

University of Groningen

Association of Age, Antipsychotic Medication, and Symptom Severity in Schizophrenia with Proton Magnetic Resonance Spectroscopy Brain Glutamate Level

1H-MRS in Schizophrenia Investigators; Merritt, Kate; McGuire, Philip K.; Egerton, Alice

Published in:
Jama psychiatry

DOI:
[10.1001/jamapsychiatry.2021.0380](https://doi.org/10.1001/jamapsychiatry.2021.0380)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

1H-MRS in Schizophrenia Investigators, Merritt, K., McGuire, P. K., & Egerton, A. (2021). Association of Age, Antipsychotic Medication, and Symptom Severity in Schizophrenia with Proton Magnetic Resonance Spectroscopy Brain Glutamate Level: A Mega-analysis of Individual Participant-Level Data. *Jama psychiatry*, 78(6), 667-681. <https://doi.org/10.1001/jamapsychiatry.2021.0380>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Association of Age, Antipsychotic Medication, and Symptom Severity in Schizophrenia With Proton Magnetic Resonance Spectroscopy Brain Glutamate Level

A Mega-analysis of Individual Participant-Level Data

Kate Merritt, PhD; Philip K. McGuire, FMedSci; Alice Egerton, PhD; and the 1H-MRS in Schizophrenia Investigators

[+ Supplemental content](#)

IMPORTANCE Proton magnetic resonance spectroscopy (1H-MRS) studies indicate that altered brain glutamatergic function may be associated with the pathophysiology of schizophrenia and the response to antipsychotic treatment. However, the association of altered glutamatergic function with clinical and demographic factors is unclear.

OBJECTIVE To assess the associations of age, symptom severity, level of functioning, and antipsychotic treatment with brain glutamatergic metabolites.

DATA SOURCES The MEDLINE database was searched to identify journal articles published between January 1, 1980, and June 3, 2020, using the following search terms: MRS or magnetic resonance spectroscopy and (1) schizophrenia or (2) psychosis or (3) UHR or (4) ARMS or (5) ultra-high risk or (6) clinical high risk or (7) genetic high risk or (8) prodrome* or (9) schizoaffective. Authors of 114 1H-MRS studies measuring glutamate (Glu) levels in patients with schizophrenia were contacted between January 2014 and June 2020 and asked to provide individual participant data.

STUDY SELECTION In total, 45 1H-MRS studies contributed data.

DATA EXTRACTION AND SYNTHESIS Associations of Glu, Glu plus glutamine (Glx), or total creatine plus phosphocreatine levels with age, antipsychotic medication dose, symptom severity, and functioning were assessed using linear mixed models, with study as a random factor.

MAIN OUTCOMES AND MEASURES Glu, Glx, and Cr values in the medial frontal cortex (MFC) and medial temporal lobe (MTL).

RESULTS In total, 42 studies were included, with data for 1251 patients with schizophrenia (mean [SD] age, 30.3 [10.4] years) and 1197 healthy volunteers (mean [SD] age, 27.5 [8.8] years). The MFC Glu ($F_{1,1211.9} = 4.311, P = .04$) and Glx ($F_{1,1079.2} = 5.287, P = .02$) levels were lower in patients than in healthy volunteers, and although creatine levels appeared lower in patients, the difference was not significant ($F_{1,1395.9} = 3.622, P = .06$). In both patients and volunteers, the MFC Glu level was negatively associated with age (Glu to Cr ratio, $F_{1,1522.4} = 47.533, P < .001$; cerebrospinal fluid-corrected Glu, $F_{1,1216.7} = 5.610, P = .02$), showing a 0.2-unit reduction per decade. In patients, antipsychotic dose (in chlorpromazine equivalents) was negatively associated with MFC Glu (estimate, 0.10 reduction per 100 mg; SE, 0.03) and MFC Glx (estimate, -0.11; SE, 0.04) levels. The MFC Glu to Cr ratio was positively associated with total symptom severity (estimate, 0.01 per 10 points; SE, 0.005) and positive symptom severity (estimate, 0.04; SE, 0.02) and was negatively associated with level of global functioning (estimate, 0.04; SE, 0.01). In the MTL, the Glx to Cr ratio was positively associated with total symptom severity (estimate, 0.06; SE, 0.03), negative symptoms (estimate, 0.2; SE, 0.07), and worse Clinical Global Impression score (estimate, 0.2 per point; SE, 0.06). The MFC creatine level increased with age (estimate, 0.2; SE, 0.05) but was not associated with either symptom severity or antipsychotic medication dose.

CONCLUSIONS AND RELEVANCE Findings from this mega-analysis suggest that lower brain Glu levels in patients with schizophrenia may be associated with antipsychotic medication exposure rather than with greater age-related decline. Higher brain Glu levels may act as a biomarker of illness severity in schizophrenia.

JAMA Psychiatry. 2021;78(6):667-681. doi:10.1001/jamapsychiatry.2021.0380
Published online April 21, 2021.

Author Affiliations: Division of Psychiatry, Institute of Mental Health, UCL, London, United Kingdom (Merritt); Psychosis Studies Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom (Merritt, McGuire, Egerton).

Group Information: The 1H-MRS in Schizophrenia Investigators authors and nonauthor collaborators appear at the end of the article.

Corresponding Author: Kate Merritt, PhD, Division of Psychiatry, Institute of Mental Health, UCL, Sixth Floor, Maple House, London W1T 7BN, United Kingdom (k.merritt@ucl.ac.uk).

Glutamatergic dysfunction is implicated in the pathophysiology of schizophrenia,^{1,2} but the nature of this dysfunction may change over the course of illness.^{2,3} Aspects of glutamatergic dysfunction can be investigated in vivo using proton magnetic resonance spectroscopy (1H-MRS), which measures the total amount of intracellular and extracellular glutamate (Glu) in a predefined voxel of interest. Meta-analyses of 1H-MRS studies indicate that glutamatergic metabolites are elevated in patients with schizophrenia compared with healthy volunteers²; however, a recent meta-analysis of 7-T MRS studies reports lower Glu levels in patients,⁴ and individual studies show variable results. This heterogeneity may be associated with factors such as age, illness duration, symptom severity, illicit substance use, and antipsychotic medication exposure, which vary between cohorts. The associations of such factors are best examined in large data sets incorporating patients across different stages of illness.

There is some indication that elevations in 1H-MRS glutamatergic metabolite levels may be most apparent in early psychosis⁵⁻⁸ but reduced in chronic schizophrenia.⁹⁻¹⁴ This finding may be associated with the expression of dysfunctional compensatory processes that emerge secondary to the illness¹⁵ but may also be associated with other factors (eg, divergence from normal aging processes or medication exposure lasting many years). Large studies have not yet reached a consensus on the associations of aging with Glu levels in patients with schizophrenia. An age-related decrease in medial frontal cortex (MFC) Glu level has been observed in both patients and healthy volunteers,¹⁶ but these findings were not replicated by another large study.¹⁷ Alternatively, metaregression analysis has detected accelerated MFC glutamatergic reductions in patients with schizophrenia compared with healthy volunteers,¹⁸⁻²⁰ but this finding was not apparent in a more recent analysis.² Metaregression analyses are limited to using group mean data extracted from individual studies, and thus it is difficult to disentangle age-dependent associations from other clinical factors that correlate with age, such as the duration of illness or the duration of antipsychotic treatment. Indeed, a number of longitudinal studies have reported reductions in brain glutamatergic metabolite levels following antipsychotic treatment in the frontal and temporal lobes among other regions.²¹

There is also a lack of consensus about whether brain glutamatergic metabolite levels are associated with symptom severity and global functioning. A systematic review found inconsistent evidence to correlate Glu levels to symptom severity,²² although many studies were limited by small sample sizes of patients with similar symptom profiles. Individual studies comparing symptomatic and nonsymptomatic patients have reported higher Glu plus glutamine (Glx) levels in the symptomatic group²³ and elevated Glu levels in nonremitted patients compared with remitted patients.²⁴⁻²⁶ However, age may confound these associations if patients with more severe symptoms are younger.

With the aim of better characterizing glutamatergic dysfunction in schizophrenia, we conducted a mega-analysis of individual participant-level data examining the associations of age, antipsychotic medication exposure, diagnosis, symp-

Key Points

Question Are clinical and demographic factors associated with brain glutamate or glutamate plus glutamine (Glx) levels in schizophrenia?

Findings In this mega-analysis of 1251 patients with schizophrenia and 1197 healthy volunteers, medial frontal cortex glutamatergic metabolite levels were lower in patients and negatively associated with the dose of antipsychotic medication, although a reduction in glutamate levels with age was not accelerated in patients with schizophrenia compared with healthy individuals. Higher medial frontal cortex and medial temporal lobe glutamate levels were associated with more severe symptoms in patients with schizophrenia.

Meaning Lower brain glutamate levels may be associated with antipsychotic exposure rather than with greater age-related decline, whereas higher glutamate levels may serve as a biomarker of illness severity in patients with schizophrenia.

tom severity, and functioning with 1H-MRS measures of glutamatergic metabolite levels. We hypothesized that (1) glutamatergic metabolite levels would decrease in association with age in both healthy volunteers and patients; (2) glutamatergic metabolite levels would be associated with a decrease in the context of higher antipsychotic medication doses; (3) glutamatergic metabolite levels would be lower in patients than in healthy volunteers; and (4) more severe symptoms and worse global functioning would be associated with higher Glu levels. In addition, we tested the assumption that these factors are not associated with the combined creatine and phosphocreatine signal (Cr) because Glu is commonly reported in ratio to Cr for analyses.

Methods

The MEDLINE database was searched to identify journal articles published between January 1, 1980, and June 3, 2020, using the following search terms: MRS or magnetic resonance spectroscopy and (1) schizophrenia or (2) psychosis or (3) UHR or (4) ARMS or (5) ultra-high risk or (6) clinical high risk or (7) genetic high risk or (8) prodrome* or (9) schizoaffective. Authors of 1H-MRS studies were contacted at least twice between January 2014 and June 2020 to request anonymized participant-level 1H-MRS metabolite data, which included levels of Glu, glutamine, Glx, and Cr and Cramér-Rao Lower Bound values, which estimate metabolite goodness of fit.²⁷ Clinical and demographic data included positive, negative, general, and total subscores of the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF) scores, Clinical Global Impression (CGI) scores, age, duration of illness, antipsychotic medication dose, and duration of treatment. All methods and results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Analyses were restricted to variables for which a minimum of 3 independent data sets were available.²⁸ Brain metabolite data were categorized into (1) the MFC, including the

anterior cingulate cortex and (2) medial temporal lobe (MTL), including the hippocampus. Data with Cramér-Rao Lower Bound values higher than 20% were excluded. Glutamate values are often corrected for the amount of cerebrospinal fluid (CSF) in the voxel because CSF contains negligible metabolites of interest. Alternatively, Glu is estimated relative to Cr. Herein, CSF-corrected and Cr-scaled values were aggregated separately.

Associations of Glu, Glx, or creatine levels with variables of interest were assessed using linear mixed models in R, version 3.6 (R Core Team),²⁹ with the lmer and ggplot2 packages.³⁰ Independent variables were entered as fixed factors, and study was entered as a random factor. Glutamate and Glx measures are not independent and thus were not corrected for multiple comparisons. Tests of collinearity determined which variables to include in the model. For analyses investigating the association of age with metabolites, model 1 investigated the direct association of age plus group (patient vs healthy volunteers), and model 2 assessed their interaction. The linear mixed models were estimated with maximum likelihoods because residual likelihoods are not comparable across models with different fixed effects.³¹ The lowest Akaike information criterion value indicates the best model,²⁸ and χ^2 tests were used to assess which model was superior. To determine whether metabolite values in patients were best estimated by age or with chlorpromazine equivalent (CPZE) dose (when both were significantly associated with metabolite levels), model 1 included CPZE dose, and model 2 included both age and CPZE dose.

For symptom severity, we reduced the number of comparisons by first testing the association between metabolite levels and PANSS total score. When the association was significant, follow-up analyses investigated the PANSS positive and negative score in one model with restricted maximum likelihoods.²⁸ To investigate the association between Glu level and functioning, GAF scores were examined. If GAF scores were unavailable, then CGI scores were examined. To determine whether patient metabolite values were best estimated by age or by PANSS total scores, model 1 included PANSS total scores, and model 2 included both age and PANSS total scores. For all comparisons, a 2-sided $P < .05$ was considered statistically significant.

Results

The literature search identified 114 studies (eFigure in the Supplement). Of those studies, 45 contributed data (eTable 1 in the Supplement). Two of these studies were not included because data were only available for ultra-high-risk participants,^{32,33} and 1 study was excluded because 1H-MRS was conducted using a J-resolved acquisition approach.³⁴ A total sample size of 1251 patients with schizophrenia (mean [SD] age, 30.3 [10.4] years) and 1197 healthy volunteers (mean [SD] age, 27.5 [8.8] years) were included in the analyses. Sample sizes from each study ranged from 10 to 89 healthy volunteers and from 10 to 147 patients. Twenty-four studies examined patients with first-episode psychosis,^{5,7,11,24,35-53}

and 20 studies examined patients with established schizophrenia.^{11,14,25,35,36,38-40,44,54-63} Four studies did not include healthy volunteer data.^{24,32,61,64}

Association of Demographic and Clinical Factors With Cr Level

In the MFC, Cr levels increased with age ($F_{1,1399.1} = 20.678$, $P < .001$; $n = 1417$) (Figure 1) at a rate of 0.2 units per decade (SE = 0.05). This association did not differ between patients and healthy volunteers (Table 1). In the MTL, there was no association between Cr level and age. There were no significant associations of Cr level with CPZE dose, PANSS total symptoms, or GAF score in either the MFC or MTL.

Association of Age and CPZE Dose With Glutamatergic Metabolite Levels

Duration of illness was associated with age and therefore was not included in the model. Age was not significantly associated with CPZE dose (eTable 2 in the Supplement).

Across all participants, MFC Glu levels decreased with age (Glu to Cr ratio: $F_{1,1522.4} = 47.533$, $P < .001$; $n = 1534$; CSF-corrected Glu level: $F_{1,1216.7} = 5.610$, $P = .02$; $n = 1226$) (Figure 1). The Glu to Cr ratio decreased by 0.04 units per decade (SE = 0.006), and CSF-corrected Glu levels decreased by 0.2 units per decade (SE = 0.07). There was no interaction between age and group (Table 1). The MFC Glx to Cr ratio also decreased with age ($F_{1,1345.4} = 15.685$, $P < .001$; $n = 1357$), by 0.04 units per decade (SE = 0.01). The MFC CSF-corrected Glx level was not significantly associated with age.

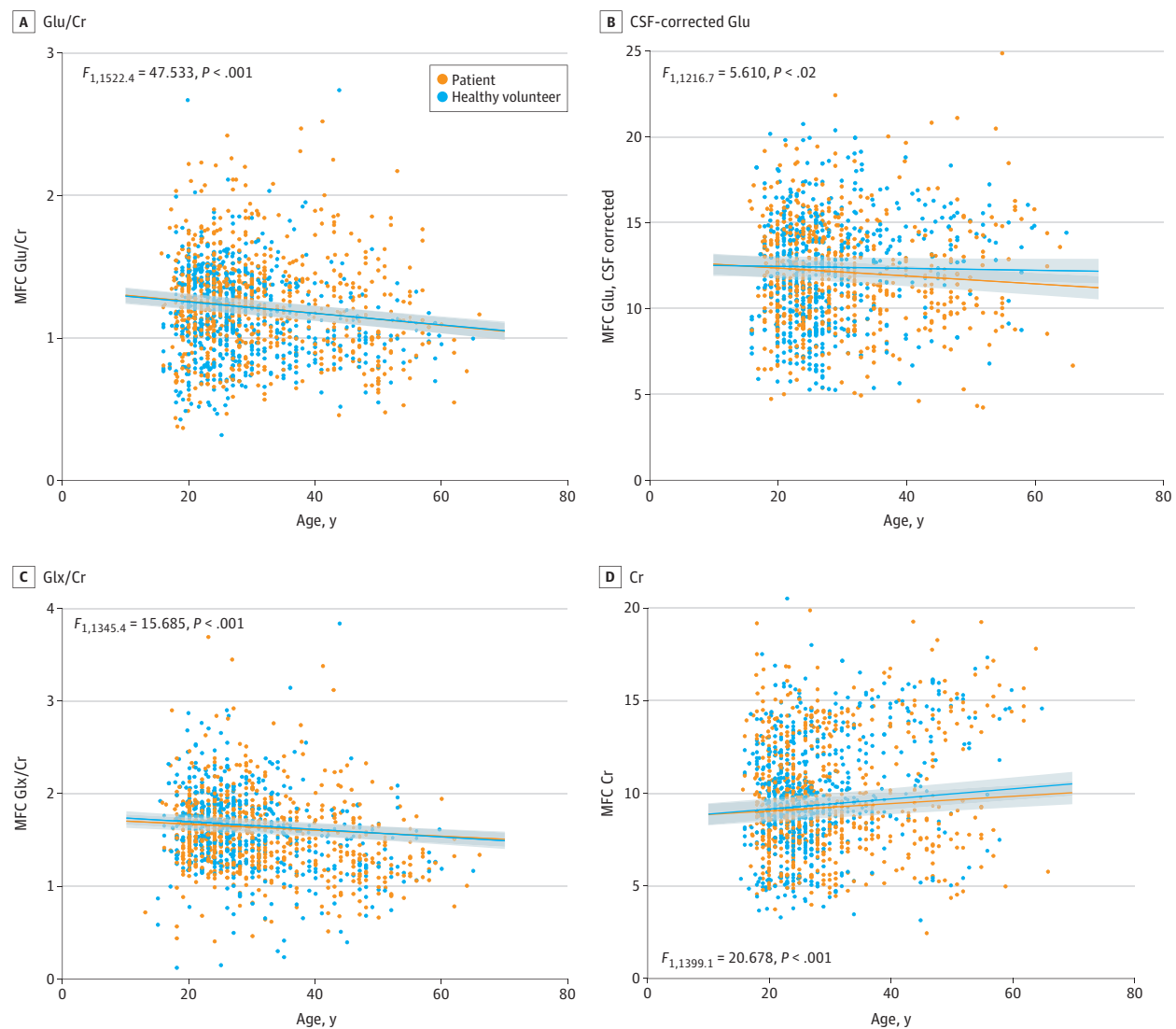
Both the MFC CSF-corrected Glu and CSF-corrected Glx levels were negatively associated with CPZE dose (CSF-corrected Glu level: $F_{1,269.3} = 7.583$, $P = .006$, $n = 276$; CSF-corrected Glx level: $F_{1,251.3} = 6.326$, $P = .01$, $n = 259$) (Figure 2). The CSF-corrected Glu level decreased by 0.10 per 100 mg of the CPZE dose (SE = 0.03), and the CSF-corrected Glx level decreased by 0.11 per 100 mg of the CPZE dose (SE = 0.04). The associations of the CPZE dose with the Glu to Cr and Glx to Cr ratios were nonsignificant.

When assessing the association of age with CPZE dose in the same model, the model combining age and CPZE dose best estimated the MFC CSF-corrected Glu level (Table 1). In contrast to the MFC, in the MTL, the Glx to Cr ratio was not significantly associated with age ($n = 143$ patients with schizophrenia, $n = 151$ healthy volunteers) or with CPZE dose ($n = 94$). There were insufficient data to examine the Glu to Cr ratio, the CSF-corrected Glu level, or the CSF-corrected Glx level in the MTL.

Associations With Group

Both MFC CSF-corrected Glu and CSF-corrected Glx levels were lower in the schizophrenia group compared with the healthy volunteer group while controlling for age ($F_{1,1211.9} = 4.311$, $P = .04$, $n = 596$ healthy volunteers, $n = 630$ patients with schizophrenia; $F_{1,1079.2} = 5.287$, $P = .02$, $n = 519$ healthy volunteers, $n = 573$ patients with schizophrenia) (Table 1). There was no association of group with MFC Glu to Cr ratio or Glx to Cr ratio. However, although not statistically significant, MFC Cr levels were lower in patients com-

Figure 1. Medial Frontal Cortex (MFC) Glutamatergic Metabolite Levels by Age in Patients and in Healthy Volunteers



A, MFC glutamate to creatinine plus phosphocreatine ratio (Glu/Cr). B, Cerebrospinal fluid (CSF)-corrected Glu levels. C, MFC Glu plus glutamine to Cr ratio (Glx/Cr). D, Cr levels. Glu and Glx levels in the MFC decrease with age in patients and healthy volunteers. Cr levels in the MFC increase with age in patients and healthy volunteers. Lines represent the linear mixed model for patients and healthy volunteers, with SEs represented by the gray shaded areas. The CSF-corrected Glu levels and the Cr levels are in arbitrary units.

pared with healthy volunteers while controlling for age ($F_{1,1395.9} = 3.622$, $P = .06$, $n = 712$ healthy volunteers, $n = 705$ patients with schizophrenia). In the MTL, the Cr level and the Glx to Cr ratio did not differ between patients and healthy volunteers.

Association Between Glutamatergic Metabolite Levels and Symptom Severity

The PANSS total, positive, general, and negative subscores were all intercorrelated (eTable 2 in the Supplement); therefore, the initial model examined the PANSS total score. When significant, follow-up analyses investigated the PANSS positive score and the PANSS negative score in 1 model.

The MFC Glu to Cr ratio was positively associated with the PANSS total score ($F_{1,659.1} = 5.819$, $P = .02$, $n = 668$

(Figure 3). The Glu to Cr ratio increased by 0.01 per 10 points on the PANSS scale (SE = 0.005). Subsequent analysis found a positive association between the Glu to Cr ratio and the PANSS positive score ($F_{1,615.7} = 4.382$, $P = .004$, $n = 625$), whereby the Glu to Cr ratio increased by 0.04 per 10 points (SE = 0.02). The PANSS negative score was nonsignificant. The MFC Glu to Cr ratio was negatively associated with the GAF score ($F_{1,171.8} = 13.152$, $P < .001$, $n = 178$) (Figure 3), such that the Glu to Cr ratio increased by 0.04 per 10-point reduction on the GAF scale (SE = 0.01). There were no associations of CSF-corrected Glu or Glx level with the PANSS total or GAF score (Table 2).

The MTL Glx to Cr ratio was positively associated with the PANSS total score ($F_{1,128.7} = 4.508$, $P = .04$, $n = 132$) (Figure 3). The Glx to Cr ratio increased by 0.06 per 10 points

Table 1. Association of Age and Antipsychotic Medication With Glutamatergic Metabolite Levels and Total Creatine Plus Phosphocreatine Levels in Patients and Healthy Volunteers^a

Brain region and source	P or HV, No.	Metabolite, estimated mean (SE)	Clinical variable, mean (SD)	Model 1: main effects	Model 2: interaction effects (age × diagnosis or CPZE dose + age)	Model comparison			
						AIC	Residual deviance	P value ^b	Model selected
Medial frontal cortex									
Cr									
24 Studies ^{5,7,11,14,24,35-38,40,42-47,50,51,54,65-69}	P: 705 HV: 712	P: 9.20 (0.57) HV: 9.37 (0.57)	Age P: 29.55 (10.26) HV: 27.54 (8.62)	Age $F_{1,1399.1} = 20.678, P < .001$ Est (SE), 0.0227 (0.0050) Diagnosis $F_{1,1395.9} = 3.622, P = .06$	Age $F_{1,1399.4} = 21.442, P < .001$ Est (SE), 0.0197 (0.0061) Diagnosis $F_{1,1395.1} = 0.042, P = .84$ Age × diagnosis $F_{1,1394.1} = 0.754, P = .38$	Model 1: 5314.0 Model 2: 5315.3	Model 1: 5304.0 Model 2: 5303.3	.38	1
11 Studies ^{7,11,14,24,37,38,40,42,44,45,65}	P: 283	9.43 (0.68)	CPZE 364.14 (367.76)	CPZE $F_{1,273.8} = 2.179, P = .14$	NA				
Glutamate, Cr-scaled									
25 Studies ^{5,7,11,14,24,25,35,37,38,40,42-47,50,51,57,59,60,65,66,68,69}	P: 797 HV: 737	P: 1.21 (0.05) HV: 1.21 (0.05)	Age P: 30.53 (10.61) HV: 28.14 (8.85)	Age $F_{1,1522.4} = 47.533, P < .001$ Est (SE), -0.0042 (0.0006) Diagnosis $F_{1,1514.8} = 0.071, P = .79$	Age $F_{1,1522.3} = 45.030, P < .001$ Est (SE), -0.0042 (0.0007) Diagnosis $F_{1,1512.2} = 0.060, P = .81$ Age × diagnosis $F_{1,1511.2} = 0.028, P = .87$	Model 1: -577.18 Model 2: -575.21	Model 1: -550.5 Model 2: -543.2	.87	1
13 Studies ^{7,11,14,24,37,38,40,42,44,45,57,60,65}	P: 348	1.27 (0.08)	CPZE 394.10 (369.42)	CPZE $F_{1,338.5} = 0.154, P = .70$	NA				
Glutamate, CSF-corrected									
18 Studies ^{5,7,11,14,24,35,38,40,42-47,50,65,66,69}	P: 630 HV: 596	P: 12.10 (0.59) HV: 12.40 (0.59)	Age P: 29.87 (10.33) HV: 28.18 (8.81)	Age $F_{1,1216.7} = 5.610, P = .02$ Est (SE), -0.0161 (0.0068) Diagnosis $F_{1,1211.9} = 4.311, P = .04$ Est (SE), 0.2522 (0.1215)	Age $F_{1,1216.8} = 4.241, P = .04$ Est (SE) -0.0229 (0.0083) Diagnosis $F_{1,1209.9} = 0.441, P = .51$ Age × diagnosis $F_{1,1208.9} = 2.001, P = .16$	Model 1: 5243.5 Model 2: 5243.5	Model 1: 5233.5 Model 2: 5231.5	.16	1
10 Studies ^{7,11,14,24,38,40,42,44,45,65}	P: 276	12.00 (0.70)	CPZE 382.09 (393.57)	CPZE $F_{1,269.3} = 7.583, P = .006$ Est (SE), -0.0010 (0.0003)	Age $F_{1,274.3} = 17.109, <P = .001$ Est (SE), -0.0574 (0.0139) CPZE $F_{1,269.4} = 7.141, P = .008$ Est (SE), -0.0009 (0.0003)	Model 1: 1223.3 Model 2: 1208.7	Model 1: 1215.3 Model 2: 1198.7	<.001	2
Glx, Cr-scaled									
24 Studies ^{5,7,11,14,24,35-38,40,42-44,46,47,49,50,54,57,59,65-68}	P: 705 HV: 652	P: 1.65 (0.07) HV: 1.66 (0.07)	Age P: 30.74 (10.47) HV: 28.71 (9.04)	Age $F_{1,1345.4} = 15.685, P < .001$ Est (SE), -0.0036 (0.0009) Diagnosis $F_{1,1340.0} = 1.036, P = .31$	Age $F_{1,1346.2} = 15.842, P < .001$ Est (SE), -0.0033 (0.0011) Diagnosis $F_{1,1339.3} = 0.650, P = .42$ Age × diagnosis $F_{1,1336.6} = 0.256, P = .61$	Model 1: 543.84 Model 2: 545.58	Model 1: 533.84 Model 2: 533.58	.61	1
12 Studies ^{7,11,14,24,37,38,40,42,44,49,57,65}	P: 324	1.61 (0.11)	CPZE 400.64 (394.52)	CPZE $F_{1,314.9} = 2.133, P = .14$	NA				

(continued)

Table 1. Association of Age and Antipsychotic Medication With Glutamatergic Metabolite Levels and Total Creatine Plus Phosphocreatine Levels in Patients and Healthy Volunteers^a (continued)

Brain region and source	P or HV, No.	Metabolite, estimated mean (SE)	Clinical variable, mean (SD)	Model 1: main effects	Model 2: interaction effects (age × diagnosis or CPZE dose + age)	Model comparison			
						AIC	Residual deviance	P value ^b	Model selected
Glx, CSF-corrected									
16 Studies ^{5,7,11,14,24,35,38,40,42-44,46,47,50,65,66}	P: 573 HV: 519	P: 16.85 (1.04) HV: 17.31 (1.04)	Age P: 30.48 (10.57) HV: 28.78 (9.02)	Age $F_{1,1082.0} = 0.631, P = .43$ Diagnosis $F_{1,1079.2} = 5.287, P = .02$ Est (SE), 0.4574 (0.1989)	Age $F_{1,1082.5} = 0.472, P = .49$ Diagnosis $F_{1,1077.6} = 1.321, P = .25$ Age × diagnosis $F_{1,1076.8} = 0.181, P = .67$	Model 1: 5615.3 Model 2: 5617.1	Model 1: 5605.3 Model 2: 5605.1	.67	1
9 Studies ^{7,11,14,24,38,40,42,44,65}	P: 259	15.80 (1.45)	CPZE 400.48 (424.59)	CPZE $F_{1,1251.3} = 6.326, P = .01$ Est (SE), -0.0011 (0.0004)	NA				
Medial temporal lobe									
Cr									
7 Studies ^{6,40,43,52,53,67,68}	P: 120 HV: 157	P: 5.15 (1.09) HV: 5.13 (1.09)	Age P: 23.81 (5.75) HV: 24.40 (6.01)	Age $F_{1,270.5} = 1.738, P = .19$ Diagnosis $F_{1,270.6} = 0.033, P = .86$	Age $F_{1,270.5} = 1.755, P = .19$ Diagnosis $F_{1,270.3} = 0.036, P = .85$ Age × diagnosis $F_{1,270.2} = 0.022, P = .88$	Model 1: 731.91 Model 2: 733.89	Model 1: 721.91 Model 2: 721.89	.88	1
3 Studies ^{40,52,53}	P: 68	4.78 (2.83)	CPZE 237.49 (157.83)	$F_{1,65.1} = 1.278, P = .26$	NA				
Glx, Cr-scaled									
8 Studies ^{6,40,43,52,53,56,67,70}	P: 143 HV: 151	P: 1.90 (0.14) HV: 1.91 (0.13)	Age P: 25.70 (6.93) HV: 24.20 (5.16)	Age $F_{1,293.7} = 2.650, P = .10$ Diagnosis $F_{1,293.9} = 0.041, P = .84$	Age $F_{1,293.7} = 2.074, P = .15$ Diagnosis $F_{1,290.6} = 0.396, P = .53$ Age × diagnosis $F_{1,288.9} = 0.494, P = .48$	Model 1: 352.46 Model 2: 353.96	Model 1: 342.46 Model 2: 341.96	0.48	1
4 Studies ^{40,52,53,56}	P: 94	1.93 (0.25)	CPZE 241.16 (154.68)	$F_{1,92.4} = 0.450, P = .50$	NA				

Abbreviations: AIC, Akaike information criterion; CPZE, chlorpromazine equivalent dose; Cr, creatine plus phosphocreatine; CSF, cerebrospinal fluid; Est, estimate; Glx, glutamate plus glutamine; HV, healthy volunteers; NA, not applicable; P, patients.

^a If age and CPZE dose are significantly associated with glutamatergic metabolites, then model 1 including CPZE is compared with model 2 including both CPZE and age. When χ^2 test for model comparison is not significant, then the simplest model is selected.

^b Determined by use of the χ^2 test.

(SE = 0.03). Subsequent analysis found a positive association between the Glx to Cr ratio and the PANSS negative score ($F_{1,129.8} = 10.162, P = .002, n = 132$), such that the ratio increased by 0.2 per 10 points (SE = 0.07). No significant association was found for the PANSS positive score. The GAF data were unavailable. A higher Glx to Cr ratio was associated with a worse CGI score ($F_{1,73.0} = 10.914, P = .002, n = 76$), whereby the ratio increased by 0.2 per point on the CGI scale (SE = 0.06).

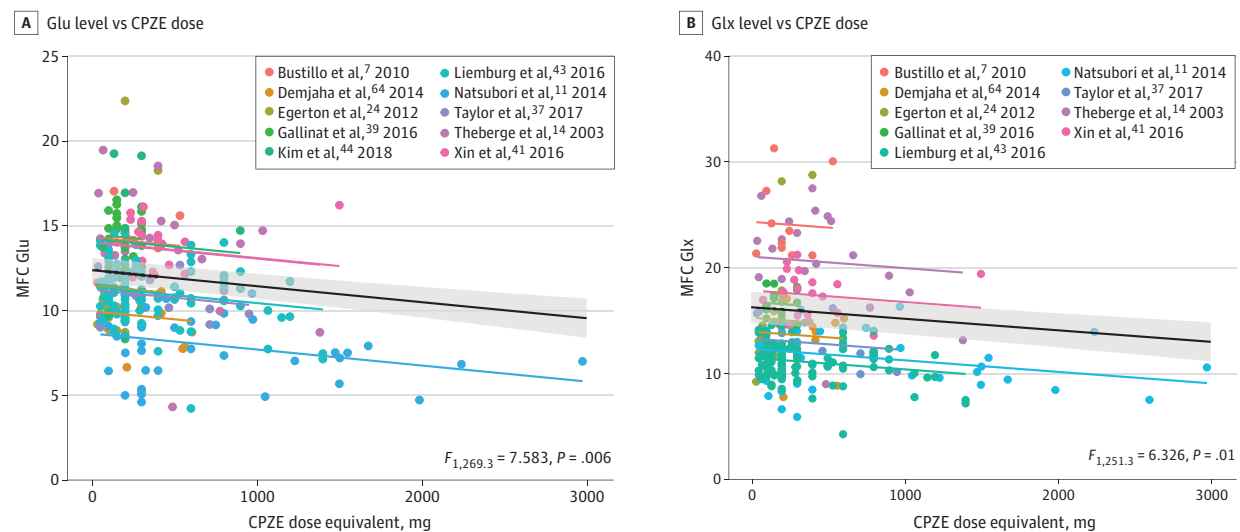
In the MFC, the PANSS total score was negatively associated with age, such that younger patients had more severe symptoms (eTable 2 in the Supplement). We compared whether the variance in the Glu to Cr ratio was best explained by age, PANSS total score, or both. The model including both age and PANSS total score showed the best fit (Table 2). The PANSS total score and CPZE dose were positively associated in the mega-analysis sample, such that

patients with more severe symptoms received a higher CPZE dose (eTable 2 in the Supplement).

Discussion

We conducted a participant-level mega-analysis to assess the association between 1H-MRS glutamatergic metabolite levels and the clinical and demographic features of schizophrenia. The main findings were negative associations of glutamatergic metabolite levels in the MFC with age in both patients with schizophrenia and healthy individuals and with the dose of antipsychotic medication in patients. Higher MFC Glu to Cr ratios were associated with more severe total and positive symptoms and with a lower level of overall functioning. In the MTL, elevated Glx to Cr ratios were associated with more severe total and negative symp-

Figure 2. Correlations Between Chlorpromazine Equivalent (CPZE) Dose and Medial Frontal Cortex (MFC) Glutamatergic Metabolites



A, Cerebrospinal fluid (CSF)-corrected glutamate (Glu) levels.^{7,11,14,24,38,40,42,44,45,65} B, CSF-corrected Glu plus glutamine (Glx) levels.^{7,11,14,24,38,40,42,44,65} The black line represents the linear mixed model, with SE represented by the gray shaded areas; the random-intercept models for each study listed are shown in different colors.

toms and with worse CGI scores. In patients, MFC Glu levels were lower than in healthy volunteers irrespective of age, and there was a nonsignificant trend for lower Cr levels in patients. In the MFC, Cr levels, a measure commonly thought to be independent of age, increased with age in both patients and healthy volunteers. Overall, these results indicate that higher Glu levels may be associated with greater illness severity but that Glu levels may be reduced through effective antipsychotic treatment to below those observed in healthy volunteers.

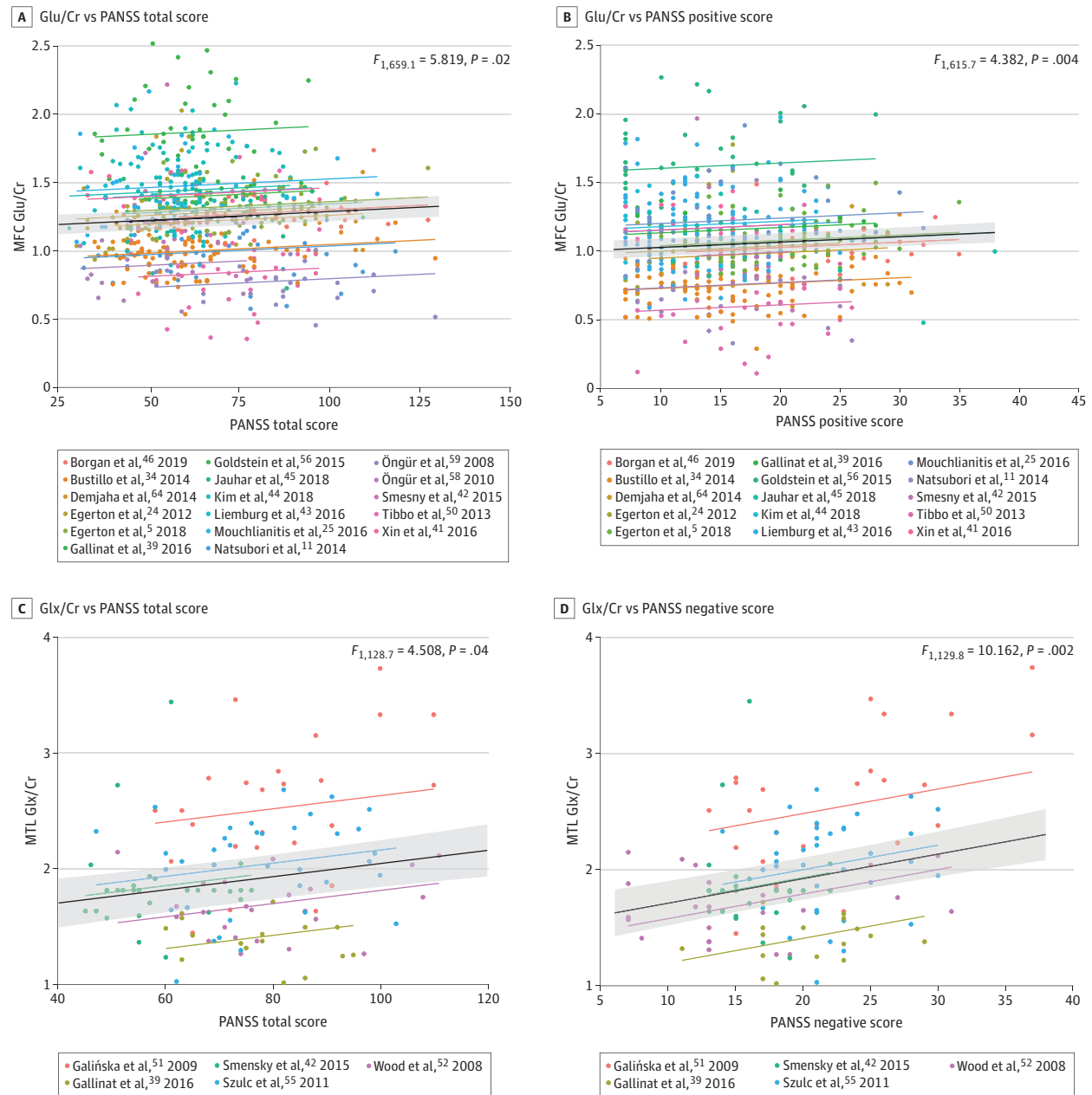
The finding that MFC Glu levels decrease with age in patients with schizophrenia in a manner similar to healthy volunteers suggests that these reductions may reflect normal aging processes in this brain region (2%-3% reduction of mean Glu metabolite per decade). This is consistent with a recent meta-analysis of brain Glu metabolite levels in normal aging, which reports a larger effect size for Glu than Glx for age, as glutamine (part of the Glx signal) increases with age.⁷¹ In contrast to that meta-analysis, our mega-analysis did not detect changes associated with age in the MTL. This inconsistency may be due to the smaller number of studies available in this brain region, limiting our analysis to Glx levels and precluding assessment of Glu levels. One previous meta-regression observed an accelerated effect of aging in patients compared with healthy volunteers²⁰; however, this association may have been caused by a group of patients at ultra-high risk. Therefore, reduced Glu levels in patients compared with healthy volunteers in previous reports may not have been caused by greater age-related decline.

Conversely, MFC Cr levels increased with age in both patients and healthy volunteers (2% increase of mean Cr level per decade), consistent with previous studies,⁷²⁻⁷⁵ although 1 study reports no association.⁷⁶ Creatine and

phosphocreatine are involved in energy metabolism, and increased levels may reflect more burden on this system or increased glial cell numbers and activation with age.^{77,78} Caution should be taken when using Cr as a reference metabolite in the MFC because there was a trend for lower levels in patients. This lower level may have masked Glu differences between cases and controls, and thus lower patient Glu levels were detected only for CSF-corrected metabolites. Our findings are consistent with a report that the anterior cingulate cortex Cr level is negatively associated with schizophrenia spectrum liability.⁷⁹ Therefore, future studies should prioritize CSF-corrected measures.

Our finding of lower MFC glutamatergic metabolite levels in patients with schizophrenia relative to healthy volunteers is consistent with a recent meta-analysis.⁴ Our study indicates that age and antipsychotic medication were independently associated with MFC Glu levels because the model incorporating both of these uncorrelated measures showed the best fit. This result suggests that findings of reduced Glu levels in patients compared with healthy volunteers are not associated with accelerated aging in patients but may be explained by greater antipsychotic exposure, although lower Glu levels have been reported in minimally treated patients with first-episode psychosis.^{80,81} This finding may explain reports of reduced anterior cingulate cortex Glu levels in patients with chronic schizophrenia compared with healthy volunteers.⁹⁻¹⁴ Indeed, a large longitudinal study reports a decrease in Cr-scaled Glu levels with treatment.⁵ Antipsychotic medication may reduce Glu levels indirectly, secondary to a reduction in dopaminergic signaling via striatal-cortical feedback loops.⁸² Studies indicate that this result is not necessarily associated with symptom improvement^{5,49,83} and that Glu levels remain elevated in

Figure 3. Correlations Between Medial Frontal Cortex (MFC) and Medial Temporal Lobe (MTL) Glutamatergic Metabolites and Positive and Negative Syndrome Scale (PANSS) Scores



A, Positive association between the MFC glutamate to total creatinine plus phosphocreatine ratio (Glu/Cr) and the PANSS total score.^{5,11,24,25,35,40,42-47,51,57,60,65}
 B, PANSS positive score.^{5,11,24,25,35,40,42-47,51,57,65}
 C, Positive association between the MTL glutamate plus glutamine to Cr ratio (Glx/Cr) and PANSS total score.
 D, PANSS negative score.^{40,43,52,53,56} The black line represents the linear mixed model with SE represented by the gray shaded areas; the random-intercept models for each study listed are shown in different colors.

patients nonresponsive to treatment, despite higher or similar doses of medication.^{5,24,25,65,84-86}

Our third finding was that higher glutamatergic metabolite levels in both the MFC and MTL were associated with more severe symptoms and lower functioning. In the sample, younger patients were more likely to have severe symptoms, and the model incorporating both age and symptoms provided the best fit for the Glu data. Patients with more severe symptoms received

a higher CPZE dose; thus, the association of symptoms with Glu level is not better explained by medication exposure. When symptom dimensions were subsequently examined, Glu metabolite levels in the MFC were associated with positive symptoms, whereas those in the MTL were associated with negative symptoms. The MFC and MTL are key brain regions implicated in schizophrenia. Glutamatergic outputs from these regions regulate dopamine release in the striatum, and excess dopamine

Table 2. Associations of Measures of Symptom Severity and Social and Occupational Functioning With Glutamatergic Metabolites and Total Creatine and Phosphocreatine Levels

Brain region and source	No.	Glutamatergic metabolite, estimated mean (SE)	Clinical variable, mean (SD)	Statistics	Estimate (SE)
Medial frontal cortex					
Cr					
14 Studies ^{5,11,24,35,40,42-47,51,54,65}	559	9.21 (0.55)	PANSS total: 65.90 (18.36)	$F_{1,548.9} = 0.365, P = .55$	NA
6 Studies ^{5,24,40,46,51,65}	169	9.06 (0.42)	GAF: 49.76 (12.50)	$F_{1,164.2} = 2.013, P = .16$	NA
Glutamate, Cr-scaled					
17 Studies ^{5,11,24,25,35,40,42-47,51,57,65}	668	1.25 (0.07)	Model 1: PANSS total: 65.44 (18.90) Model 2: age + PANSS Total ^a	$F_{1,659.1} = 5.819, P = .02$ $F_{1,661.5} = 14.960, P < .001$ $F_{1,659.3} = 4.735, P = .03$	0.0012 (0.0005) -0.0036 (0.0009) 0.0011 (0.0005)
15 Studies ^{5,11,24,25,35,40,42-47,51,57,65}	625	1.30 (0.06)	PANSS positive: 16.15 (6.04) PANSS negative: 16.87 (6.30)	$F_{1,615.7} = 4.382, P = .004$ $F_{1,614.3} = 0.478, P = .49$	0.0035 (0.0017) NA
6 Studies ^{5,24,40,46,51,65}	178	1.23 (0.09)	GAF: 50.04 (12.85)	$F_{1,171.8} = 13.152, P = .001$	-0.0041 (0.0011)
Glutamate, CSF-corrected					
12 Studies ^{5,11,24,35,40,42-47,65}	527	11.90 (0.62)	PANSS total: 65.46 (18.49)	$F_{1,520.8} = 2.231, P = .14$	NA
5 Studies ^{5,24,40,46,65}	140	11.55 (0.72)	GAF: 50.57 (12.81)	$F_{1,135.1} = 2.043, P = .16$	NA
Glx, Cr-scaled					
15 Studies ^{5,11,24,35,40,42-44,46,47,49,57,59,65}	581	1.60 (0.09)	PANSS total: 64.97 (18.26)	$F_{1,571.3} = 0.487, P = .48$	NA
6 Studies ^{5,24,40,46,49,65}	155	1.56 (0.17)	GAF: 48.93 (14.07)	$F_{1,149.6} = 1.720, P = .19$	NA
Glx, CSF-corrected					
11 Studies ^{5,11,24,35,40,42-44,46,47,65}	497	15.48 (0.86)	PANSS total: 65.99 (18.54)	$F_{1,492.4} = 0.227, P = .63$	NA
5 Studies ^{5,24,40,46,65}	131	15.30 (0.87)	GAF: 50.53 (13.05)	$F_{1,128.1} = 0.373, P = .54$	NA
Medial temporal lobe					
Cr					
4 Studies ^{40,43,52,53}	109	5.03 (2.03)	PANSS total: 71.79 (15.46)	$F_{1,104.1} = 0.797, P = .37$	NA
Glx, Cr-scaled					
5 Studies ^{40,43,52,53,56}	132	1.90 (0.19)	PANSS total: 73.94 (15.50) PANSS positive: 17.42 (5.08) PANSS negative: 19.28 (5.86)	$F_{1,128.7} = 4.508, P = .04$ $F_{1,129.7} = 0.000, P = .98$ $F_{1,129.8} = 10.162, P = .002$	0.0057 (0.0027) -0.0212 (0.0067)
3 Studies ^{40,52,56}	76	1.97 (0.34)	CGI: 4.30 (0.98)	$F_{1,73.0} = 10.914, P = .002$	0.1976 (0.0598)

Abbreviations: AIC, Akaike information criterion; CGI, Clinical Global Impression; Cr, creatine plus phosphocreatine; GAF, Global Assessment of Functioning; Glu, glutamate; Glx, glutamate plus glutamine; NA, not applicable; PANSS, Positive and Negative Syndrome Scale.

^a Age and PANSS total score are both significantly associated with the medial frontal cortex Glu to Cr ratio, so we compared whether variance in the Glu to Cr ratio was best explained by model 1 including PANSS total score or model 2 including both PANSS total score and age (linear mixed methods estimated with maximum likelihoods). Model 2 showed the best fit (AIC, -98.7; residual deviance, -108.7) compared with model 1 (AIC, -85.9; residual deviance, -93.9) ($P < .001$, determined by use of the χ^2 test).

release may underlie the development of psychotic symptoms.⁸⁷ Hippocampal Glu level alterations may also be associated with learning and memory,⁸⁸ relevant to negative symptoms. Associations with symptoms were observed for Cr-scaled but not CSF-corrected values. This association appears unlikely to be caused by creatine because creatine level was not associated with symptom severity.

Strengths and Limitations

The strengths of the present study include the large patient sample (more than 700 patients), which enabled linear mixed models to account for potential collinearity. Mega-analyses are reported to be more sensitive than meta-analyses owing to narrower confidence intervals.⁸⁹ Because data were assembled from different countries, the sample represents varying demographic features and clinical treatments.

The process of combining data from multiple independent sites also has limitations. The 1H-MRS acquisition protocols, MR imaging platforms, and scaling methods differed among studies, which we controlled for in the analysis by using linear mixed models to control for site effects and by separately considering CSF-corrected data from Cr-scaled data. Ideally, future prospective multicenter studies would further harmonize 1H-MRS acquisition and correction methods to enable more reliable data synthesis.⁹⁰ Nevertheless, harmonization will always be constrained by the use of different MR imaging platforms across centers. Despite using established rating scales, there is a possibility of site effects associated with clinical assessment scores and CPZE dose calculations. Owing to a lack of data, we were unable to examine other brain regions

that may be associated with schizophrenia pathophysiology. Therefore, we cannot determine whether the observed associations extend to other brain regions. The CPZE dose was not available for all studies; thus, analyses were restricted to smaller samples. Our analysis of the association between medication and Glu levels relied on cross-sectional data. Longitudinal studies can better examine the causal association between these factors, but our results are consistent with longitudinal studies reporting reduced MFC glutamatergic metabolite levels with treatment.^{5,39,49,83,91,92} Antipsychotic dose was associated with CSF-corrected Glu metabolite levels but not with Cr-scaled values. This finding contrasts with a large longitudinal 1H-MRS study finding a reduction in Cr-scaled Glu level with treatment.⁵ Finally, mega-analyses rely on contributed data, resulting in data omission.

Conclusions

These findings have important implications for MRS studies in schizophrenia. They highlight the value of matching or adjusting for age, prioritizing CSF-corrected measures over Cr-scaled metabolite levels, and considering antipsychotic dose as an explanatory factor when comparing Glu levels between patients and healthy volunteers. The finding of elevated Glu levels in patients with more severe symptoms provides further support for the use of glutamatergic measures as a potential biomarker of illness severity, alongside other measures, and the development of novel treatments that target brain glutamatergic function.

ARTICLE INFORMATION

Accepted for Publication: February 10, 2021.

Published Online: April 21, 2021.

doi:10.1001/jamapsychiatry.2021.0380

Open Access: This is an open access article distributed under the terms of the [CC-BY License](https://creativecommons.org/licenses/by/4.0/).

© 2021 Merritt K et al. *JAMA Psychiatry*.

The 1H-MRS in Schizophrenia Investigator

Authors: André Aleman, PhD; Wolfgang Block, PhD; Oswald J. N. Bloemen, PhD; Faith Borgan, MSc, PhD; Juan R. Bustillo, MD; Aristides A. Capizzano, MD, MSc; Jennifer Marie Coughlin, MD; Camilo De la Fuente-Sandoval, MD, PhD; Arsime Demjaha, MBBS, PhD; Kara Dempster, PhD; Kim Q. Do, PhD; Fei Du, PhD; Peter Falkai, PhD; Beata Galinska-Skok, MD, PhD; Jurgen Gallinat, MD; Charles Gasparovic, PhD; Cedric E. Ginestet, PhD; Naoki Goto, MD; Ariel Graff-Guerrero, MD, PhD; Beng Choon Ho, MD; Oliver D. Howes, MD, PhD; Sameer Jauhar, MRCPsych, PhD; Peter Jeon, MSc; Tadafumi Kato, MD, PhD; Charles A. Kaufmann, MD; Lawrence S. Kegeles, MD, PhD; Matcheri Keshavan, MD; Sang-Young Kim, PhD; Hiroshi Kunugi, MD, PhD; John Lauriello, MD; Edith Jantine Liemburg, PhD; Meghan E. McIlwain, PhD; Gemma Modinos, PhD; Elias D. Mouchlianitis, MSc, PhD; Jun Nakamura, MD, PhD; Igor Nenadic, MD; Dost Öngür, MD, PhD; Miho Ota, MD, PhD; Lena Palaniyappan, MBBS, MRCPsych, PhD; Christos Pantelis, MBBS, MD, MRCPsych; Eric Plitman, PhD; Sotirios Posporelis, MD, MRCPsych; Scot E. Purdon, PhD; Jürgen R. Reichenbach, PhD; Perry F. Renshaw, MD,

PhD; Bruce R. Russell, PhD; Akira Sawa, MD, PhD; Martin Schaefer, MD; Dikoma C. Shungu, PhD; Stefan Smesny, MD, PhD; Jeffrey A. Stanley, PhD; James M. Stone, MBBS, MRCPsych, PhD; Agata Szulc, MD, PhD; Reggie Taylor, PhD; Katy Thakkar, PhD; Jean Théberge, PhD; Philip G. Tibbo, MD; Therese van Amelsvoort, MD, PhD; Jerzy Walecki, PhD; Peter C. Williamson, MD; Stephen James Wood, PhD; Lijing Xin, PhD; Hidenori Yamasue, MD, PhD.

Affiliations of The 1H-MRS in Schizophrenia

Investigator Authors: Psychosis Studies Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom (Borgan, Demjaha, Howes, Jauhar, Modinos, Mouchlianitis, Posporelis); Center for Brain Disorder and Cognitive Science, Shenzhen University, Shenzhen, China (Aleman); University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Aleman); Department of Diagnostic and Interventional Radiology, University Hospital Bonn, Bonn, Germany (Block); Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands (Bloemen, van Amelsvoort); Department of Psychiatry and Behavioral Sciences, Center for Psychiatric Research, University of New Mexico School of Medicine, Albuquerque (Bustillo); Department of Radiology, Division of Neuroradiology, University of Michigan, Ann Arbor (Capizzano); Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

(Coughlin); Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico (De la Fuente-Sandoval); Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico (De la Fuente-Sandoval); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (Dempster); Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital-CHUV, Prilly-Lausanne, Switzerland (Do); Psychotic Disorders Division, McLean Hospital, Harvard Medical School, Belmont, Massachusetts (Du, Öngür); Department of Psychiatry, University Hospital, LMU Munich, Munich, Germany (Falkai); Department of Psychiatry, Medical University of Białystok, Białystok, Poland (Galinska-Skok); Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf (UKE), Germany (Gallinat, Nenadic); Mind Research Network, Albuquerque, New Mexico (Gasparovic); Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience King's College London, London, United Kingdom (Ginestet); Department of Psychiatry, Kokura Gamo Hospital, Kitakyushu, Fukuoka, Japan (Goto); Multimodal Neuroimaging Schizophrenia Group, Research Imaging Centre, Geriatric Mental Health Program at Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Graff-Guerrero); Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City (Ho); Department of Medical Biophysics,

University of Western Ontario, London, Ontario, Canada (Jeon, Palaniyappan, Théberge); Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, Tokyo, Japan (Kato); Department of Psychiatry, Columbia University, New York State Psychiatric Institute, New York (Kaufmann, Kegeles); Harvard Medical School, Boston, Massachusetts (Keshavan); Philips Healthcare, Seoul, Republic of Korea (Kim); National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan (Kunugi, Ota); Jefferson Health-Sidney Kimmel Medical College, Philadelphia, Pennsylvania (Lauriello); Rob Giel Research Center, Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands (Liemburg); School of Pharmacy, University of Auckland, Grafton, Auckland, New Zealand (McIlwain); Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London, United Kingdom (Modinos, Stone); Department of Psychiatry, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan (Nakamura); Editor, *JAMA Psychiatry* (Öngür); Department of Psychiatry, Western University, London, Ontario, Canada (Palaniyappan, Théberge, Williamson); Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Carlton, Victoria, Australia (Pantelis); The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia (Pantelis); Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, Quebec, Canada (Plitman); Department of Psychiatry, McGill University, Montreal, Quebec, Canada (Plitman); South London and Maudsley, Bethlem Royal Hospital, Beckenham, United Kingdom (Posporelis); Neuropsychology Department, Alberta Hospital Edmonton, Edmonton, Alberta, Canada (Purdon); Edmonton Early Intervention in Psychosis Clinic, Edmonton, Alberta, Canada (Purdon); Medical Physics Group, Institute for Diagnostic and Interventional Radiology, Jena University Hospital, Jena, Germany (Reichenbach); Department of Psychiatry, University of Utah, Salt Lake City (Renshaw); School of Pharmacy, University of Otago, Dunedin, New Zealand (Russell); Department of Psychiatry, Johns Hopkins University, Baltimore, Maryland (Sawa); Department of Neuroscience, Johns Hopkins University, Baltimore, Maryland (Sawa); Department of Mental Health, Johns Hopkins University, Baltimore, Maryland (Sawa); Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland (Sawa); Department of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland (Sawa); Department of Psychiatry, Psychotherapy, Psychosomatics and Addiction Medicine, Kliniken Essen-Mitte, Essen, Germany (Schaefer); Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany (Schaefer); Department of Radiology, Weill Cornell Medical College, New York, New York (Shungu); Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany (Smesny); Brain Imaging Research Division, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan (Stanley); Brighton and Sussex Medical School, University of Sussex, Brighton, United Kingdom (Stone, Taylor); Department of Psychiatry, Medical University of

Warsaw, Poland (Szulc); Lawson Health Research Institute, London, Ontario, Canada (Taylor, Théberge, Williamson); Department of Psychology, Michigan State University, East Lansing (Thakkar); Division of Psychiatry and Behavioral Medicine, Michigan State University, East Lansing (Thakkar); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (Tibbo); Postgraduate Medical School, Warsaw, Poland (Walecki); Orygen, Melbourne, Australia (Wood); Institute for Mental Health, University of Birmingham, Edgbaston, United Kingdom (Wood); Centre for Youth Mental Health, University of Melbourne, Australia (Wood); Animal Imaging and Technology Core, Center for Biomedical Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland (Xin); Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan (Yamasue).

Author Contributions: Dr Merritt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Merritt, Bloemen, Borgan, Coughlin, Falkai, Howes, McGuire, Egerton, Théberge.

Acquisition, analysis, or interpretation of data: Merritt, Aleman, Block, Borgan, Bustillo, Capizzano, Coughlin, de la Fuente-Sandoval, Demjaha, Dempster, Do, Du, Galinska-Skok, Gallinat, Gasparovic, Ginestet, Goto, Graff-Guerrero, Ho, Howes, Jauhar, Jeon, Kato, Kaufmann, Kegeles, Keshavan, Kim, Kunugi, Lauriello, Liemburg, McIlwain, Modinos, Mouchlianitis, Nakamura, Nenadic, Öngür, Ota, Palaniyappan, Pantelis, Plitman, Posporelis, Purdon, Reichenbach, Renshaw, Russell, Sawa, Schaefer, Shungu, Smesny, Stanley, Stone, Szulc, Taylor, Thakkar, Théberge, Tibbo, van Amelsvoort, Walecki, Williamson, Wood, Xin, Yamasue, McGuire, Egerton.

Drafting of the manuscript: Merritt, Coughlin, de la Fuente-Sandoval, Howes, Jauhar, Kunugi, Nakamura, Palaniyappan, Posporelis, Sawa, Williamson, Egerton.

Critical revision of the manuscript for important intellectual content: Merritt, Aleman, Block, Bloemen, Borgan, Bustillo, Capizzano, Coughlin, de la Fuente-Sandoval, Demjaha, Dempster, Do, Du, Falkai, Galinska-Skok, Gallinat, Gasparovic, Ginestet, Goto, Graff-Guerrero, Ho, Jeon, Kato, Kaufmann, Kegeles, Keshavan, Kim, Lauriello, Liemburg, McIlwain, Modinos, Mouchlianitis, Nenadic, Öngür, Ota, Palaniyappan, Pantelis, Plitman, Purdon, Reichenbach, Renshaw, Russell, Schaefer, Shungu, Smesny, Stanley, Stone, Szulc, Taylor, Thakkar, Théberge, Tibbo, van Amelsvoort, Walecki, Wood, Xin, Yamasue, McGuire, Egerton.

Statistical analysis: Merritt, Borgan, Dempster, Galinska-Skok, Ginestet, Mouchlianitis, Nakamura, Egerton.

Obtained funding: Bustillo, de la Fuente-Sandoval, Ho, Palaniyappan, Purdon, Russell, Smesny, Stone, Théberge, Walecki.

Administrative, technical, or material support: Borgan, de la Fuente-Sandoval, Du, Gallinat, Graff-Guerrero, Ho, Howes, Jeon, Kim, Kunugi, Lauriello, Nenadic, Pantelis, Plitman, Purdon, Renshaw, Schaefer, Smesny, Stone, Szulc, Taylor, Thakkar, Théberge, Tibbo, van Amelsvoort, Xin, Yamasue, McGuire.

Supervision: Block, Coughlin, Kaufmann, Ota, Palaniyappan, Posporelis, Russell, Smesny, Théberge, Walecki, McGuire, Egerton.

Conflict of Interest Disclosures: Dr Borgan reported being an employee at COMPASS Pathways plc after the completion of and unrelated to the present work. Dr Bustillo reported receiving royalties from UptoDate outside the submitted work. Dr de la Fuente-Sandoval reported receiving personal fees from Janssen (Johnson & Johnson) during the conduct of the study. Dr Do reported receiving grants from Boehringer Ingelheim outside the submitted work. Dr Falkai reported receiving research grants or personal fees from Abbott, Boehringer Ingelheim, Essex, Janssen, Lundbeck, Otsuka, Recordati, Richter, Servier, and Takeda. Dr Gallinat reported receiving grants from the German Federal Ministry of Education and Research and from German Science Foundation; and receiving personal fees from Boehringer Ingelheim, Eli Lilly and Company, Janssen-Cilag, Lundbeck, and Otsuka. Dr Goldstein is now referred to by her maiden name, Dr McIlwain. Dr Goto reported receiving personal fees from Meiji Seika, Yoshitomiya, and Novartis outside the submitted work. Dr Howes reported receiving investigator-initiated research funding or personal fees from Angellini, Autifony, Biogen, Boehringer Ingelheim, Eli Lilly and Company, Heptares, Global Medical Education, Invivo, Janssen, Lundbeck, Mylan, Neurocrine, Otsuka, Sunovion, Rand, Recordati, and Roche; and having a patent for the use of dopaminergic imaging. Dr Jauhar reported receiving personal fees from Sunovion and nonfinancial support from Lundbeck outside the submitted work. Dr Kato reported receiving grants from Eisai, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, Shionogi & Co, and Takeda Pharmaceutical; and receiving personal fees from Astellas Pharma Inc, Eisai, Eli Lilly Japan, GlaxoSmithKline, Kanae Foundation for the Promotion of Medical Science, Kyowa Hakkō Kirin, Kyowa Pharmaceutical Industry, Janssen Asia Pacific, Janssen Pharmaceutical, Meiji Seika Pharma, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical, Nippon Boehringer Ingelheim, Otsuka Pharmaceutical, Pfizer Japan, Shionogi & Co, Sumitomo Dainippon Pharma, Taisho Pharmaceutical, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Yoshitomiya outside the submitted work. Dr Kegeles reported receiving grants from the National Alliance for Research on Schizophrenia and Depression during the conduct of the study. Dr Lauriello reported being on the advisory panel for Alkermes and on the data management safety board for Bioexcel Therapeutic. Dr Liemburg reported receiving grants from AstraZeneca, European Research Council, European Young Investigator Awards, and Stichting Roos during the conduct of the study. Dr McGuire reported receiving personal fees from Sunovion and Takeda. Dr McIlwain reported receiving grants from the New Zealand Schizophrenia Research Group and a fellowship from the New Zealand Federation of Graduate Women during the conduct of the study; and becoming employed at Syneos Health after the collection and analysis of data for the present work but has not worked on any projects there related to schizophrenia or psychiatry. Dr Palaniyappan reported receiving personal fees from the Canadian Psychiatric Association, Janssen Canada, Otsuka Canada, and the SPMM Course UK outside the submitted work; receiving grants from Janssen Canada, Otsuka

Canada, and Sunovion outside the submitted work; and receiving royalties from Oxford University Press. Dr Pantelis reported receiving grants from the Australian National Health & Medical Research Council during the conduct of the study; grants from Lundbeck Foundation; and personal fees from Lundbeck Australia Pty Ltd outside the submitted work. Dr Purdon reported receiving grants from the Canadian Institute of Health Research during the conduct of the study; and personal fees from Lundbeck Canada outside the submitted work. Dr Schaefer reported receiving grants from The Stanley Medical Research Institute during the conduct of the study; and receiving personal fees from Janssen-Cilag, Gilead Sciences GmbH, Hexal-AG, and Servier outside the submitted work. Dr Shungu reported receiving personal fees from Icahn School of Medicine at Mount Sinai and the US National Institutes of Health outside the submitted work. Dr Stone reported being a principal investigator or subinvestigator on studies sponsored by Takeda, Janssen, and Lundbeck; and attending investigator meetings at Allergan outside the submitted work. Dr Taylor reported receiving grants from the Ontario Mental Health Foundation and the Canadian Institute of Health Research during the conduct of the study. Dr Théberge reported receiving grants from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council, and the Canada Foundation for Innovation during the conduct of the study; and receiving personal fees from Siemens Healthineers Canada. Dr Tibbo reported receiving grants from the Alberta Health Foundation for Medical Research and the Canadian Institutes for Medical Research during the conduct of the study; and personal fees from Janssen, Lundbeck, and Otsuka outside the submitted work. Dr Xin reported receiving grants from the Swiss National Science Foundation and Société des Produits Nestlé SA outside the submitted work. Dr Yamasue reported receiving personal fees from Eli Lilly and Company, Janssen, Meiji Seika Pharma, Merck Sharp & Dohme, Mochida, Otsuka, Pfizer, Sumitomo Dainippon, Takeda, and Yoshitomyakuhin; and receiving a research grant from Eisai. No other disclosures were reported.

Funding/Support: This study was supported by a PhD studentship from the UK Medical Research Council and grant MR/S003436/1 from the Medical Research Council to Dr Merritt; grant MR/L003988/1 from the Medical Research Council to Dr Egerton, and grant HEALTH-F2-2010-242114 from the European Commission within the 7th Framework Programme. This study presents independent research funded in part by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London. Dr Camilo de la Fuente-Sandoval was awarded research grants 119280, 182279, and 261895 from the Consejo Nacional de Ciencia y Tecnología-Mexico (CONACyT), a grant from CONACyT Sistema Nacional de Investigadores, and grant R21 MH117434 from the US National Institutes of Health. Dr Howes was awarded grant MC_U120097115 from the Medical Research Council-UK, grant 666 from the Maudsley Charity, and grant 094849/Z/10/Z from the Wellcome Trust. Dr Théberge received discovery grant RG-PIN-2016-05055 from the National Science and Engineering Research Council-Canada and was a co-applicant on grant MT-12078 from the Canadian

Institutes of Health Research. Dr Palaniyappan received Foundation Grant 375104/2017 from the Canadian Institutes of Health Research and salary support from the Tanna Schulich Chair of Neuroscience and Mental Health. A clinical investigator fellowship was awarded to Kara Dempster from the Schulich School of Medicine. Mr Jeon received salary support from Discovery Grant RGPIN2016-05055 from the Natural Sciences and Engineering Research Council of Canada to Dr Théberge. Data acquisition was supported by the Canada First Excellence Research Fund to BrainSCAN, Western University (Imaging Core).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The IH-MRS in Schizophrenia Investigators:

Institute of Mental Health, Division of Psychiatry, UCL, London, United Kingdom: Kate Merritt, PhD; Psychosis Studies Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom: Kate Merritt, PhD, Faith Borgan, PhD, Arsime Demjaha, MD, PhD, Oliver Howes, MD, PhD, Sameer Jauhar, MD, PhD, Gemma Modinos, PhD, Elias Mouchlianitis, PhD, Sotirios Posporelis, MD, MRCPsych, Philip K. McGuire, MD, FMedSci, Alice Egerton, PhD; Center for Brain Disorder and Cognitive Science, Shenzhen University, Shenzhen, China: André Aleman, PhD; University Medical Center Groningen, University of Groningen, Groningen, the Netherlands: André Aleman, PhD; Department of Diagnostic and Interventional Radiology, University Hospital Bonn, Bonn, Germany: Wolfgang Block, PhD; Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands: Oswald J. N. Bloemen, MD, PhD, Thérèse van Amelsvoort, MD, PhD; Department of Psychiatry and Behavioral Sciences, Center for Psychiatric Research, University of New Mexico School of Medicine, Albuquerque: Juan R. Bustillo, MD; Department of Radiology, Division of Neuroradiology, University of Michigan, Ann Arbor: Aristides A. Capizzano, MD, MSc; Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland: Jennifer M. Coughlin, MD; Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico: Camilo de la Fuente-Sandoval, MD, PhD; Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico: Camilo de la Fuente-Sandoval, MD, PhD; Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital-CHUV, Prilly-Lausanne, Switzerland: Kim Q. Do, PhD; Lawson Health Research Institute, London, Ontario, Canada: Reggie Taylor, PhD, Jean Théberge, PhD, Peter C. Williamson, MD; Department of Biostatistics and Health Informatics (S2.06), Institute of Psychiatry, Psychology, and Neuroscience King's College London, London, United Kingdom: Cedric E. Ginestet, PhD; Department of Psychiatry, University Hospital, LMU Munich, Nussbaumstrasse, Munich, Germany: Peter Falkai, PhD; Department of Psychiatry, Medical University of Białystok, Białystok, Poland: Beata Galińska-Skok, MD, PhD; Department of Psychiatry, Medical University of Warsaw, Poland: Agata Szulc, MD,

PhD; Mind Research Network, Albuquerque, New Mexico: Charles Gasparovic, PhD; Department of Psychiatry, Kokura Gamo Hospital, Kitakyushu, Fukuoka, Japan: Naoki Goto, PhD; Multimodal Neuroimaging Schizophrenia Group, Research Imaging Centre, Geriatric Mental Health Program at Centre for Addiction and Mental Health, and Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada: Ariel Graff-Guerrero, MD, PhD; Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City: Beng-Choon Ho, MD; Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, Tokyo, Japan: Tadafumi Kato, MD, PhD; Department of Psychiatry, Columbia University, New York State Psychiatric Institute (NYSPI), New York: Charles A. Kaufmann, MD; Columbia University, Department of Psychiatry, NYSPI, New York, New York: Lawrence S. Kegeles, MD, PhD; Harvard Medical School, Boston, Massachusetts: Matcheri S. Keshavan, PhD; Philips Healthcare, Seoul, Republic of Korea: Sang-Young Kim, PhD; National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan: Hiroshi Kunugi, PhD, Miho Ota, PhD; Jefferson Health-Sidney Kimmel Medical College, Philadelphia, Pennsylvania: John Lauriello, PhD; Rob Giel Research Center, Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands: Edith Liemburg, PhD; School of Pharmacy, University of Auckland, Grafton, Auckland, New Zealand: Meghan E. McIlwain, PhD; Department of Psychiatry, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan: Jun Nakamura, PhD; South London and Maudsley, Bethlem Royal Hospital, Beckenham, London, UK: Sotirios Posporelis, MD, MRCPsych; Psychotic Disorders Division, McLean Hospital, Harvard Medical School, Belmont, Massachusetts: Fei Du, PhD, Dost Öngür, MD, PhD; Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Carlton, Victoria, Australia: Christos Pantelis, PhD; The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia: Christos Pantelis, PhD; Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, QC, Canada: Eric Plitman, PhD; Montreal, QC, Canada; Department of Psychiatry, McGill University, Montreal, QC, Canada: Eric Plitman, PhD; Neuropsychology Department, Alberta Hospital Edmonton, AB, Canada; Edmonton Early Intervention in Psychosis Clinic, Edmonton, AB, Canada: Scot E. Purdon, PhD; Medical Physics Group, Institute for Diagnostic and Interventional Radiology (IDIR), Jena University Hospital, Jena, Germany: Jürgen R. Reichenbach, PhD; Department of Psychiatry, University of Utah, Salt Lake City: Perry F. Renshaw, MD, PhD; School of Pharmacy, University of Otago, Dunedin, New Zealand: Bruce R. Russell, PhD; Departments of Psychiatry, Neuroscience, Mental Health, Biomedical Engineering, and Genetic Medicine, Johns Hopkins University, Baltimore, Maryland: Akira Sawa, MD, PhD; Department of Psychiatry, Psychotherapy, Psychosomatics and Addiction Medicine, Kliniken Essen-Mitte, Essen, Germany: Martin Schaefer, MD; Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany: Martin Schaefer, MD; Department of Radiology, Weill Cornell Medical College, New York, New York: Dikoma C. Shungu, PhD; Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena,

Germany: Stefan Smesny, MD, PhD; Brain Imaging Research Division, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan; Jeffrey A. Stanley, PhD; Department of Psychology, Michigan State University, East Lansing; Katharine N. Thakkar, PhD; Division of Psychiatry and Behavioral Medicine, Michigan State University, East Lansing; Katharine N. Thakkar, PhD; Department of Psychiatry, Western University, London, Ontario, Canada; Lena Palaniyappan, MD, PhD, Jean Théberge, PhD, Peter C. Williamson, MD; Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; Philip G. Tibbo, MD; Postgraduate Medical School, Warsaw, Poland; Jerzy Walecki, PhD; Orygen, Melbourne, Australia; Stephen J. Wood, PhD; Institute for Mental Health, University of Birmingham, Edgbaston, United Kingdom; Stephen J. Wood, PhD; Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan; Hidenori Yamasue, PhD; Department of Medical Biophysics, University of Western Ontario, London, ON, Canada; Lena Palaniyappan, MD, PhD; Reggie Taylor, PhD, Jean Théberge, PhD; Peter Jeon, MSc; Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; Kara Dempster, MD; Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London, United Kingdom; Gemma Modinos, PhD, James Stone, MD, PhD; Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf (UKE), Germany; Jürgen Gallinat, MD, Igor Nenadic, MD; Animal Imaging and Technology Core (AIT), Center for Biomedical Imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; Lijing Xin, PhD; Centre for Youth Mental Health, University of Melbourne, Australia; Stephen J. Wood, PhD; Brighton and Sussex Medical School, University of Sussex, Brighton, United Kingdom; James Stone, MD, PhD.

Disclaimer: Dr Öngür is the editor of *JAMA Psychiatry*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES

- Ripke S, Neale BM, Corvin A, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427. doi:10.1038/nature13595
- Merritt K, Egerton A, Kempton MJ, Taylor MJ, McGuire PK. Nature of glutamate alterations in schizophrenia: a meta-analysis of proton magnetic resonance spectroscopy studies. *JAMA Psychiatry*. 2016;73(7):665-674. doi:10.1001/jamapsychiatry.2016.0442
- Anticevic A, Corlett PR, Cole MW, et al. N-methyl-D-aspartate receptor antagonist effects on prefrontal cortical connectivity better model early than chronic schizophrenia. *Biol Psychiatry*. 2015;77(6):569-580. doi:10.1016/j.biopsych.2014.07.022
- Sydnor VJ, Roalf DR. A meta-analysis of ultra-high field glutamate, glutamine, GABA and glutathione IHMRS in psychosis: Implications for studies of psychosis risk. *Schizophr Res*. 2020;226 (July):61-69. doi:10.1016/j.schres.2020.06.028
- Egerton A, Broberg BV, Van Haren N, et al. Response to initial antipsychotic treatment in first episode psychosis is related to anterior cingulate glutamate levels: a multicentre ¹H-MRS study (OPTiMISE). *Mol Psychiatry*. 2018;23(11):2145-2155. doi:10.1038/s41380-018-0082-9
- Stone JM, Day F, Tsagaraki H, et al; OASIS. Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. *Biol Psychiatry*. 2009;66(6):533-539. doi:10.1016/j.biopsych.2009.05.006
- Bustillo JR, Rowland LM, Mullins P, et al. 1H-MRS at 4 tesla in minimally treated early schizophrenia. *Mol Psychiatry*. 2010;15(6):629-636. doi:10.1038/mp.2009.121
- Bartha R, Williamson PC, Drost DJ, et al. Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 1997;54(10):959-965. doi:10.1001/archpsyc.1997.01830220085012
- Ohrmann P, Siegmund A, Suslow T, et al. Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophr Res*. 2005;73(2-3):153-157. doi:10.1016/j.schres.2004.08.021
- Ohrmann P, Siegmund A, Suslow T, et al. Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naïve and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. *J Psychiatry Res*. 2007;41(8):625-634. doi:10.1016/j.jpsychires.2006.07.002
- Natsubori T, Inoue H, Abe O, et al. Reduced frontal glutamate + glutamine and N-acetylaspartate levels in patients with chronic schizophrenia but not in those at clinical high risk for psychosis or with first-episode schizophrenia. *Schizophr Bull*. 2014;40(5):1128-1139. doi:10.1093/schbul/sbt124
- Lutkenhoff ES, van Erp TG, Thomas MA, et al. Proton MRS in twin pairs discordant for schizophrenia. *Mol Psychiatry*. 2010;15(3):308-318. doi:10.1038/mp.2008.87
- Tayoshi S, Sumitani S, Taniguchi K, et al. Metabolite changes and gender differences in schizophrenia using 3-Tesla proton magnetic resonance spectroscopy (1H-MRS). *Schizophr Res*. 2009;108(1-3):69-77. doi:10.1016/j.schres.2008.11.014
- Théberge J, Al-Semaan Y, Williamson PC, et al. Glutamate and glutamine in the anterior cingulate and thalamus of medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS. *Am J Psychiatry*. 2003;160(12):2231-2233. doi:10.1176/appi.ajp.160.12.2231
- Palaniyappan L. Progressive cortical reorganization: a framework for investigating structural changes in schizophrenia. *Neurosci Biobehav Rev*. 2017;79:1-13. doi:10.1016/j.neubiorev.2017.04.028
- Wijtenburg SA, Wright SN, Korenic SA, et al. Altered glutamate and regional cerebral blood flow levels in schizophrenia: a ¹H-MRS and pCASL study. *Neuropsychopharmacology*. 2017;42(2):562-571. doi:10.1038/npp.2016.172
- Bustillo JR, Jones T, Chen H, et al. Glutamatergic and neuronal dysfunction in gray and white matter: a spectroscopic imaging study in a large schizophrenia sample. *Schizophr Bull*. 2017;43(3):611-619. doi:10.1093/schbul/sbw122
- Théberge J, Williamson KE, Aoyama N, et al. Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *Br J Psychiatry*. 2007;191:325-334. doi:10.1192/bjp.bp.106.033670
- Aoyama N, Théberge J, Drost DJ, et al. Grey matter and social functioning correlates of glutamatergic metabolite loss in schizophrenia. *Br J Psychiatry*. 2011;198(6):448-456. doi:10.1192/bjp.bp.110.079608
- Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE. Glutamate in schizophrenia: a focused review and meta-analysis of ¹H-MRS studies. *Schizophr Bull*. 2013;39(1):120-129. doi:10.1093/schbul/sbr069
- Egerton A, Bhachu A, Merritt K, McQueen G, Szulc A, McGuire P. Effects of antipsychotic administration on brain glutamate in schizophrenia: a systematic review of longitudinal ¹H-MRS studies. *Front Psychiatry*. 2017;8:66. doi:10.3389/fpsy.2017.00066
- Merritt K, McGuire P, Egerton A. Relationship between glutamate dysfunction and symptoms and cognitive function in psychosis. *Front Psychiatry*. 2013;4:151. doi:10.3389/fpsy.2013.00151
- Ota M, Ishikawa M, Sato N, et al. Glutamatergic changes in the cerebral white matter associated with schizophrenic exacerbation. *Acta Psychiatr Scand*. 2012;126(1):72-78. doi:10.1111/j.1600-0447.2012.01853.x
- Egerton A, Brugger S, Raffin M, et al. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. *Neuropsychopharmacology*. 2012;37(11):2515-2521. doi:10.1038/npp.2012.113
- Mouchlianitis E, Bloomfield MAP, Law V, et al. Treatment-resistant schizophrenia patients show elevated anterior cingulate cortex glutamate compared to treatment-responsive. *Schizophr Bull*. 2016;42(3):744-752. doi:10.1093/schbul/sbv151
- Merritt K, Perez-Iglesias R, Sendt KV, et al. Remission from antipsychotic treatment in first episode psychosis related to longitudinal changes in brain glutamate. *NPJ Schizophr*. 2019;5(1):12. doi:10.1038/s41537-019-0080-1
- Provencher S. LCMModel & LCMgui User's Manual. Published February 4, 2021. Accessed March 6, 2021. <http://s-provencher.com/pub/LCMModel/manual/manual.pdf>
- Harrison XA, Donaldson L, Correa-Cano ME, et al. A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*. 2018;6(5):e4794. doi:10.7717/peerj.4794
- R Core Team. The R Project for Statistical Computing. Accessed March 6, 2021. <https://www.r-project.org/>.
- Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. 2nd ed. Springer-Verlag; 2009. doi:10.1007/978-0-387-98141-3
- Verbyla AP. A note on model selection using information criteria for general linear models estimated using REML. *Aust N Z J Stat*. 2019;61(1):39-50. doi:10.1111/anzs.12254

32. de la Fuente-Sandoval C, León-Ortiz P, Favila R, et al. Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology*. 2011;36(9):1781-1791. doi:10.1038/npp.2011.65
33. Modinos G, Şimşek F, Horder J, et al. Cortical GABA in subjects at ultra-high risk of psychosis: relationship to negative prodromal symptoms. *Int J Neuropsychopharmacol*. 2018;21(2):114-119. doi:10.1093/ijnp/pyx076
34. de la Fuente-Sandoval C, Reyes-Madrigrá F, Mao X, et al. Cortico-striatal GABAergic and glutamatergic dysregulations in subjects at ultra-high risk for psychosis investigated with proton magnetic resonance spectroscopy. *Int J Neuropsychopharmacol*. 2015;19(3):pyv105. doi:10.1093/ijnp/pyv105
35. Bustillo JR, Chen H, Jones T, et al. Increased glutamine in patients undergoing long-term treatment for schizophrenia: a proton magnetic resonance spectroscopy study at 3 T. *JAMA Psychiatry*. 2014;71(3):265-272. doi:10.1001/jamapsychiatry.2013.3939
36. Coughlin JM, Tanaka T, Marsman A, et al. Decoupling of N-acetyl-aspartate and glutamate within the dorsolateral prefrontal cortex in schizophrenia. *Curr Mol Med*. 2015;15(2):176-183. doi:10.2174/1566524015666150303104811
37. Posporelis S, Coughlin JM, Marsman A, et al. Decoupling of brain temperature and glutamate in recent onset of schizophrenia: a 7T proton magnetic resonance spectroscopy study. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(3):248-254. doi:10.1016/j.bpsc.2017.04.003
38. Taylor R, Osuch EA, Schaefer B, et al. Neurometabolic abnormalities in schizophrenia and depression observed with magnetic resonance spectroscopy at 7 T. *BJPsych Open*. 2017;3(1):6-11. doi:10.1192/bjpo.bp.116.003756
39. Stanley JA, Williamson PC, Drost DJ, et al. An in vivo proton magnetic resonance spectroscopy study of schizophrenia patients. *Schizophr Bull*. 1996;22(4):597-609. doi:10.1093/schbul/22.4.597
40. Gallinat J, McMahon K, Kühn S, Schubert F, Schaefer M. Cross-sectional study of glutamate in the anterior cingulate and hippocampus in schizophrenia. *Schizophr Bull*. 2016;42(2):425-433. doi:10.1093/schbul/sbv124
41. Stanley JA, Vemulapalli M, Nutche J, et al. Reduced N-acetyl-aspartate levels in schizophrenia patients with a younger onset age: a single-voxel 1H spectroscopy study. *Schizophr Res*. 2007;93(1-3):23-32. doi:10.1016/j.schres.2007.03.028
42. Xin L, Mekte R, Fournier M, et al. Genetic polymorphism associated prefrontal glutathione and its coupling with brain glutamate and peripheral redox status in early psychosis. *Schizophr Bull*. 2016;42(5):1185-1196. doi:10.1093/schbul/sbw038
43. Smesny S, Gussew A, Biesel NJ, et al. Glutamatergic dysfunction linked to energy and membrane lipid metabolism in frontal and anterior cingulate cortices of never treated first-episode schizophrenia patients. *Schizophr Res*. 2015;168(1-2):322-329. doi:10.1016/j.schres.2015.07.013
44. Liemburg E, Sibeijn-Kuiper A, Bais L, et al. Prefrontal NAA and Glx levels in different stages of psychotic disorders: a 3T 1H-MRS study. *Sci Rep*. 2016;6(1):21873. doi:10.1038/srep21873
45. Kim SY, Kaufman MJ, Cohen BM, et al. In vivo brain glycine and glutamate concentrations in patients with first-episode psychosis measured by echo time-averaged proton magnetic resonance spectroscopy at 4T. *Biol Psychiatry*. 2018;83(6):484-491. doi:10.1016/j.biopsych.2017.08.022
46. Jauhar S, McCutcheon R, Borgan F, et al. The relationship between cortical glutamate and striatal dopamine in first-episode psychosis: a cross-sectional multimodal PET and magnetic resonance spectroscopy imaging study. *Lancet Psychiatry*. 2018;5(10):816-823. doi:10.1016/S2215-0366(18)30268-2
47. Borgan FR, Jauhar S, McCutcheon RA, et al. Glutamate levels in the anterior cingulate cortex in un-medicated first episode psychosis: a proton magnetic resonance spectroscopy study. *Sci Rep*. 2019;9(1):8685. doi:10.1038/s41598-019-45018-0
48. Plitman E, de la Fuente-Sandoval C, Reyes-Madrigrá F, et al. Elevated myo-inositol, choline, and glutamate levels in the associative striatum of antipsychotic-naïve patients with first-episode psychosis: a proton magnetic resonance spectroscopy study with implications for glial dysfunction. *Schizophr Bull*. 2016;42(2):415-424. doi:10.1093/schbul/sbv118
49. Goto N, Yoshimura R, Kakeda S, et al. Six-month treatment with atypical antipsychotic drugs decreased frontal-lobe levels of glutamate plus glutamine in early-stage first-episode schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8:119-122. doi:10.2147/ndt.s25582
50. Théberge J, Bartha R, Drost DJ, et al. Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *Am J Psychiatry*. 2002;159(11):1944-1946. doi:10.1176/appi.ajp.159.11.1944
51. Tibbo PG, Bernier D, Hanstock CC, Seres P, Lakusta B, Purdon SE. 3-T proton magnetic spectroscopy in unmedicated first episode psychosis: a focus on creatine. *Magn Reson Med*. 2013;69(3):613-620. doi:10.1002/mrm.24291
52. Galińska B, Szulc A, Tarasów E, et al. Duration of untreated psychosis and proton magnetic resonance spectroscopy (1H-MRS) findings in first-episode schizophrenia. *Med Sci Monit*. 2009;15(2):CR82-CR88.
53. Wood SJ, Berger GE, Wellard RM, et al. A 1H-MRS investigation of the medial temporal lobe in antipsychotic-naïve and early-treated first episode psychosis. *Schizophr Res*. 2008;102(1-3):163-170. doi:10.1016/j.schres.2008.03.012
54. Wood SJ, Yücel M, Wellard RM, et al. Evidence for neuronal dysfunction in the anterior cingulate of patients with schizophrenia: a proton magnetic resonance spectroscopy study at 3 T. *Schizophr Res*. 2007;94(1-3):328-331. doi:10.1016/j.schres.2007.05.008
55. Kegeles LS, Shungu DC, Anjilvel S, et al. Hippocampal pathology in schizophrenia: magnetic resonance imaging and spectroscopy studies. *Psychiatry Res*. 2000;98(3):163-175. doi:10.1016/S0925-4927(00)00044-5
56. Szulc A, Galinska B, Tarasow E, et al. Proton magnetic resonance spectroscopy study of brain metabolite changes after antipsychotic treatment. *Pharmacopsychiatry*. 2011;44(4):148-157. doi:10.1055/s-0031-1279739
57. Goldstein ME, Anderson VM, Pillai A, Kydd RR, Russell BR. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. *Int J Neuropsychopharmacol*. 2015;18(6):pyu117. doi:10.1093/ijnp/pyu117
58. Block W, Bayer TA, Tepest R, et al. Decreased frontal lobe ratio of N-acetyl aspartate to choline in familial schizophrenia: a proton magnetic resonance spectroscopy study. *Neurosci Lett*. 2000;289(2):147-151. doi:10.1016/S0304-3940(00)01264-7
59. Öngür D, Prescott AP, McCarthy J, Cohen BM, Renshaw PF. Elevated gamma-aminobutyric acid levels in chronic schizophrenia. *Biol Psychiatry*. 2010;68(7):667-670. doi:10.1016/j.biopsych.2010.05.016
60. Öngür D, Jensen JE, Prescott AP, et al. Abnormal glutamatergic neurotransmission and neuronal-glia interactions in acute mania. *Biol Psychiatry*. 2008;64(8):718-726. doi:10.1016/j.biopsych.2008.05.014
61. Ota M, Wakabayashi C, Sato N, et al. Effect of L-theanine on glutamatergic function in patients with schizophrenia. *Acta Neuropsychiatr*. 2015;27(5):291-296. doi:10.1017/neu.2015.22
62. Kegeles LS, Mao X, Stanford AD, et al. Elevated prefrontal cortex γ -aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 2012;69(5):449-459. doi:10.1001/archgenpsychiatry.2011.1519
63. Yamasue H, Fukui T, Fukuda R, et al. Drug-induced parkinsonism in relation to choline-containing compounds measured by 1H-MR spectroscopy in putamen of chronically medicated patients with schizophrenia. *Int J Neuropsychopharmacol*. 2003;6(4):353-360. doi:10.1017/S1461145703003687
64. Modinos G, Şimşek F, Azis M, et al. Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. *Neuropsychopharmacology*. 2018;43(13):2652-2659. doi:10.1038/s41386-017-0004-6
65. Demjaha A, Egerton A, Murray RM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry*. 2014;75(5):e11-e13. doi:10.1016/j.biopsych.2013.06.011
66. Egerton A, Stone JM, Chaddock CA, et al. Relationship between brain glutamate levels and clinical outcome in individuals at ultra high risk of psychosis. *Neuropsychopharmacology*. 2014;39(12):2891-2899. doi:10.1038/npp.2014.143
67. Capizzano AA, Toscano JLN, Ho BC. Magnetic resonance spectroscopy of limbic structures displays metabolite differences in young unaffected relatives of schizophrenia probands. *Schizophr Res*. 2011;131(1-3):4-10. doi:10.1016/j.schres.2011.05.024
68. Bloemen OJN, Gleich T, de Koning MB, et al. Hippocampal glutamate levels and striatal dopamine D_{2/3} receptor occupancy in subjects at ultra high risk of psychosis. *Biol Psychiatry*. 2011;70(1):e1-e2. doi:10.1016/j.biopsych.2010.11.030
69. Dempster K, Jeon P, MacKinley M, Williamson P, Théberge J, Palaniyappan L. Early treatment response in first episode psychosis: a 7-T magnetic resonance spectroscopic study of glutathione and glutamate.

- Mol Psychiatry*. 2020;25(8):1640-1650. doi:10.1038/s41380-020-0704-x
70. Bloemen OJN, de Koning MB, Schmitz N, et al. White-matter markers for psychosis in a prospective ultra-high-risk cohort. *Psychol Med*. 2010;40(8):1297-1304. doi:10.1017/S0033291709991711
71. Roalf DR, Sydnor VJ, Woods M, et al. A quantitative meta-analysis of brain glutamate metabolites in aging. *Neurobiol Aging*. 2020;95:240-249. doi:10.1016/j.neurobiolaging.2020.07.015
72. Angelie E, Bonmartin A, Boudraa A, Gonnard PM, Mallet JJ, Sappey-Marini D. Regional differences and metabolic changes in normal aging of the human brain: proton MR spectroscopic imaging study. *AJNR Am J Neuroradiol*. 2001;22(1):119-127.
73. Gruber S, Pinker K, Riederer F, et al. Metabolic changes in the normal ageing brain: consistent findings from short and long echo time proton spectroscopy. *Eur J Radiol*. 2008;68(2):320-327. doi:10.1016/j.ejrad.2007.08.038
74. Chang L, Ernst T, Poland RE, Jenden DJ. In vivo proton magnetic resonance spectroscopy of the normal aging human brain. *Life Sci*. 1996;58(22):2049-2056. doi:10.1016/0024-3205(96)00197-x
75. Pfefferbaum A, Adalsteinsson E, Spielman D, Sullivan EV, Lim KO. In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: effects of normal aging. *Magn Reson Med*. 1999;41(2):276-284. doi:10.1002/(SICI)1522-2594(199902)41:2<276::AID-MRM10>3.0.CO;2-8
76. Brooks JCW, Roberts N, Kemp GJ, Gosney MA, Lye M, Whitehouse GH. A proton magnetic resonance spectroscopy study of age-related changes in frontal lobe metabolite concentrations. *Cereb Cortex*. 2001;11(7):598-605. doi:10.1093/cercor/11.7.598
77. Mrak RE, Griffin ST, Graham DI. Aging-associated changes in human brain. *J Neuropathol Exp Neurol*. 1997;56(12):1269-1275. doi:10.1097/00005072-199712000-00001
78. Terry RD, DeTeresa R, Hansen LA. Neocortical cell counts in normal human adult aging. *Ann Neurol*. 1987;21(6):530-539. doi:10.1002/ana.410210603
79. Legind CS, Broberg BV, Mandl RCW, et al. Heritability of cerebral glutamate levels and their association with schizophrenia spectrum disorders: a ¹H]-spectroscopy twin study. *Neuropsychopharmacology*. 2019;44(3):581-589. doi:10.1038/s41386-018-0236-0
80. Jeon P, Limongi R, Ford S, et al. Progressive changes in glutamate concentration in early stages of schizophrenia: a longitudinal 7-Tesla MRS study. *Schizophr Bull*. 2021;2(1):sgaa072. doi:10.1093/schizbullopen/sgaa072 doi:10.101/2020.08.11.20172841
81. Wang J, Tang Y, Zhang T, et al. Reduced γ -aminobutyric acid and glutamate+glutamine levels in drug-naïve patients with first-episode schizophrenia but not in those at ultrahigh risk. *Neural Plast*. 2016;2016:3915703. doi:10.1155/2016/3915703
82. Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003;26(4):317-330. doi:10.1016/j.jchemneu.2003.10.003
83. de la Fuente-Sandoval C, Reyes-Madriral F, Mao X, et al. Prefrontal and striatal gamma-aminobutyric acid levels and the effect of antipsychotic treatment in first-episode psychosis patients. *Biol Psychiatry*. 2018;83(6):475-483. doi:10.1016/j.biopsych.2017.09.028
84. Iwata Y, Nakajima S, Plitman E, et al. Glutamatergic neurometabolite levels in patients with ultra-treatment-resistant schizophrenia: a cross-sectional 3T proton magnetic resonance spectroscopy study. *Biol Psychiatry*. 2019;85(7):596-605. doi:10.1016/j.biopsych.2018.09.009
85. Tarumi R, Tsugawa S, Noda Y, et al. Levels of glutamatergic neurometabolites in patients with severe treatment-resistant schizophrenia: a proton magnetic resonance spectroscopy study. *Neuropsychopharmacology*. 2020;45(4):632-640. doi:10.1038/s41386-019-0589-z
86. Egerton A, Murphy A, Donocik J, et al. Dopamine and glutamate in antipsychotic-responsive compared with antipsychotic-nonresponsive psychosis: a multicenter positron emission tomography and magnetic resonance spectroscopy study (STRATA). *Schizophr Bull*. 2020;47(2):505-516. doi:10.1093/schbul/sbaa128
87. Grace AA, Gomes FV. The circuitry of dopamine system regulation and its disruption in schizophrenia: insights into treatment and prevention. *Schizophr Bull*. 2019;45(1):148-157. doi:10.1093/schbul/sbx199
88. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*. 2005;46(5):703-713. doi:10.1016/j.neuron.2005.05.002
89. Boedhoe PSW, Heymans MW, Schmaal L, et al; ENIGMA-OCD Working-Group. An empirical comparison of meta- and mega-analysis with data from the ENIGMA Obsessive-Compulsive Disorder Working Group. *Front Neuroinform*. 2019;12(9):102. doi:10.3389/fninf.2018.00102
90. Tognin S, van Hell HH, Merritt K, et al; PSYSCAN Consortium. Towards precision medicine in psychosis: benefits and challenges of multimodal multicenter studies—PSYSCAN: translating neuroimaging findings from research into clinical practice. *Schizophr Bull*. 2020;46(2):432-441. doi:10.1093/schbul/sbz067
91. Choe BY, Suh TS, Shinn KS, Lee CW, Lee C, Paik IH. Observation of metabolic changes in chronic schizophrenia after neuroleptic treatment by in vivo hydrogen magnetic resonance spectroscopy. *Invest Radiol*. 1996;31(6):345-352. doi:10.1097/00004424-199606000-00006
92. Kubota M, Moriguchi S, Takahata K, Nakajima S, Horita N. Treatment effects on neurometabolite levels in schizophrenia: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. *Schizophr Res*. 2020;222:122-132. doi:10.1016/j.schres.2020.03.069