect of antipsychotic treatment on ACC glutamate levels in this study, though alternative methods for estimating antipsychotic exposure may have yielded different results.

In conclusion, 7T MRS revealed decreased ACC glutamate with age in schizophrenia patients treated with antipsychotics, suggesting a potential role of 7T as a powerful tool for establishing biomarkers for schizophrenia. Larger scale studies of both younger and older unmedicated individuals, as well as longitudinal assessment of specific individuals, will serve to validate the findings here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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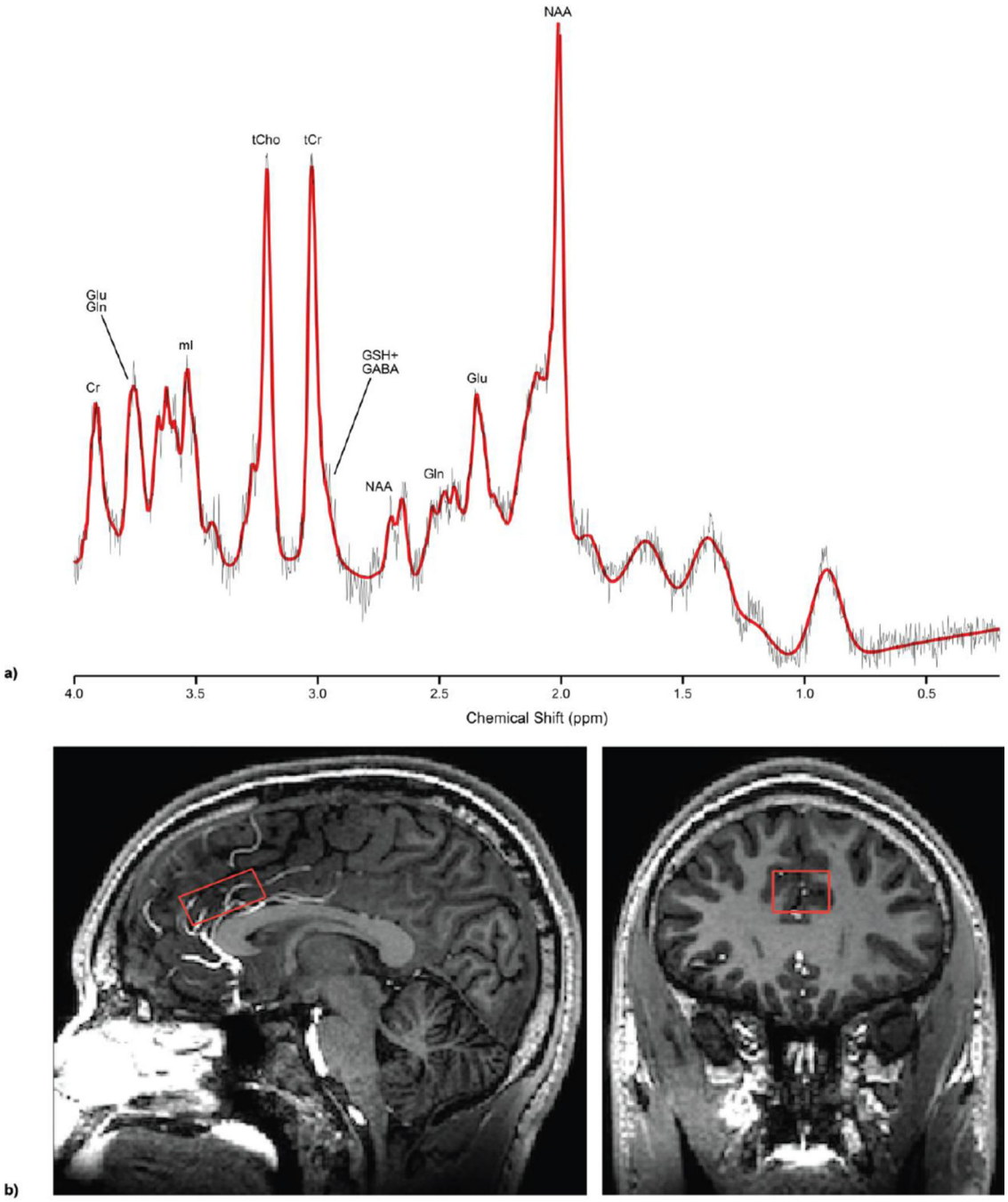

Figure 1.

a) Representative LCModel spectral fit in red with metabolites of interest labeled, b) Location of MRS voxel used in the anterior cingulate cortex region

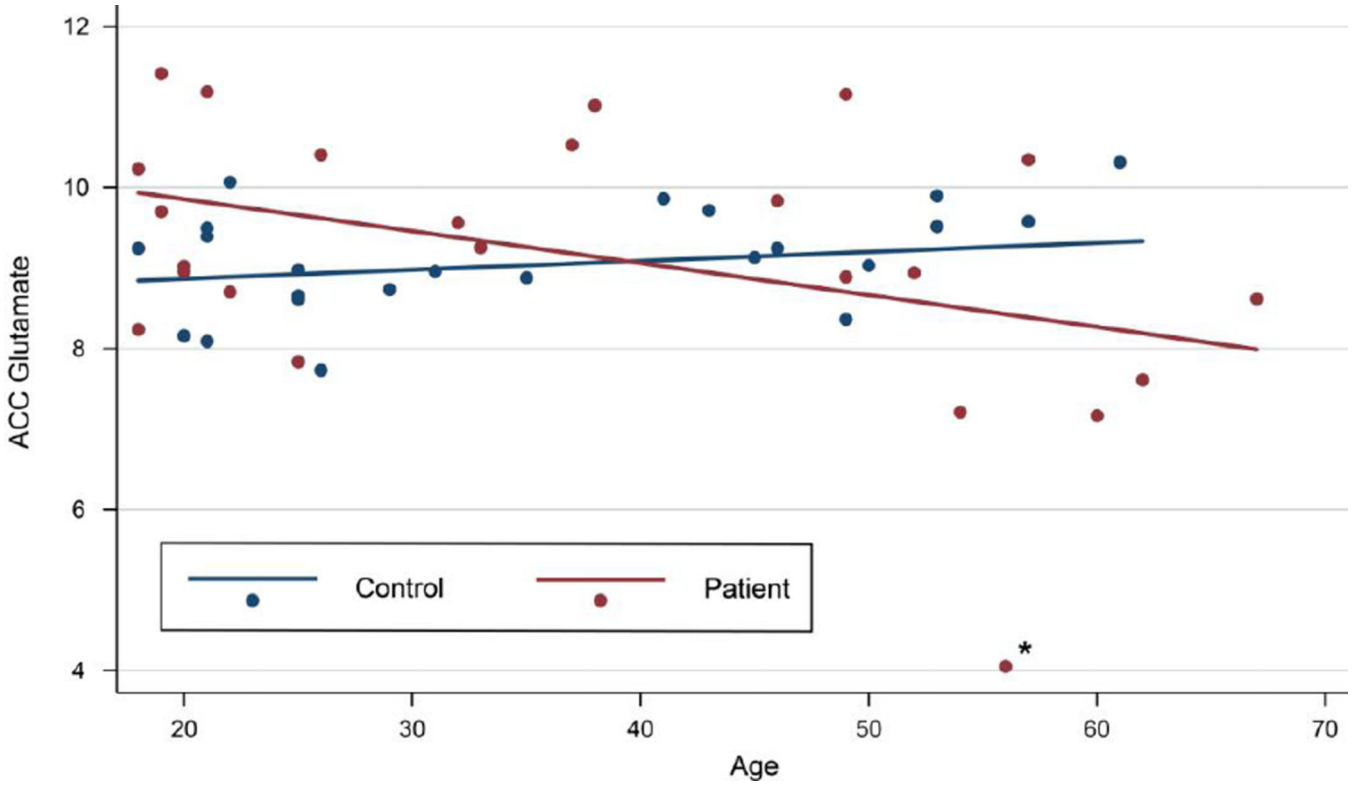

Figure 2. Glutamate levels versus age in control (blue) and patient (red) data sets

By multiple regression ($R^2 = 0.16$), when covarying for age and smoking status, patients showed higher levels of ACC glutamate (β=1.89, p=0.047) than controls. ACC glutamate decreases with age for patients but not controls (β=−0.050, p=0.036). Smoking (β=0.37, p=0.34) did not contribute significantly to the model. When the patient indicated by the asterisk was excluded from the model, patients had significantly higher glutamate than controls (β=1.68, p=0.036), and there was a trend of glutamate decreasing with age for patients (β=−0.037, p=0.065). The intersection between patients and controls occurs at age 40.

Table 1

Demographic and neuropsychological information for controls and schizophrenia patients

Demographics and neuropsychological testing scores for controls and schizophrenia patients. There were no significant differences in mean age, years of education, or premorbid IQ (HART FSIQ), as measured by independent sample t-tests. As measured by Fisher's exact test, patients and controls were equally likely to be male or female and smokers or non-smokers. MOCA scores were significantly lower in patients than controls ($p = 0.003$). Data are presented as mean (standard deviation). A cutoff of $p < 0.05$ was used for significance.

	Control	Patient	*p* - Value
Male/Female	20/4	19/5	n.s.
Age (y)	36.6 (14.6)	37.5 (16.7)	n.s.
Education (y)	12.7 (1.5)	12.6 (1.7)	n.s.
Smoker/Non-smoker	9/15	14/10	n.s.
MOCA	26 (3.3)	23.1 (3.2)	0.003
HART FSIQ	103.6 (9.8)	100.4 (8.8)	n.s.

Table 2
Metabolite concentrations for controls and schizophrenia patients

ACC metabolite concentrations for 24 controls and 24 patients with schizophrenia. Data are presented as mean (standard deviation). A cutoff of $p < 0.05$ was used for significance.

	Control	Patient	*t* Test (*p*)
Glu	9.05 (0.72)	9.16 (1.66)	n.s.
Gln	2.42 (0.51)	2.32 (0.64)	n.s.
Gln/Glu	0.27 (0.06)	0.25 (0.01)	n.s.
NAA	7.87 (0.76)	7.33 (1.83)	n.s.
NAAG	0.68 (0.24)	0.87 (0.52)	n.s.
mI	6.69 (0.88)	6.36 (1.34)	n.s.
GABA	2.24 (0.31)	2.36 (0.41)	n.s.
GSH	1.73 (0.22)	1.74 (0.31)	n.s.
tCr	6.44 (0.58)	6.21 (1.15)	n.s.
tCh	2.16 (0.29)	2.10 (0.47)	n.s.