Glutamatergic Dysregulation in Pediatric Psychiatric Disorders: A Systematic Review of the Magnetic Resonance Spectroscopy Literature

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ABSTRACT

Objective: As the major excitatory neurotransmitter in the brain, glutamate plays a critical role in normal brain function; thus, its dysregulation could lead to psychopathology in youth. A growing body of literature has investigated the role of glutamate in the pathophysiology of childhood psychiatric disorders through magnetic resonance spectroscopy (MRS). The aim of this study was to review the existing literature to gauge the specificity of such findings.

Data Sources: PubMed was searched for all scientific, peer-reviewed articles published in English that included MRS measurements of glutamatergic metabolites in pediatric psychiatric populations through August 14, 2013.

Study Selection: 50 articles were included in this review. These studies included measurements of glutamate or related metabolites with MRS in children with psychiatric disorders.

Data Extraction: All relevant data (eg, population; number, sex, and age of subjects; method of comparison; treatment history; MRS Tesla; brain regions of interest; glutamatergic findings; other findings; and comorbidities) were extracted from the included articles. The direction and significance of glutamate dysregulation and brain region(s) examined were used to compare the studies.

Results: Most consistently, increases in glutamatergic metabolites were found in the anterior cingulate cortex (ACC) and other regions in youth with attention-deficit/hyperactivity disorder (ADHD). Limited data suggested increases in glutamatergic metabolites in youth with autism spectrum disorders, emotional dysregulation, and high risk for schizophrenia and decreases in youth with major depression, bipolar disorder, and obsessive-compulsive disorder. There was limited but consistent evidence for normalization of glutamatergic levels with treatment, particularly in bipolar disorder and ADHD.

Conclusions: A relatively small number of studies have examined the role of glutamatergic dysregulation in pediatric psychiatric disorders. Some consistencies can be found, but interpretation of the data is limited by differences in methodology, including age of subjects, severity of current symptoms, treatment, and scanning parameters.

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Glutamate is the major excitatory neurotransmitter in the brain.[1] Glutamate is crucial for normal brain development and neuroplasticity, but its malfunction is correlated with a wide range of psychiatric difficulties, implicating it in the pathology of many psychiatric disorders,[2] many of which have their onset in childhood.

Studies have used a variety of methods to elucidate the role of glutamate in psychiatric disorders. Elevated serum concentrations of glutamate have been found in several psychiatric disorders, including bipolar disorder,[3] autism spectrum disorders,[4] and Tourette's syndrome.[5] Lower glutamic acid and higher glutamine levels have been found in the serum and cerebrospinal fluid in anorexia nervosa.[6,7] Cerebrospinal fluid glutamate levels have been found to be low in patients with schizophrenia[8] and high in patients with Rett syndrome[9] and obsessive-compulsive disorder (OCD).[10] Cerebrospinal fluid glutamine has been found to be high in major depressive disorder (MDD).[11] Genetic studies have uncovered polymorphisms in genes that code for subunits of glutamate receptors, transporters, and carriers in bipolar disorder (reviewed by Gigante et al[3] and Machado-Vieira et al[12]), schizophrenia,[8] autism spectrum disorders,[13,14] OCD,[15–18] MDD,[12] Tourette's syndrome,[19] anorexia nervosa,[17] and attention-deficit/hyperactivity disorder (ADHD).[20,21]

Although glutamatergic neurotransmission is pervasive in the brain and seems to play a variety of roles in normal development and brain function, it has been hypothesized that dysregulation of glutamatergic neurotransmission in specific brain regions could account for specific psychopathology. Using postmortem brain tissue, studies have in fact found evidence of aberrations in glutamatergic neurotransmission in specific brain regions implicated in various disorders. Abnormal expression of glutamate receptors has been found in the postmortem dorsolateral prefrontal cortex (DLPFC), hippocampus, and striatum in bipolar disorder.[3] Increased levels of glutamate have been found in the frontal cortex of postmortem bipolar disorder and MDD brains.[22] In Tourette's syndrome, reduced levels of glutamate were found in areas of the globus pallidus and substantia nigra.[23] In schizophrenia, abnormalities in glutamate receptor properties have been found in prefrontal cortex (PFC), temporal lobe, and thalamus of postmortem samples.[8] Elevated messenger RNA and protein levels of glutamatergic transporters and receptors were found in postmortem neuropathological studies, largely from cerebellar regions in autism spectrum disorders.[24]

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Clinical Points

- The most consistent finding in our review of literature was increases in glutamatergic metabolites in the anterior cingulate cortex in youth with ADHD that normalized with stimulant treatment.
- Limited data suggested increases in glutamatergic metabolites in youth with autism spectrum disorders, emotional dysregulation, and high risk for schizophrenia and decreases in youth with major depression, bipolar disorder, and obsessive-compulsive disorder.

Furthermore, glutamatergic dysregulation at different developmental stages could be one mechanism by which the interaction of genetic predisposition and environmental factors mediates differential expression of psychiatric disorders,[8] including ADHD, schizophrenia, and major mood disorders. Most of these disorders have their onset in childhood, have overlapping genetic and environmental risk factors,[25] and can be difficult to distinguish clinically at their onset. This raises the crucial question of whether glutamatergic dysregulation can be detected in pediatric psychiatric disorders with any degree of specificity, and whether it could ultimately show promise as a diagnostic tool.

Because glutamate, glutamine, and their combination can be measured in specific brain regions, noninvasively, in vivo by using proton magnetic resonance spectroscopy (MRS), spectroscopic-based studies have been used to investigate glutamatergic abnormalities in various child and adolescent psychiatric disorders.[26] Interpretation of such studies is challenging, since in typically developing children and adolescents, metabolite ratios including glutamate have been found to change with age.[27,28] However, by defining the consistencies and inconsistencies in the current literature regarding the role of glutamate in pediatric psychiatric disorders, we can set the stage for further research, pathophysiologic understanding, and targeted treatments.

The main aim of this study was to examine the available evidence linking glutamatergic dysregulation to pediatric psychiatric disorders. To this end, we conducted a review of the spectroscopic literature reporting glutamate metabolite levels in child and adolescent psychiatric disorders to examine whether glutamatergic dysregulation can be detected in these disorders with any degree of consistency and specificity. We hypothesized that disorder-specific alterations in glutamatergic metabolites would be evident, that these glutamatergic abnormalities would correlate with severity of psychopathology, and that they would normalize with treatment.

DATA SOURCES

A systematic literature search was conducted using the Harvard eCommons's PubMed database to identify peer-reviewed proton MRS studies written in the English language of pediatric psychiatric disorders measuring glutamate and related metabolites, including glutamine, glutamate + glutamine, glutamate + glutamine + γ-aminobutyric acid (GABA), and ratios of glutamate to other metabolites. Our search criteria, detailed below, included articles that had in their title or abstract a word related to each of these 4 categories: (1) a psychiatric disorder; (2) glutamate, glutamine, or glutamate + glutamine; (3) childhood or adolescence; and (4) spectroscopy. This search spanned all articles through August 14, 2013. In addition, we performed a backward search of bibliographic references from the identified articles and examined suggested relevant articles to verify that all relevant articles were included. The detailed PubMed search algorithm is provided in Supplementary material at PSYCHIATRIST.COM.

STUDY SELECTION

Our search strategy yielded 60 articles from PubMed and 8 additional articles from the backward search of bibliographies and recommended articles. Each article was reviewed to determine its inclusion or exclusion according to the following criteria: Included articles compared a psychiatric population to controls or before and after therapeutic interventions, measured glutamate or a related metabolite (glutamine, glutamate + glutamine, glutamate + glutamine + GABA, or glutamate in relation to other metabolites) in the brain with MRS, and included primarily children, with all subjects aged 21 years or younger and a mean age under 18. Excluded articles comprised adults aged 22 years or older or subjects with a mean age over 18 in the study population and involved animal research, case reports, and reviews.

DATA EXTRACTION

Those articles determined to fit the inclusion criteria were read by a child psychiatrist or the research assistant, and all relevant data were extracted. We recorded the following variables from each article: population type (ie, disorder studied), number of subjects, sex of participants, mean age and age range of participants (if available), method of study comparison, treatment history of participants, MRS Tesla, brain regions of interest, glutamatergic findings, and other metabolic findings. The research assistant then reviewed all articles in comparison to the extracted data to check for errors. The information regarding direction and significance of glutamate dysregulation and brain region(s) examined was then used to compare the studies.

RESULTS

Our PubMed search strategy yielded 60 articles, 42 of which met our inclusion criteria. The remaining articles were excluded because they were reviews or meta-analyses (7 articles) or case studies (2 articles); included primarily adults in the subject population (2 articles); did not report data about glutamate or related metabolites (2 articles); or were studies of animals (2 articles), genetics (1 article), methods (1 article), or urinary metabolites (1 article). The additional 8 articles were found through backward searches of bibliographic references (7 articles) and through suggested relevant articles (1 article). Our analysis ultimately included 50 studies (47 including controlled comparisons;

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15 including studies of treatment effects). These studies measured glutamate, glutamine, glutamate + glutamine, glutamate + glutamine + GABA, and ratios of glutamate to other metabolites in pediatric psychiatric populations using proton MRS. We aggregated the articles by disorder. Table 1 shows the characteristics of each study, compares glutamatergic metabolites in subjects versus controls, and lists other characteristics of each sample, including comorbidities and medications.

Spectroscopic Glutamatergic Studies of ADHD

Thirteen studies used MRS to examine glutamate and related metabolites in pediatric ADHD. The mean age of subjects ranged from 8.12 to 13 years old, and no specific pattern related to mean age emerged among these studies. Four studies showed a significantly higher level of glutamatergic metabolites in youth with ADHD than in controls in the striatum,[31,37] the PFC,[31] and the anterior cingulate cortex (ACC).[36,39] Two studies reported nominal increases in glutamatergic metabolites in the striatum[31] and ACC[39] in ADHD versus controls that did not meet threshold for statistical significance. Likewise, a few studies reported positive correlations between glutamatergic metabolite levels and ADHD symptoms or associated features, including age at ADHD onset,[31] learning and memory difficulties assessed in neuropsychological measures,[34] and severity of ADHD as assessed through scores on the ADHD symptom rating scale.[39] One study[36] specifically compared subjects with ADHD alone to those with comorbid ADHD and bipolar disorder and to controls, and it showed significantly higher glutamate + glutamine ratios in the ACC of subjects with ADHD alone versus those with both or neither disorders. On the other hand, 6 studies found no significant differences between ADHD subjects and controls in the striatum,[33] including the globus pallidus[29] and lenticular nucleus,[35] the frontal regions, including the right PFC[33,37,38] and right middle frontal gyrus,[41] the occipital cortex[4] and the left cerebellum.[38]

A number of studies examined the effects of stimulant treatment on glutamatergic metabolite levels. Three studies showed statistically significant reductions of glutamatergic metabolites following the administration of stimulant medication in the PFC[30,40] and striatum.[30,32] In contrast, 3 studies reported no change in glutamatergic levels after treatment with medication in the globus pallidus,[29] left striatum, and PFC.[30,37,40]

Aside from the study by Moore et al[36] comparing comorbid ADHD and bipolar disorder to ADHD alone or neither disorder, the effect of comorbid conditions on results was not assessed. However, comorbidities were reported among ADHD subjects in several studies, most commonly oppositional defiant disorder.

Spectroscopic Glutamatergic Studies of Autism Spectrum Disorders

Nine MRS studies examining glutamatergic metabolite levels in pediatric populations with autism spectrum disorders were identified. The mean age of subjects among these studies spanned a wide range, from 3.7 to 14 years old, and no specific pattern related to mean age emerged. Two of these studies found increased glutamate or related metabolites in the ACC[46] and pregenual ACC (replicated with 2 patient pools)[48] in autism spectrum disorder populations versus controls. Additionally, 1 study found a trend toward a lower rate of decrease in concentration of glutamate + glutamine over time in autism spectrum disorders compared to a delayed development group.[49] Four studies of subjects with autism spectrum disorders versus controls found significantly decreased glutamatergic metabolites (measured as glutamate + glutamine or glutamate metabolite ratios) in the frontal lobes,[28,45,47] cerebral gray matter, occipital lobes, the cerebellum,[28] and cerebral white matter of 3- to 4-year-olds.[49] Two studies reported nonsignificant trends for decreased glutamatergic metabolites in the temporal lobes.[28,46]

Six studies of subjects with autism spectrum disorders and controls found no difference in glutamatergic metabolites in several brain regions examined. Four of these studies found no difference in glutamate metabolite levels in the thalamus,[44] lenticular nucleus, frontal lobe,[45] or cerebral white matter,[28] specifically in children aged 6–7 and 9–10 years,[49] and gray matter in children aged 3–4, 6–7, and 9–10 years.[49] The 2 other studies found no difference in glutamate metabolite levels when averaged over various brain regions (frontal/parietal/temporal lobes, cingulate gyrus, caudate/putamen, insula, superior temporal gyrus, corpus callosum, occiput, and thalamus),[42] including when comparing averaged concentrations for total white and gray matter.[43] When these same averaged glutamate metabolite measures were used, no differences were found between subjects with delayed development and those with autism spectrum disorders or healthy controls.[42,43] Aside from the comparison between autism spectrum disorders and delayed development, these studies either did not assess or did not include psychiatric comorbidities.

Spectroscopic Glutamatergic Studies of Bipolar Disorder

Nine studies examined MRS glutamate levels in pediatric bipolar disorder. The mean age of subjects ranged from 8 to 15.89 years, and no specific pattern related to mean age was evident. Only 1 controlled study[50] reported increased glutamatergic metabolites in the frontal lobes and basal ganglia in youth with bipolar disorder when compared to controls. On the other hand, 2 controlled studies[53,56] found decreased glutamatergic metabolites in the ACC. Of these, Moore et al[53] reported decreased glutamine but not glutamate in unmedicated bipolar youth. Singh et al[56] reported decreased glutamate but not glutamine in bipolar disorder versus subsyndromal mania and controls. Also, unlike high-risk youth meeting criteria for bipolar disorder, those with subsyndromal mania did not differ from controls.[56] Four controlled studies of bipolar disorder and controls found no difference in glutamatergic metabolites in the ACC,[51,57]

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Table 1. Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Attention-deficit/hyperactivity disorder (ADHD)								
Jin et al[29]	12 ADHD (mean age = 13 y; all male), 10 controls (mean age = 13 y; all male); age range, 10–16 y	ADHD and control, before and after medication (methylphenidate short acting 10 mg × single dose)	Not applicable	1.5	Globus pallidus	→Glu/Cr, Glx/Cr	↓NAA/Cr, ↑Cho/Cr	None
Carrey et al[30]	4 ADHD (mean age = 9.3 y; 2 females), no controls; age range, 8–11 y	Before and after medication (methylphenidate [n = 2], atomoxetine [n = 2] × 14–18 weeks)	Not applicable	1.5	L striatum, PFC	↓Glx + GABA/Cr after medication in L striatum ↓Glx + GABA/Cr after amoxetine only in PFC →Glx + GABA/Cr after methylphenidate only	→NAA/Cr, Cho/Cr	ODD (n = 2)
MacMaster et al[31]	9 ADHD (mean age = 9.60 y; 3 females), 9 controls (mean age = 9.36 y; 3 females); age range, 7–16 y	ADHD and control	All ADHD subjects but 1 had history of being on stimulants; no medication > 48 h prior to the scan	1.5	R PFC, L striatum	↑Glu/Cr + PCr in R PFC ↑Glu/Cr + PCr in L striatum (NS) Glx/Cr + PCr correlated with age at onset of ADHD	No findings reported	ODD (n = 6)
Carrey et al[32]	14 ADHD (mean age not specified; 3 females), no controls; age range, 7–13 y	Before and after medication (methylphenidate [n = 4], atomoxetine [n = 3], dexedrine [n = 8] × 13 weeks)	Not applicable	1.5	L striatum	↓Glx + GABA/Cr + PCr after medication	→NAA/Cr + PCr, Cho/Cr + PCr	ODD (n = 3), mild learning disability (n = 7)
Sparkes et al[33]	8 ADHD (mean age = 9.354 y; 2 females), 6 controls (mean age = 9.444 y; 2 females); age range, 7–11 y	ADHD and control	No medication 24 h prior to scan	1.5	L striatum, R PFC	→Glx + GABA/Cr	→NAA/Cr, Cho/Cr	ODD (n = 5), Tourette's syndrome (n = 1), GAD (n = 1)
Courvoisie et al[34]	8 ADHD (mean age not specified per group; 1 female), 8 controls (1 female); mean age of all subjects = 8.93 y; age range, 6–12 y	ADHD and control	All ADHD subjects were on stimulants, no medication 24 h prior to the scan	1.5	Anterior frontal regions	↑Glu/Cr Correlation between learning and memory difficulties assessed by neuropsychiatric measures and Glu/Cr	↑ NAA/Cr, Cho/Cr	None
Sun et al[35]	10 ADHD inattentive (mean age = 12.43 y; 0 females), 10 ADHD combined type (mean age = 12.64 y; 0 females), 10 controls (mean age = 12.67 y; 0 females); age range, 10–14 y	ADHD, combined type; ADHD, inattentive type; and control	All subjects medication naive	1.5	Bilateral lenticular nucleus	→α-Glx/Cr	↓NAA/Cr, →Cho/Cr, mIno	ODD (n = 2), CD (n = 1), tic disorder (n = 3), learning problems (n = 7)
Moore et al[36]	15 ADHD (no mean age or gender specified), 8 ADHD + BPD, 7 controls; age range, 6–13 y	ADHD, ADHD + BPD, and control	ADHD (n = 3) and ADHD + BPD (n = 2) on medication: amphetamine, bupropion, and sertraline (n = 1); atomoxetine (n = 1); amphetamine (n = 1); clonazepam (n = 1); clonazepam, desmopressin, and sertraline (n = 1)	1.5	ACC	↑Glx/mIno in ADHD vs ADHD + BPD ↑Glx/Cr + PCr in ADHD →Glx/mIno, →Glx/Cr + PCr in ADHD + BPD vs controls ↑Glx/mIno, ↑Glx/Cr + PCr in ADHD vs controls	→mIno/Cr + PCr	ADHD comorbidities: ODD (n = 7) ADHD + BPD comorbidities: ODD (n = 8), GAD (n = 2), CD (n = 1)

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Carrey et al[37]	12 ADHD (mean age = 8.12 y; 0 females), 10 controls (mean age = 8.39 y; 0 females); age range, 6–11 y	ADHD and control; before and after medication (immediate-release methylphenidate × 8 wk)	Not applicable	2.0	L striatum, R PFC, L occipital cortex	↑Glx in L striatum, →Glx in R PFC or occipital cortex in ADHD vs control →Glx after medication	↑Cr + PCr in striatum in ADHD vs control, ↓Cr + PCr in striatum after medication, →NAA, Cho, mIno	None
Soliva et al[38]	17 ADHD (mean age = 10.41 y; 2 females), 17 controls (mean age = 10.76 y; 2 females); age range not specified	ADHD and control	Methylphenidate (all ADHD subjects), no medication on day of scan	1.5	L cerebellum, R PFC	→Glx, Glu	↓mIno, NAA in L cerebellum, ↓Cr in R PFC and L cerebellum (at α = .05)	None
Hammerness et al[39]	10 ADHD (mean age = 14.2 y), 12 controls (mean age = 12.8 y); sex distribution not specified ("majority male"); age range not specified	ADHD and control; before and after medication (osmotic release oral system methylphenidate × 6–8 wk)	Not applicable	4.0	ACC	↑Glu/mIno, Gln/mIno, Glx/mIno (NS) in ADHD vs control ↓Glu/mIno, Gln/mIno, and Glx/mIno in ADHD after medication (NS) Correlation between Gln/mIno and ADHD rating scale scores	No findings reported	None
Wiguna et al[40]	21 ADHD (mean age = 8.52 y; 4 females), no controls; age range not specified	Before and after medication (methylphenidate long acting × single dose)	Not applicable	1.5	L and R PFC	↓Glu/Cr after medication	↑NAA/Cr, ↓Cho/Cr in L and R PFC ↓mIno/Cr in L PFC →mIno/Cr in R PFC after medication	None
Tafazoli et al[41]	13 ADHD (mean age = 12.3 y; 5 females), 13 controls (mean age = 12.2 y; 5 females); age range not specified	ADHD and control	Methylphenidate (n = 1), amphetamine (n = 2), no medication 24 h prior to scan	1.5	R middle frontal gyrus	→Glx	↓tNAA, Cr + PCr, Cho, mIno	Not reported
Autism spectrum disorders (ASD)								
Friedman et al[42]	45 ASD (mean age = 3.9 y; 7 females), 12 DD (mean age = 4 y; 7 females), 10 controls (mean age = 3.9 y; 2 females); age range, 3–4 y	ASD, DD, and control	No medication; intravenous propofol for ASD and DD groups for scan	1.5	Average concentration from frontal WM, cingulate, caudate, putamen, thalamus, insula, superior temporal gyrus, corpus callosum, parietal WM, occiput	→Glx	↓NAA, Cr + PCr, mIno, →Cho in ASD vs controls ↓NAA, →Cr + PCr, mIno, Cho in ASD vs DD	Not assessed
Friedman et al[43]	45 ASD (mean age = 3.9 y; 7 females), 15 DD (mean age = 4 y; 9 females), 13 controls (mean age = 3.7 y; 2 females); age range, 3–4 y	ASD, DD, and control	No medication; intravenous propofol for ASD and DD groups scan	1.5	Cerebral GM, cerebral WM	→Glx	↓NAA, Cho, Cr + PCr, mIno in GM ↓NAA, mIno, →Cho, Cr + PCr in WM in ASD vs control ↓Cho, mIno, →NAA in GM →NAA, Cho, Cr + PCr, mIno in WM in ASD vs DD	Not assessed
DeVito et al[28]	26 ASD (mean age = 9.8 y; 0 females), 29 controls (mean age = 11.1 y; 0 females); age range, 6–17 y	ASD and control	ASD medication: medication naive (n = 14), stimulants (n = 9), risperidone (n = 5), SSRI (n = 4), cholinesterase inhibitor (n = 1); sedation for scan with midazolam (n = 18)	3.0	Cerebral GM, cerebral WM, frontal GM, temporal GM, occipital GM, cerebellum	↓Glx in cerebral GM, frontal GM, occipital GM and cerebellum ↓Glx in temporal lobe (NS) →Glx cerebral WM	↓NAA in cerebral, frontal, occipital GM ↓Cr + PCr in L temporal and occipital GM →Cr + PCr in R temporal, cerebral, frontal GM →NAA in temporal GM →NAA, Cr + PCr in cerebral WM, cerebellum →Cho, mIno	Not assessed

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Hardan et al[44]	18 ASD (mean age = 11.9 y; 0 females), 16 controls (mean age = 11.6 y; 0 females); age range, 8–15 y	ASD and control	Not reported	1.5	Thalamus	→Glx	↓NAA in L thalamus →NAA in R thalamus →Cho, mIno, Cr + PCr	Not assessed
Harada et al[45]	12 Autistic disorder (mean age = 5.2 y; gender not reported), 10 controls (mean age = 5.9 y); age range, 2–12 y	Autistic disorder and control	Sedation with triclofos sodium (n = 19)	3.0	Frontal lobe, Lenticular nuclei	→Glu ↓GABA/Glu in the frontal lobe	↓GABA, GABA/NAA in frontal lobe →GABA, GABA/NAA in lenticular nucleus →NAA, Cr, Cho, mIno	Not assessed
Joshi et al[46]	7 Autistic disorder (mean age = 14 y; 0 females), 7 controls (mean age = 14 y; 0 females); age range, 12–17 y	Autistic disorder and control	ASD medication naive (n = 3), SSRI (n = 1), combination therapy (stimulant, SSRI/SNRI, atypical) (n = 3)	4.0	ACC, medial temporal lobe	↑Glu in ACC ↓Glu in R medial temporal lobe (NS)	No findings reported	Anxiety disorder (n = 3), ADHD and anxiety disorder (n = 3), mood disorder (n = 1)
Kubas et al[47]	12 ASD (mean age = 10.55 y; 5 females), 16 controls (mean age = 11.35 y; 7 females); age range, 7–17 y	ASD and control	Not reported	1.5	Frontal lobe	↓Glx/Cr	↓NAA/Cr, GABA/Cr, ↑mIno/Cr, →Cho/Cr	Not assessed
Bejjani et al[48]	First study: 8 ASD (mean age = 11.2 y; 1 female), 10 controls (mean age = 13.2 y; 5 females); age range, 7.4–16.5 y Second study: 26 ASD (mean age = 10.2 y, 7 females), 16 controls (mean age = 11.8 y; 5 females); age range, 6.1–17.5 y	ASD and control	First study: ASD SSRI (n = 1), stimulant (n = 2); ASD sedated with propofol (n = 1) Second study: ASD subjects on stimulants (n = 5), atomoxetine (n = 1), anticonvulsant (n = 1), SSRI (n = 2), atypical (n = 1)	1.5	First study: midline pACC Second study: bilateral pACC	First study: ↑Glx in pACC Second study: ↑Glx in R pACC, →Glx in L pACC	First study: ↓Cr + PCr in pACC, →Cho, mIno Second study: ↑Cr + PCr and tNAA in R pACC →Cr + PCr, tNAA in L pACC, →Cho, mIno	Not reported
Corrigan et al[49]	Ages 3–4 y: 45 ASD (mean age = 4.0 y; 7 females), 13 DD (mean age = 3.9 y; 7 females), 10 controls (mean age = 3.8 y, 2 females) Ages 6–7 y: 31 ASD (mean age = 6.6 y; 7 females), 14 DD (mean age = 6.4 y; 5 females), 18 controls (mean age = 6.6, 2 females) Ages 9–10 y: 29 ASD (mean age = 9.6 y; 5 females), 12 DD (mean age = 9.5 y; 5 females), 29 controls (mean age = 9.6 y; 4 females)	ASD, DD, and control	ASD: stimulants (n = 8), antidepressant (n = 14), antipsychotic (n = 6), anticonvulsant (n = 3); DD: stimulant (n = 6); intravenous propofol for ASD and DD groups for scan	1.5	Cerebral GM, cerebral WM	Ages 3–4 y: ↓Glx in WM in ASD vs control Ages 6–7 y: ↑Glx (NS) in GM of ASD vs DD Ages 9–10 y: →Glx	Ages 3–4 y: ↓NAA, Cho, Cr, →mIno in WM + GM in ASD vs control ↓mIno, Cr (NS), →NAA, Cho, Cr in WM in ASD vs DD Ages 6–7 y: ↓Cho, →NAA, Cr, mIno in GM in ASD vs control →In WM in ASD vs control ↓mIno, ↑Cr (NS), →NAA, Cho in WM in ASD vs DD Ages 9–10 y: ↓NAA, →Cho, Cr, mIno in WM in ASD vs control →In GM in ASD vs control and DD vs control →In GM ASD vs DD	Not assessed
Bipolar disorder								
Castillo et al[50]	10 BPD (mean age = 8; 1 female), 10 controls (age not specified; 2 females); age range, 6–12 y (BPD)	BPD and control	Unmedicated for 1 wk prior to scan, diphenhydramine hydrochloride for scan sedation (n = 1)	1.5	Frontal and temporal (including external capsule, insular cortex, deep GM structures and WM tracts) lobes	↑Glx/Cr	↑Lipids in frontal lobes, →NAA/Cr, Cho/Cr	Present in 88%; specifics not reported

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Davanzo et al[51]	10 IED (mean age = 9.6 y; 2 females), 10 BPD (mean age = 9.8 y; 2 females), 13 controls (mean age = 11.7 y; gender not specified); age range, 6–15 y	IED, BPD, control	7 IED on medication (stimulants [n = 4], α-agonist [n = 2], divalproex sodium [n = 2]), 5 BPD on medication (stimulants [n = 2], α-agonist [n = 1], divalproex sodium [n = 2], risperidone [n = 2])	1.5	ACC, occipital cortex	→Glx	↑mIno/Cr + PCr, mIno in ACC in BPD vs IED and control ↓Cho/Cr + PCr in BPD vs control	BPD comorbidities: ADHD (n = 8), ODD (n = 9), CD (n = 7) IED comorbidities: ADHD (n = 7), ODD (n = 9), CD (n = 2)
DelBello et al[52]	19 BPD taking olanzapine for mania: 11 remitters (mean age = 14 y; 7 females) and 8 nonremitters (mean age = 15 y; 6 females); 10 controls (mean age = 15 y; 6 females), age range, 12–18 y	Acute mania during treatment with olanzapine and control	All naive to anticonvulsant, antidepressant, antipsychotic medication	1.5	Medial, L and R lateral, ventral prefrontal	→Glx	↓NAA in nonremitters ↑NAA in remitters after treatment ↑Cho in BPD vs control and in remitters vs nonremitters at baseline in medial prefrontal →In lateral and ventral prefrontal, mIno, or Cr	ADHD (5 remitters, 3 nonremitters)
Moore et al[36]	15 ADHD (no mean age or gender specified), 8 ADHD + BPD, 7 controls; age range, 6–13 y	ADHD, ADHD + BPD, and control	ADHD (n = 3) and ADHD + BPD (n = 2) on medication: amphetamine, bupropion, and sertraline (n = 1); atomoxetine (n = 1); amphetamine (n = 1); clonazepam (n = 1); clonazepam, desmopressin, and sertraline (n = 1)	1.5	ACC	↑Glx/mIno in ADHD vs ADHD + BPD ↑Glx/Cr + PCr in ADHD →Glx/mIno →Glx/Cr + PCr in ADHD + BPD vs controls ↑Glx/mIno, ↑Glx/Cr + PCr in ADHD vs controls	→mIno/Cr + PCr	ADHD comorbidities: ODD (n = 7) ADHD + BPD comorbidities: ODD (n = 8), GAD (n = 2), CD (n = 1)
Moore et al[53]	22 BPD: 7 unmedicated, 15 medicated (mean = age 12.6 y; 13 females); 10 controls (mean age = 12.3 y; 7 females); age range, 5–19 y	BPD with medications, BPD without medications, and control	7 BPD unmedicated (3 medication naive), 15 medicated: anticonvulsant (n = 8), lithium (n = 2), atypical antipsychotic (n = 12), antidepressant (n = 3), clonidine (n = 3), atomoxetine (n = 1), methylphenidate (n = 1)	4.0	ACC	↓Gln in unmedicated BPD vs controls and vs medicated BPD →Glu in medicated BPD vs controls vs unmedicated BPD Negative correlation between CDRS score and Gln (NS) among all subjects	→NAA, Cho, Cr + PCr, mIno	ADHD (n = 9), ODD (n = 3), PTSD (n = 2), anxiety (n = 1)
Moore et al[54]	10 Manic unmedicated (mean age = 11.10 y; 5 females); 8 BPD taking risperidone (mean age = 10.88 y, 1 female); age range, 6–17 y	BPD medicated with risperidone for acute symptoms (5 in remission, 3 responders) vs manic and not receiving risperidone	5 not receiving risperidone on other medication (clonidine [n = 2], SSRI [n = 1], atomoxetine [n = 1], stimulant [n = 1]) 3 receiving risperidone on other medication (SSRI [n = 1], bupropion [n = 1], atomoxetine [n = 1], stimulant [n = 1])	1.5	ACC	↓Glx/Cr in manic and unmedicated vs treated with antipsychotic YMRS and Clinical Global Impressions-mania score negatively correlated with Glx/Cr	→NAA/Cr, inositol-containing compounds/Cr, Cho/Cr	Untreated comorbidities: alcohol abuse (n = 2), substance abuse (n = 3), OCD (n = 2), GAD (n = 3), PTSD (n = 1), ODD (n = 9), CD (n = 5), PDD (n = 1) Treated comorbidities: GAD (n = 3), PTSD (n = 2), ODD (n = 5), CD (n = 2), autism (n = 1)
Olvera et al[55]	35 BPD I and II (mean age = 13.2 y; 18 females); 36 controls (mean age = 13.7 y, 17 females); age range, 8–17 y	BPD and control	Medication free (n = 11; 10 naive), mood stabilizer and/or antipsychotic (n = 20), other medication (n = 4)	1.5	L dorsolateral PFC	→Glu	↓NAA →Cr + PCr, Cho, mIno	ADHD (60%), anxiety (60%), CD or ODD (40%)

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Singh et al[56]	20 HR/BPD (mean age = 15.89 y; 7 females); 20 HR/ subsyndromal mania (mean age = 12.9 y; 10 females); 20 controls (mean age = 15.1 y; 5 females); age range, 9–18 y	HR offspring with BPD and subsyndromal mania and control	BPD: stimulant (n = 11), antidepressant (n = 9), antipsychotic (n = 6), lithium (n = 6), valproate (n = 7), lamotrigine (n = 1) Subsyndromal: stimulant (n = 6), antidepressant (n = 7), antipsychotic (n = 8), lithium (n = 1), valproate (n = 3), lamotrigine (n = 1) Stimulant discontinued 24 h prior to scan	3.0	ACC	↓Glu, Glu/Cr in BPD vs control ↓Glu, Glu/Cr in BPD vs subsyndromal mania →Glu, Glu/Cr in subsyndromal mania vs control →Gln, Gln/Cr	→Cr, NAA, NAA/Cr, mIno, mIno/Cr	BPD comorbidities: ADHD (85%), anxiety (15%), ODD (60%) Subsyndromal comorbidities: ADHD (65%), anxiety (30%), ODD (25%)
Strawn et al[57]	7 BPD remitters (mean age = 15.4 y; 3 females); 18 BPD nonremitters (mean age = 14.1 y; 12 females); 15 controls (mean age = 14.4 y; 9 females); age range, 12–18 y	Acutely manic/mixed undergoing treatment with divalproex before and after medication and control	Extended-release divalproex (serum levels 85–125 g/mL); no other medications for 1 wk prior to scanning	4.0	ACC, L VLPFC, R VLPFC	→Glu, Glx + GABA in baseline BPD vs control ↑Glx + GABA from day 0 to 7, ↓Glx + GABA from day 7 to 28 in BPD in ACC ↓Glx + GABA, →Glu at baseline in L VLPFC in BPD remitters vs nonremitters and control →Glx + GABA, Glu in R VLPFC Positive correlation of Glu in L VLPFC with YMRS score in BPD remitters Positive correlation of Glu in L VLPFC with day 28 valproic acid concentration	→Cho, NAA, Cr, mIno	BPD remitters: ADHD (n = 4), anxiety (n = 2), DBD (n = 3), substance abuse (n = 1) BPD nonremitters: ADHD (n = 11), anxiety (n = 4), DBD (n = 5), substance abuse (n = 1)
Emotional dysregulation								
Dickstein et al[58]	36 Severe mood dysregulation (mean age = 12.2 y; 11 females); 48 controls (mean age = 12.9 y; 21 females); age range, 7–18 y	Severe mood dysregulation and control	Medication-free for 4 drug half-lives	1.5	R frontal cortex, L temporal cortex, central parieto-occipital lobe, L parietal lobe	↑Glx/Cr in parietal lobe in females (NS) →Glx/Cr in other brain regions and in males	↓mIno/ Cr, →NAA/Cr, Cr	ADHD (n = 32), ODD (n = 32), MDD (n = 8), GAD (n = 13), separation anxiety disorder (n = 9), simple phobia (n = 6), social phobia (n = 6)
Wozniak et al[59]	10 HR (for BPD)/ED (mean age = 11.50 y, 2 females), 14 HR without ED (mean age = 12.04 y, 6 females), 13 controls (mean age = 11.50 y, 4 females), age range, 6–17 y	HR offspring with and without ED and control	HR/ED: atypical antipsychotic (n = 3), antidepressant (n = 4), stimulant (n = 1), mood stabilizer (n = 2), other medications (n = 4) HR without ED: atypical antipsychotic (n = 3), antidepressant (n = 4)	4.0	ACC	↑Glu in HR/ED vs control Positive correlation of Glu with Child Behavior Checklist scores in HR/ED	No findings reported	HR/ED comorbidities: BPD (n = 8), MDD (n = 7), GAD (n = 5), ODD (n = 7), CD (n = 3) ADHD (n = 6) HR without ED comorbidities: BPD (n = 5), MDD (n = 3), ODD (n = 2), CD (n = 1), ADHD (n = 2)

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Major depressive disorder								
Rosenberg et al[60]	14 MDD (mean age = 15.63 y; 9 females), 14 controls (mean age = 15.47 y; 9 females), 20 OCD (mean age = 11.39 y; 11 females); MDD and control age range, 10–19 y; OCD age range, 7–19 y	MDD, OCD, and control	Medication naive	1.5	ACC	↓Glx in MDD vs controls ↓Glx in OCD vs controls →Glx in MDD vs OCD	↓Cr + PCr, →Cho, mIno, NAA in MDD vs controls →Cr + PCr, Cho, mIno, NAA in MDD vs OCD	OCD group: anxiety disorder (n = 2), ADD without hyperactivity (n = 1), ODD (n = 1), dysthymia (n = 1) MDD group: anxiety disorder (n = 5), ODD (n = 1), ADD without hyperactivity (n = 1), anxiety disorder and OCD (n = 2)
Mirza et al[61]	13 MDD (mean age = 15.54 y; 8 females), 13 controls (mean age = 15.63 y; 8 females); age range, 10–19 y	MDD and control	Medication naive	1.5	ACC (all subjects), occipital cortex GM (10 matched)	↓Glx in ACC →Glx in occipital cortex	↓Cr + PCr, →NAA Cho, mIno in ACC →NAA Cho, mIno, Cr + PCr in occipital cortex	Anxiety disorder (n = 4), ADD without hyperactivity (n = 1), ODD (n = 1), anxiety disorder and ODD (n = 2)
Rosenberg et al[62]	14 MDD (mean age = 15.63 y; 9 females), 14 controls (mean age = 15.47 y; 9 females); age range, 10–19 y	MDD and control	Medication naive	1.5	ACC (all for Glu, 12 matched for Gln), occipital cortex GM (10 matched)	↓Glu, →Gln in ACC →Glu, Gln in occipital cortex	No findings reported	Anxiety disorder (n = 5), ODD (n = 1), ADD without hyperactivity (n = 1), anxiety disorder and OCD (n = 2)
Caetano et al[63]	14 MDD (mean age = 13.3 y; 4 females), 22 controls (mean age = 13.6 y; 9 females); age range, 8.5–17.7 y	MDD and control	Medication-free (n = 8), medication naive (n = 6), sertraline (n = 2), escitalopram (n = 2), paroxetine (n = 1), methylphenidate (n = 1), atomoxetine (n = 1)	1.5	L dorsolateral PFC	→Glu, Gln Negative correlation of Glu with duration of illness and no. of episodes Positive correlation of Gln with age in controls	↓Cho, ↑mIno, →NAA, Cr + PCr, GABA	ADHD (n = 4), GAD (n = 5), separation anxiety (n = 3), social phobia (n = 2), panic disorder (n = 1)
Obsessive-compulsive disorder								
Rosenberg et al[64]	Group 1: 11 OCD (mean age = 11 y; 7 females), 11 controls (mean age = 12 y; 7 females); age range, 8–17 y Group 2: 8 OCD (mean age and gender not specified), 8 controls (mean age and gender not specified); age range, 8–17 y	Group 1: OCD before and after medication (paroxetine; 10–60 mg/d × 12 wk) and control; Group 2: OCD and control	Group 1: medication naive prior to study intervention Group 2: medication naive	1.5	Group 1: L HOC Group 2: occipital GM	Group 1: ↑Glx + GABA in OCD vs control ↓Glx + GABA in OCD premedication vs postmedication Group 2: →Glx + GABA in OCD vs control	Group 1: ↑Cr + PCr, →NAA, Cho, mIno in OCD vs control and premedication vs postmedication Group 2: →NAA, Cr + PCr, mIno in OCD vs control	Group 1: anxiety disorder (n = 4), dysthymia (n = 1), ODD (n = 2) Group 2: Not reported
Benazon et al[65]	21 OCD (mean age = 11.6 y; 11 females), no controls; age range, 6–16 y	OCD before and after CBT (12 sessions, 3–4 mo)	Medication naive	1.5	L HOC	→Glx	→Cr + PCr, Cho, mIno, NAA	Dysthymia (n = 1), dysthymia and ODD (n = 1), ADD without hyperactivity (n = 1), separation anxiety disorder (n = 1), GAD (n = 1)
Rosenberg et al[60]	14 MDD (mean age = 15.63 y; 9 females), 14 controls (mean age = 15.47 y; 9 females), 20 OCD (mean age = 11.39 y; 11 females); MDD and control age range, 10–19 y; OCD age range, 7–19 y	MDD, OCD, and control	Medication naive	1.5	ACC	↓Glx in MDD vs controls ↓Glx in OCD vs controls →Glx in MDD vs OCD	↓Cr + PCr, →Cho, mIno, NAA in MDD vs controls →Cr + PCr, Cho, mIno, NAA in MDD vs OCD	OCD group: anxiety disorder (n = 2), ADD without hyperactivity (n = 1), ODD (n = 1), dysthymia (n = 1) MDD group: anxiety disorder (n = 5), ODD (n = 1), ADD without hyperactivity (n = 1), anxiety disorder and OCD (n = 2)

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Whiteside et al[66]	15 OCD (mean age = 13.53 y; 7 females); 15 controls (mean age = 13.64 y; 7 females); age range, 8–18 y	OCD before (medicated and unmedicated) and after behavioral therapy (up to 18 individual therapy sessions × 50–70 min) and control	Psychotherapy (n = 12), fluoxetine (n = 5), fluvoxamine (n = 1), medication naive (n = 7), treatment naive (n = 2)	1.5	HOC, pACC	→Glx in OCD vs control ↓Glx in R HOC in OCD after treatment →Glx in pACC →Glx/Cr + PCr	↓NAA, Cr + PCr, ↑mIno/Cr + PCr, →Cho, mIno, Cho/Cr + PCr, mIno/Cr + PCr in unmedicated vs medicated in L HOC →In pACC	7 Subjects had comorbidities, including GAD, MDD, specific phobia, ADHD, social phobia, and ODD
Lazaro et al[67]	11 OCD (mean age = 12.5 y; 5 females), 12 controls (mean age = 14.5 y; 7 females); age range, 9–17 y	OCD before and after medication (fluoxetine; 20–60 mg/d × 6 mo) and control	Medication naive prior to study intervention	1.5	ACC-medial frontal cortex, L and R striatal region (including caudate and putamen)	→Glx	↓Cho in L striatum, →Cr, mIno, NAA in OCD before medication vs control	None
O'Neill et al[68]	5 OCD (mean age = 13.5 y; 4 females), 9 healthy controls (mean age = 13.0 y; 7 females); age range not specified	OCD before and after CBT (12-wk exposure-based) and control	Unmedicated, no CBT prior to intervention	1.5	Bilateral putamen, thalamus, pACC	→Glx	↑tNAA in L pACC, ↓Cr + PCr in R putamen, →Cho, mIno in OCD before CBT vs control ↓tNAA and Cr + PCr in L pACC, ↑Cho in R thalamus, →Cr + PCr mIno in OCD before vs after CBT	Not reported
Generalized anxiety disorder								
Strawn et al[69]	10 GAD (mean age = 14 y; 6 females), 10 controls (mean age = 14.5 y; 6 females); age range, 11–17 y	GAD and control	No current medication	4	ACC	→Glu, Glu/Cr Positive correlation between Glu/Cr ratio and Pediatric Anxiety Rating Scale and Hamilton Anxiety Rating Scale	→NAA, Cr, mIno	Not reported
Schizophrenia								
Thomas et al[70]	13 Schizophrenia (mean age = 14 y; 6 females), 12 controls (mean age = 11 y; 6 females); age range not specified	Schizophrenia and control	Medication naive (n = 3), risperidone (n = 3), other (benztropine, trihexyphenidyl, fluoxetine, thiothixene, sertraline, diphenhydramine) (n = 7)	1.5	Frontal lobe, occipital lobes	↓Glx/Cr occipital ↓Glx/Cr frontal (NS)	↓NAA/Cr frontal, →NAA/Cr occipital, →Cho/Cr, mIno/Cr	Not reported
Tibbo et al[71]	20 HR (mean age = 16.4 y; 13 females), 22 controls (mean age = 16.7 y; 13 females); age range not specified	HR offspring (parent with schizophrenia) and control	Not reported	3.0	R medial frontal lobe	↑Glx/Cr Glx/Cr correlated with Global Assessment of Functioning in HR group	→NAA/Cr, inositol-containing compounds/Cr, Cho/Cr	None
Keshavan et al[72]	40 HR (mean age = 15.6 y; 22 females), 46 controls (mean age = 15.6 y; 25 females); age range, 10.5–21.6 y	HR offspring (parent with schizophrenia or schizoaffective disorder) and control	Not reported	1.5	Prefrontal WM, anterior cingulate, caudate, thalamus, inferior parietal/occipital, superior temporal and posterior WM	↑Glx in inferior parietal/occipital in HR without Axis I pathology and in males ↓Glu, Glx overall in males →Glx in caudate, prefrontal WM, ACC, thalamus, superior temporal, posterior WM Glx correlated with age (positive) in controls and (negative) in HR	↓NAA, Cr + PCr, Cho in caudate ↑NAA, →Cr + PCr, Cho in prefrontal WM in HR without psychopathology →NAA, Cr + PCr, Cho in ACC, thalamus, inferior parietal/occipital, superior temporal	All comorbidities in HR group: ADHD (n = 7), bulimia nervosa (n = 1), CD (n = 1), MDD (n = 5), personality disorder (n = 1), PTSD (n = 2), specific phobia (n = 1), depressive disorder NOS (n = 1), cannabis abuse (n = 1), BPD (n = 1), ODD (n = 2)

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Table 1 (continued). Studies Assessing Glutamate and Related Metabolites Using Magnetic Resonance Spectroscopy (MRS) in Pediatric Psychiatric Disorders

Study	Subjects	Method	Treatment	MRS Tesla	Brain Region	Glutamatergic Findings	Other Findings	Comorbidities
Seese et al[73]	28 Schizophrenia (mean age = 14.1, 13 females), 34 controls (mean age = 11.5, 19 females); age range, 8.4–17.8 y	Schizophrenia and control	23 on medications (neuroleptic alone [n = 11], neuroleptic plus nonneuroleptic [n = 10], nonneuroleptic alone [n = 2])	1.5	Inferior frontal, middle frontal, and superior temporal gyri	→Glx	→tNAA, Cr + PCr, Cho, mIno	Not reported
Tandon et al[74]	23 HR (mean age = 15.9 y; 11 females), 24 controls (mean age = 15.6 y; 12 females); age range not specified	HR offspring (parent with schizophrenia) and control	Not reported	1.5	L and R thalamus, ACC, caudate	↑Glx in thalamus and caudate (R + L), →Glx in ACC (R + L) Positive correlation of Glx in thalamus and caudate with attenuated psychosis Positive correlation of Glx in caudate with perseverative errors on Wisconsin Card Sorting Test	↓NAA, →Cho in thalamus and caudate ↑Cho, ↓NAA in ACC	Not reported
Anorexia nervosa (AN)								
Castro-Fornieles et al[75]	12 AN (mean age = 14.5 y; 11 females), 12 controls (mean age = 15.1 y; 7 females); age range, 11–17 y	AN before and after recovery in 7-mo treatment program (biological management, nutritional rehab, behavioral program) and control	Fluoxetine or fluvoxamine at first evaluation (n = 1) and follow-up (n = 3)	1.5	Frontal gray matter	↓Glx in AN before treatment vs control ↑Glx (NS) in AN before vs after treatment	↓NAA, mIno, global metabolite concentrations, →Cr in AN before treatment vs control ↑NAA, →Cr, mIno, Cho in AN before vs after treatment	None
Blasel et al[76]	21 AN (mean age = 14.4 y; all female), 29 controls (mean age = 16.0 y; all female); age range, 11–18 y	AN and control	Medication-free during study period	3	Centrum semiovale including ACC (region 1: anterior; region 2: posterior)	↑Glx in GM, →Glx in WM of regions 1 and 2 ↑Glx mean concentration in regions 1 and 2	↑Cr + PCr, →Cho, NAA, mIno, Cho mean concentration in regions 1 and 2 ↑Cho, Cr + PCr, NAA, →mIno in GM of region 1 ↑Cho, Cr + PCr, →NAA, mIno in GM of region 2 →Cho, Cr + PCr, NAA, mIno in WM of regions 1 and 2	None
Tourette's syndrome								
Devito et al[77]	25 Tourette's syndrome (mean age = 10.9 y; 0 females), 32 controls (mean age = 11.5 y; 0 females); age range, 6–17 y	Tourette's syndrome and control	Medication naive (n = 4), dopamine antagonists (n = 9), α-agonists (n = 6), stimulants (n = 5), SSRI (n = 1), tricyclic antidepressant (n = 1) Sedation for scan: chloral hydrate (n = 10), midazolam (n = 6)	3	Frontal cortex (premotor cortex), caudate, putamen, thalamus	→Glx	↓NAA, Cho, Cr + PCr, →mIno in L putamen ↓Cr + PCr, →NAA, Cho, mIno in R putamen ↓Cr + PCr, NAA, →Cho, mIno in right frontal ↓mIno, NAA, →Cr + PCr, Cho in left frontal cortex → In caudate and thalamus	ADHD (n = 16)

Abbreviations: ACC = anterior cingulate cortex, ADD = attention-deficit disorder, BPD = bipolar disorder, CBT = cognitive-behavioral therapy, CD = conduct disorder, Cho = choline compounds, Cr = creatine, DBD = disruptive behavior disorders, DD = developmentally disordered, DLPFC = dorsolateral prefrontal cortex, ED = emotional dysregulation, GABA = γ-aminobutyric acid, GAD = generalized anxiety disorder, Gln = glutamine, Glu = glutamate, Glx = glutamate + glutamine, GM = gray matter, HOC = head of the caudate, HR = high risk, IED = intermittent explosive disorder, L = left, MDD = major depressive disorder, mIno = myo-inositol, NAA = *N*-acetylaspartate, NOS = not otherwise specified, NS = nonsignificant, OCD = obsessive-compulsive disorder, ODD = oppositional defiant disorder, pACC = pregenual anterior cingulate cortex, PCr = phosphocreatine, PFC = prefrontal cortex, PTSD = posttraumatic stress disorder, R = right, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, tNAA = *N*-acetyl-aspartate + *N*-acetyl-aspartyl-glutamate, VLPFC = ventrolateral prefrontal cortex, WM = white matter, YMRS = Young Mania Rating Scale.
Symbols: ↑ = increase, ↓ = decrease, → = no change.

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occipital cortex,[51] PFC,[52] left DLPFC,[55] and ventrolateral PFC (VLPFC).[57]

Three studies directly examined medication effects in bipolar disorder. One found increased glutamatergic metabolites in the ACC associated with risperidone treatment,[54] whereas another found no difference associated with olanzapine treatment in the PFC.[52] The 1 study[57] examining the effect of antiepileptic medication found decreased glutamatergic metabolites (glutamate + glutamine + GABA, but not glutamate) in the left VLPFC at baseline in bipolar disorder subjects whose symptoms remitted after 1 month of treatment with divalproex versus those who did not remit and controls. In this study, there were also positive correlations between glutamate levels in the left VLPFC, Young Mania Rating Scale score in remitters, and serum valproic acid concentrations.[57]

Most spectroscopic studies of pediatric bipolar disorder reported the comorbidities of their bipolar disorder samples, most notably including a high prevalence of ADHD. Only 2 of the above studies specifically addressed psychiatric comorbidities in bipolar disorder. One study[36] considered the high comorbidity of bipolar disorder with ADHD by comparing subjects with both disorders to those with ADHD alone as well as to controls. Although subjects with both disorders had no significant change in ACC glutamatergic metabolite levels versus controls, the levels were significantly lower compared to those in subjects with ADHD alone.[36] Another study[51] compared subjects with intermittent explosive disorder, bipolar disorder, and controls, finding no difference among the 3 groups with respect to glutamatergic metabolites.

Spectroscopic Glutamatergic Studies of Emotional Dysregulation

Only 2 controlled studies examined glutamatergic metabolites in youth with emotional dysregulation. One showed significantly increased glutamate in the ACC of youth at high genetic risk for bipolar disorder with high emotional dysregulation.[59] The second study[58] found in a sample of youth with severe mood dysregulation a nonsignificant increase in glutamatergic metabolites in the left parietal lobe in females only, but no difference in males or in either sex in the right frontal cortex, left temporal cortex, and central parietal-occipital lobe. Many subjects with emotional dysregulation were diagnosed with various disorders, including bipolar disorder, MDD, ADHD, and oppositional defiant disorder.

Spectroscopic Glutamatergic Studies of MDD

Four studies examined MRS glutamate levels in pediatric MDD. In 1 sample, MDD subjects versus controls had lower glutamate levels in the ACC,[60–62] even when subjects with comorbid ADHD were excluded. In another sample,[63] no significant difference between MDD subjects and controls was found in glutamatergic metabolites in the left DLPFC, although there was an inverse correlation between glutamate levels and duration and number of episodes. One study[60] compared MDD to OCD and found that glutamatergic metabolite levels were not different between disorders. The majority of subjects included in these samples had comorbid conditions, most notably anxiety disorders as well as ADHD.

Spectroscopic Glutamatergic Studies of OCD

Six studies examined MRS glutamatergic metabolites in pediatric OCD. One study[64] reported that glutamatergic metabolites in pediatric OCD versus controls were increased in the left head of the caudate (HOC). Another study[60] found decreased glutamatergic metabolites in the ACC. Anterior cingulate cortex glutamate + glutamine levels in this study were comparable to those observed in pediatric MDD without OCD comorbidity. The 4 remaining controlled studies[65–68] did not show significant differences in glutamatergic metabolites in pediatric OCD versus controls.

Of the studies examining treatment effects, 2 studies showed decreases in glutamatergic metabolites in the HOC with treatment. In 1 study,[64] glutamate + glutamine + GABA in the left HOC decreased with paroxetine treatment; in the other,[66] glutamate + glutamine/creatine levels in the right HOC decreased with behavioral therapy. The other 3 studies[65,67,68] examining the effect of treatment on glutamate levels in pediatric OCD did not find any significant changes. The majority of these studies did not exclude subjects with comorbid disorders, including other anxiety disorders and ADHD. With the exception of MDD, the effect of comorbid disorders on glutamatergic metabolites was not specifically assessed.

Spectroscopic Glutamatergic Studies of Generalized Anxiety Disorder

The 1 MRS study on pediatric generalized anxiety disorder (GAD) found no differences in glutamatergic metabolites in the ACC of adolescents with GAD versus controls.[69] However, glutamate/creatine levels in the ACC did positively correlate with symptom severity in subjects with GAD. This study excluded subjects with comorbid substance abuse, posttraumatic stress disorder, bipolar disorder, psychosis, OCD, or autism spectrum disorders.

Spectroscopic Glutamatergic Studies of Childhood Schizophrenia

Five studies examined glutamate and related metabolites in youth with schizophrenia or at high risk of developing the disorder. The 3 studies conducted with youth at high genetic risk for schizophrenia showed increases in glutamatergic metabolites versus control subjects in some regions, including the right medial frontal lobe,[71] inferior parietal/occipital lobe,[72] left and right thalamus, and caudate.[74] All 3 of these studies assessed for psychiatric disorders, but subjects with Axis I psychopathology were excluded from only the first study. The last study[74] found a positive correlation between attenuated psychotic symptoms and glutamatergic metabolites in the thalamus and caudate of high-risk subjects.

One study[70] of children with schizophrenia compared to controls found decreased glutamate metabolite ratios in

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the occipital lobes and a trend toward decline (though not significant) in the frontal lobes. No differences were found in the other study[73] of children with schizophrenia (without other psychiatric comorbidities) versus controls in the inferior and middle frontal and superior temporal gyri.

Spectroscopic Glutamatergic Studies of Anorexia Nervosa

Two MRS studies examined glutamatergic metabolites in children and adolescents with anorexia nervosa without comorbid psychiatric conditions versus controls. One study[76] reported elevated glutamatergic metabolites in the gray matter, but not in white matter, and overall in the centrum semiovale, including the ACC, whereas the other[75] reported decreased glutamatergic levels in frontal gray matter. The latter study reported that a 7-month treatment program, including biological management, nutritional rehabilitation, and a behavioral program, was associated with nominal increased glutamate + glutamine levels in anorexia nervosa.

Spectroscopic Glutamatergic Studies of Tourette's Syndrome

The single study[77] that examined glutamatergic dysregulation in youth with Tourette's syndrome found no differences in glutamatergic metabolites in the frontal cortex, caudate, putamen, or thalamus between patients and controls. Of note, the authors reported that over half the subjects with Tourette's syndrome had comorbid ADHD.

DISCUSSION

The main aim of this study was to review the extant spectroscopic literature examining glutamate metabolite levels in child and adolescent psychiatric disorders to assess whether glutamatergic dysregulation can be detected in these disorders with any degree of consistency and specificity. We hypothesized that there would be disorder-specific alterations in glutamatergic metabolites, which would also reflect severity of psychopathology and normalize with treatment.

Overall, the available literature is quite heterogeneous and often contradictory, although a few disorder-specific alterations in glutamatergic metabolites were evident. Increases in glutamatergic metabolites were found in the ACC and other regions in youth with ADHD. Limited data suggested increases in glutamatergic metabolites in autism spectrum disorders, emotional dysregulation, and high risk for schizophrenia and decreases in MDD and bipolar disorder. There was evidence for normalization of glutamatergic levels with treatment in both bipolar disorder and ADHD.

The most consistent finding was identified in ADHD, where the literature suggests that glutamatergic metabolite levels are elevated, particularly in the ACC, PFC, and striatum. The literature also suggests that the magnitude of glutamatergic metabolite elevation in ADHD correlates with symptom severity and that levels may normalize with stimulant treatment. The majority of literature on glutamatergic metabolites and ADHD regards children, although Perlov et al[78] published a meta-analysis on 3 studies that examined this issue in adults. The meta-analysis found no significant increases or decreases in glutamatergic metabolite levels in adults with ADHD.

In autism spectrum disorders, some studies suggest increased glutamatergic metabolites in the ACC[46,48] and decreases in the frontal[28,45,47] and temporal[28,46] lobes. Since a high rate of ADHD comorbidity is well documented in autism spectrum disorders,[79] more work is needed to examine whether the finding of increased glutamate levels in the ACC are due to autism spectrum disorders, comorbidity with ADHD, or both conditions. In contrast, decreased glutamate in temporal lobes may represent a disorder-specific finding, as aberrations in glutamate + glutamine levels in similar regions among autism spectrum disorder adult populations have been described.[80] In contrast to pediatric studies, other adult autism spectrum disorder studies have shown decreased glutamatergic metabolites in the basal ganglia[81] and the ACC.[82] It has been speculated that spikes in glutamate metabolite levels in early development may lead to excitotoxicity and ultimately attenuated levels of these metabolites in adulthood.[47]

Studies of pediatric bipolar disorder report a variety of disturbances in glutamatergic metabolites, with the most consistent finding being decreased glutamatergic metabolites in the ACC, which tend to normalize with treatment. In contrast, studies of emotional dysregulation suggest an association with increased glutamatergic metabolites, particularly in the ACC. This was unexpected, given that the definition of emotional dysregulation in children significantly overlaps criteria for bipolar disorder and other mood disorders. In addition, the adult literature overall demonstrates increases in glutamate throughout the brain in bipolar disorder.[3] Magnetic resonance spectroscopy studies of pediatric bipolar disorder and emotional dysregulation are limited by high levels of comorbid illness, in particular ADHD, and the number of subjects taking a wide variety of medications prior to scanning.

Similar to findings in bipolar disorder, studies of glutamate in pediatric MDD suggest that decreased glutamate may correlate with the diagnosis of MDD as well as the duration and number of episodes. This possible link is consistent with the majority of the MDD studies in adults that showed reduced glutamatergic metabolite levels in the frontal cortex and cingulate regions.[83–85] However, much like the child literature, the studies on adults with depression report heterogeneous results, with some reporting increased glutamatergic metabolite levels in parietal and occipital regions[86] and in the frontal cortex.[87–89]

The investigators who showed decreased glutamatergic metabolites in the ACC in youth with MDD showed the same decreases in youth with OCD, making the specificity of the findings difficult to interpret, since depressive and anxiety disorders are commonly comorbid. However, most MRS studies in youth with OCD found no significant differences in glutamatergic metabolites versus controls. In adults, an increased glutamatergic metabolite level in orbitofrontal white matter among patients with OCD and a positive

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correlation between the glutamatergic metabolite levels with the severity of OCD have been reported,[90] although the size of the literature is limited.

It is notable that decreases in ACC glutamatergic metabolites were found in both MDD and bipolar disorder and that this contrasted to emotional dysregulation. This suggests that symptoms meeting diagnostic criteria for a major mood disorder may represent a distinct pathophysiology compared to children with subthreshold mood symptoms, and this neurometabolic separation is an important area for future research.

Whereas no MRS studies of children with psychotic disorders found abnormalities in glutamatergic metabolites, 3 studies of high-risk offspring showed increases in glutamatergic metabolites in a variety of brain regions including the right medial frontal lobe, thalamus, caudate, and inferior parietal/occipital regions. This is compelling in that it is partly consistent with the adult literature, which shows elevated glutamatergic metabolites in medial PFC and basal ganglia in unmedicated patients with schizophrenia.[91] Studying youth at high genetic risk has the advantage of eliminating confounding findings due to illness severity and antipsychotic medication effects; however, this strategy is limited by the fact that these youth are without psychotic symptomatology. On the other hand, 1 of these studies did find that glutamate levels in the caudate and thalamus correlated with attenuated psychotic symptoms.[74] The data reported on glutamatergic metabolites in anorexia nervosa, Tourette's syndrome, and GAD were quite limited, and consistencies among studies could not be found. The literature in adults is also limited in these disorders.

This review identified important methodological limitations within the available literature that may account for some of the discrepancies found. There was wide variability in how studies measured glutamatergic metabolite levels, including direct measurement of glutamate, combined glutamate plus glutamine with or without GABA, and glutamate metabolites in ratio to other neurometabolites that can also vary among psychiatric disorders.[92] Changes in glutamate, glutamine, or GABA alone can be distinguished only with higher Tesla imaging modalities used by only the most recent studies. Future studies using higher Tesla imaging technology will most likely improve the consistency and accuracy of results.

Clinical factors represent another important source of confounding. There was wide variation in selection criteria and in assessment for psychiatric comorbidities within samples. In addition, subjects in many studies were receiving treatment with psychotropic medication or required sedation for scanning, despite evidence that psychotropic medications, including antipsychotics,[93] SSRIs,[94] and mood stabilizers,[95] can alter glutamatergic metabolism. Finally, studies varied as to whether subjects were experiencing acute symptoms at the time of imaging. Future data could be improved by more rigorous consideration of medication effects and measurement of symptom severity at the time of scanning.

Finally, age is a particularly important possible confounder, since neurometabolites vary in typical child and adolescent development.[27,28,31,63,72] For instance, the finding that glutamatergic metabolites increased in ADHD and autism spectrum disorders and decreased in MDD and bipolar disorder could be considered an artifact of age, given that autism spectrum disorders and ADHD typically have earlier ages at onset. However, in the current literature, mean ages were fairly comparable among studies. New attempts at following the change in glutamate and other neurometabolites in disorders over time will help test this question.[49]

Despite these considerations, the extant MRS literature examining glutamatergic dysregulation in pediatric psychiatric disorders suggests that disturbances in glutamatergic metabolites can be found in various brain regions in a number of childhood psychiatric disorders. In particular, pediatric bipolar disorder and MDD are associated with decreased glutamatergic metabolites in the ACC, whereas increases in glutamatergic metabolites have been found with some consistency in ADHD, autism spectrum disorders, youth at high genetic risk for schizophrenia, and youth with emotional dysregulation. There is also limited but intriguing evidence for normalization of glutamatergic levels with treatment in bipolar disorder and ADHD. However, the methods of these studies are highly heterogeneous, with a range of brain regions scanned, field strengths used, treatments, and symptoms at the time of scanning, factors limiting interpretation of results. There is a clear need for further MRS studies examining glutamatergic dysregulation in pediatric psychiatric disorders using higher field strengths in order to provide better metabolic resolution more clearly attending to issues of age, development, psychiatric comorbidity, and treatment.

Drug names: atomoxetine (Strattera), benztropine (Cogentin and others), bupropion (Wellbutrin, Aplenzin, and others), clonazepam (Klonopin and others), clonidine (Catapres, Duraclon, and others), desmopressin (DDAVP, Minirin, and others), divalproex (Depakote and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), methylphenidate (Daytrana, Metadate, and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), propofol (Diprivan and others), risperidone (Risperdal and others), sertraline (Zoloft and others), thiothixene (Navane and others), valproic acid (Depakene, and others).

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Author contributions: Drs Spencer and Uchida are co-first authors.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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Supplementary Material

Article Title: Glutamatergic Dysregulation in Pediatric Psychiatric Disorders: A Systematic Review of the Magnetic Resonance Spectroscopy Literature

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List of Supplementary Material for the article

1. Search Algorithm — PubMed Search Algorithm

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