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Magnetic Resonance Spectroscopy Studies of Glutamate-Related Abnormalities in Mood Disorders

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Abstract

In mood disorders there is growing evidence for glutamatergic abnormalities derived from peripheral measures of glutamatergic metabolites in patients, *postmortem* studies on glutamate related markers, and animal studies on the mechanism of action of available treatments. Magnetic resonance spectroscopy (MRS) has the potential to corroborate and extend these findings with the advantage of *in vivo* assessment of glutamate-related metabolites in different disease states, in response to treatment, and in relation with functional imaging data. In this article we first review the biological significance of glutamate, glutamine, and Glx (composed mainly of glutamate and glutamine). Next we review the MRS literature in mood disorders examining these glutamate-related metabolites. Here, we find a highly consistent pattern of Glx level reductions in major depressive disorder and elevations in bipolar disorder. In addition, studies of depression regardless of diagnosis provide suggestive evidence for reduced glutamine/glutamate ratio, and in mania for elevated glutamine/glutamate ratio. These patterns suggest that the glutamate-related metabolite pool (not all of it necessarily relevant to neurotransmission) is constricted in major depressive disorder and expanded in bipolar disorder. Depressive and manic episodes may be characterized by modulation of the glutamine/glutamate ratio in opposite directions, possibly suggesting reduced vs. elevated glutamate conversion to glutamine by glial cells, respectively. We discuss the implications of these results for the pathophysiology of mood disorders, and suggest future directions for MRS studies.

Keywords

glutamate; glutamine; Glx; depression; mania; bipolar disorder; magnetic resonance spectroscopy

Introduction

Mood disorders are common and disabling psychiatric illnesses which affect individuals worldwide and cause significant negative impact on public health [1–3]. The neurobiology of these conditions has not been clarified and we lack detailed knowledge of their etiology. Treatment failures are common with existing therapies, adding urgency to the need for better

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understanding of the biology of mood disorders [4–6]. A growing body of evidence suggests that glutamate is involved [7]. Although gross disruptions in glutamatergic transmission are associated with major neurological abnormalities (e.g. seizure disorders), more subtle abnormalities are likely in psychiatric disorders. In addition to the currently used agents with glutamatergic effects (e.g. lamotrigine), therapies targeting this neurotransmitter system are under development and hold promise as alternatives to current mood disorder treatments [8–10].

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive neuroimaging technique that allows *in vivo* quantification of metabolites, including glutamate-related ones, in localized brain regions. Depending on field strength and signal-to-noise ratio, glutamate-related metabolites (especially glutamate and glutamine) can either be quantified separately or as a composite of glutamate, glutamine, γ-amino butyric acid (GABA) and other metabolites (termed Glx) in the central nervous system. In the last decade, studies using ^{1}H MRS in mood disorders have reported abnormalities in glutamate-related metabolites in diverse brain regions. In this review, we first provide a framework for understanding the role of glutamate and glutamine in neurotransmission and briefly examine the evidence implicating these metabolites in mood disorders. Next, we focus on ^{1}H MRS studies of glutamate-related metabolites in mood disorders and we discuss the implications of these findings for pathophysiology.

Glutamate neurotransmission and recycling

Glutamate is the most abundant neurotransmitter in the brain, as well as a structural component of proteins, component of intermediary energy metabolism and precursor for glutamine, GABA and glutathione [11,12].

Following its release to the synaptic cleft, glutamate is taken up by adjacent cells through excitatory amino acid transporters (EAAT). Astrocytes are responsible for uptake of most extracellular glutamate via EAAT1 (GLAST) and EAAT2 (GLT1) [12,13]. Astrocytes maintain extracellular glutamate concentrations at low levels and prevent excitotoxicity [13]. Neuronal uptake of released glutamate is low, but may help sustain the neuronal glutamate pool [14].

In astrocytes, glutamate is oxidatively degraded or converted to glutamine by the astrocyte-specific enzyme glutamine synthetase. Smaller quantities of glutamine are also synthesized *de-novo* or from GABA [12,15]. Glutamine is released from astrocytes, accumulated by neurons and converted to glutamate by the neuron-specific enzyme phosphate-activated glutaminase (Supplement: Figure S1). Glutamine is the major precursor for neuronal glutamate and GABA [15–17], but glutamate can also be synthesized *de novo* from tricyclic acid cycle intermediates. The relevance of this process was recently demonstrated by a correlation between elevated brain Glx levels and poor glycemic control in diabetic patients [18]. The rate of glutamate release into the synapse and subsequent processes are dynamically modulated by neuronal and metabolic activity via stimulation of extrasynaptic glutamate receptors (such as the metabotropic glutamate receptor subtype 2/3), among others [19].

Glutamate and Mood Disorders

The glutamatergic system was first implicated in mood disorders when D-cycloserine, a partial agonist at the NMDA receptor glycine site and an antagonist at higher doses, showed antidepressant-like properties [20]. Several other medications with glutamatergic activity have since been studied for their antidepressant properties. Ketamine, a non-competitive NMDA antagonist, showed antidepressant effects after a single dose IV infusion in two double-blind, placebo controlled studies [21,22] Lamotrigine is an anticonvulsant that reduces glutamate release via sodium, calcium, and potassium channel modulation. It is effective as mood

stabilizer in bipolar disorder especially for prevention of depressive episodes [23] and as adjunct in bipolar and unipolar depression [24,25]. Another anti-glutamatergic agent, riluzole, is effective as add-on and monotherapy for treatment resistant depression and in combination therapy for bipolar depression in open label studies [26–30].

Preclinical evidence also suggests that many other treatments for mood disorders modify the glutamatergic system [9]. Chronic administration of antidepressants from different classes reduce the expression and function of NMDA receptors [31,32], augment signaling through AMPA receptors [33,34] and reduce glutamate release in response to depolarization [35,36]. Lithium and valproic acid also have effects on glutamate release and on glutamate receptor expression and function [9].

Early studies on peripheral glutamate measures revealed abnormalities in patients with mood disorders, but results were inconsistent. In major depressive disorder, elevations of serum and plasma levels of glutamate were reported [37–40]; one study did not find any baseline abnormalities but reported reduction after antidepressant therapy [41]. Cerebrospinal fluid glutamate levels were found to be high or normal in patients with major depressive disorder [42,43], and low in a mixed group with bipolar disorder and major depressive disorder patients [44]. Glutamate level in the frontal cortex was normal in surgical samples from depressed patients [45] but was elevated in *postmortem* brains of patients with bipolar disorder and major depressive disorder [46]. Thus these studies were not conclusive for the direction of glutamate changes in mood disorders.

In *postmortem* studies, glial cell number and density reduction is consistently demonstrated in mood disorders in the subgenual prefrontal cortex [47], orbitofrontal cortex [48], supracallosal anterior cingulate cortex [49], dorsolateral prefrontal cortex [50] and amygdala [51,52]. Furthermore, expression of glial glutamate transporters EAAT1 and EAAT2 and the glia-specific enzyme glutamine synthetase is reduced in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) of individuals with major depression [53]. Finally, *postmortem* studies of mood disorders also report abnormalities in expression of NMDA [54–57] and AMPA receptor subunits [58,59].

Taken together, this literature suggests that glutamatergic abnormalities are a prominent feature of mood disorders. *In vivo* ^{1}H MRS studies of glutamate-related metabolites provide an additional window into glutamatergic abnormalities in mood disorders and we argue below that these studies may provide information about pathophysiology in these conditions.

Methods

Articles were identified on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) using keywords ‘^{1}H magnetic resonance spectroscopy’, ‘mood disorder’, ‘bipolar disorder’, ‘major depression’, ‘glutamate’, ‘glutamine’, ‘Glx’. Included studies met the following criteria: published in English; compared metabolites in bipolar disorder or major depressive disorder with normal controls; quantified Glx, glutamate and/or glutamine; and included adult subjects. Studies on children and adolescents or those including a substantial number of subjects less than 18 years of age were excluded. We considered a meta-analytic approach but concluded this was not justified given the substantial differences in MRS outcome measures, data acquisition, and data analysis among the studies included in this review.

We note that many brain regions have been studied in MRS studies of mood disorders, with special emphasis on the cerebral cortex. We have summarized this literature without any classification of studies by brain region. Our rationale was that mood disorders are characterized by emotional, cognitive, psychomotor, and neurovegetative disturbances and it would not be surprising to find widespread alterations in multiple regions in these conditions.

Indeed, we have found that the patterns of findings vary primarily by diagnosis and clinical state and not by brain region. On the other hand, we cannot rule out differential regulation of glutamatergic neurotransmission by brain region, especially across cortical vs. subcortical regions where synaptic arrangements are dramatically different.

Results

Diagnostic assessments

DSM-IV diagnosis was used in all studies except two major depressive disorder studies: Auer et al. recruited patients with ICD-1O major depressive disorder and Walter et al. did not report diagnostic criteria. Diagnoses were ascertained by structured interviews in the majority of the studies major depressive disorder and bipolar disorder, using Structured Clinical Interview for DSM-IV (SCID-IV) or Munich checklist for DSM-IV diagnoses. Diagnostic method was not reported in two studies [60,61].

Major Depressive Disorder

We identified 11 studies that quantified glutamate-related metabolites (Glx, Glutamate, Glutamine) in patients with major depressive disorder (MDD) and 2 studies in individuals with a history of MDD (Table 1). In the depressive state, all of the studies except two [61,62] reported on Glx levels and most found a reduction of this measure in several brain regions. Glx was reported to be reduced in the ACC [63,64], in the left DLPFC [65], in the dorsomedial prefrontal cortex (DMPFC) and ventromedial prefrontal cortex (VMPFC) [66], in the amygdala [67], and the hippocampus [68]. Moreover, Glx levels normalized after successful ECT treatment in the DLPFC and ACC in treatment resistant patients [64,65]. In contrast to these studies, Price at al. and Milne et al. found no difference in this measure in the ACC/occipital cortex (OCC) and the hippocampus, respectively [69,70]. Finally, Binesh et al. found a trend toward elevation in Glx/creatine (Cr) in the DLPFC in female patients over 60 years of age in a predominantly white matter voxel [60].

Only 4 studies quantified glutamate and/or glutamine. In the ACC one study found a decrease in Glx but no change in glutamate levels [63], possibly suggesting a reduction in glutamine in MDD. More recently Walter et al. documented a decrease in glutamine/Cr ratio in the subgroup of patients with high anhedonia scores and a non-significant decrease in glutamine/Cr for the overall patient group in the same region but found no abnormalities in glutamate/Cr [61]. In the hippocampus the glutamine/Cr and Glx/Cr ratios were also reduced [68]. By contrast, Sanacora and colleagues reported an elevated glutamate/Cr ratio with no significant abnormality in glutamine/Cr in the OCC [62].

Finally, in subjects with remitted MDD, Hasler et al reported no significant abnormality in Glx/Cr level in the DMPFC and VMPFC [71] and Bhagwagar et al found an increased ratio of glutamate+glutamine/Cr in the OCC when compared with healthy controls [72].

Bipolar Disorder

We identified 12 studies that measured glutamate-related metabolites (Glx, glutamate, glutamine) in bipolar disorder (BD) (Table 2). Glx levels were either reported or derivable if defined as glutamate+glutamine in 9 studies. In 6 of these, Glx was elevated in the gray matter (ACC, medial PFC, DLPFC, parieto-occipital cortex (POC), OCC, insula and hippocampus) independent of disease state (depression, euthymia, mania) [72–79]. In a seventh study, the overall BD-control comparison was not reported; subjects with rapid cycling BD (n=6) but not others in a depressive episode (N=6) had elevated Glx levels in the DLPFC [80]. This pattern makes elevated Glx (or Glu+Gln) one of the most consistent findings in the MRS literature on BD. An eighth study in this group found normal amygdala Glx levels in a group of treatment-

resistant depressed BD patients [67]. Finally, Port et al. reported normal Glx levels in the ACC, basal ganglia, and thalamus but reduced Glx in the right lentiform nucleus in a group of BD patients in depressive, manic, or euthymic phases [81]. Further supporting the notion of elevated glutamate-related metabolite levels in BD, two out of three additional studies measuring only Glu in BD report elevations [74,77], as discussed below.

Among the studies that quantified glutamate and/or glutamine levels, the results vary by disease state. Glutamate was elevated in the hippocampus in euthymic subjects and in postmortem samples from DLPFC of individuals with BD [74,77]. In depression, glutamate was increased in the mPFC with no difference in glutamine levels [76]. In that study, the administration of lamotrigine resulted in an increase in glutamine levels in the same brain region. In mania, glutamine was elevated in the ACC and POC with normal glutamate levels [73]. Finally, Frey et al. found no significant difference in glutamate levels in the DLPFC of a sample of patients in the depressive, hypomanic, mixed or euthymic phase [82].

Relation to Sample Characteristics, MRS Methodologies and Treatment Outcomes

The studies varied in sample size, clinical severity, and medication status as well as in MRS signal acquisition and post-processing (Table 1 and Table 2). Six of 13 MDD studies and 5 of 11 BD studies reported data regarding the correlation of baseline glutamate-related measures with symptom severity. With 2 exceptions [61,63], scores of depression symptom severity were not correlated with glutamate-related MRS measures in MDD. Likewise, no BD study reported a relationship between glutamate-related MRS measures and depression or mania symptom severity. In the two exceptions the interpretation of results was complicated because findings varied depending on population entered into the analysis. Two MDD reports and one BD report provided correlation analyses between glutamate-related MRS measures and treatment outcome; no correlations were found [68,70,76].

Among MDD studies only 3 included patients using antidepressants along with patients free of medication for various durations (Table 1) [63,64,69]. These studies did not report data regarding correlation of medication use with glutamate-related measures. Seven of 12 BD studies included patients on various medications (Table 2). 3 studies provided comparisons between medicated subjects and controls or between medication groups and no difference was reported [73,76,77].

Field strengths varied from 1.5 Tesla (T) to 4T, with majority of studies in both diagnoses using 1.5T (Table 1 and Table 2). Single voxel spectroscopy was used in all MDD and all but 2 BD studies; 2 BD studies used MRS imaging. PRESS was the most widely used MRS sequence in both diagnoses, followed by STEAM; J-editing, L-COSY, PRESS-CI and PEPSI were used in one study each. Quantification of metabolites also varied among studies. Approaches used included internal reference to Cr or water concentration, normalization to an external standard (e.g. phantom), and reporting in institutional units or arbitrary units (Table 1, Table 2). We did not detect a systematic effect of differences in these methodological variables on the patterns/direction of change of glutamate-related metabolites.

Discussion

There is a large and compelling literature on glutamatergic abnormalities in mood disorders, consisting of peripheral glutamate and related metabolite measures, *postmortem* markers related to glutamatergic neurotransmission, and insights into mechanisms of action of psychotropic agents. Proton MRS studies are crucial in this field because they provide noninvasive, *in vivo* assessments of glutamatergic function. The sophistication and utility of proton MRS studies has been improving over recent years and this approach can now be used to examine the relationship between glutamatergic function and diagnosis, clinical state (mania,

euthymia, depression), treatment response, or specific emotional/cognitive interventions. On the other hand, we consider our current observations provisional due to the methodological and study design variability of studies as discussed further below; additional work is needed before we can draw firm conclusions from the data.

The Meaning of Glutamate-related Measures

As our ability to quantify glutamate and glutamine improved, the debate over the exact meaning of these measures has intensified. Glutamate and glutamine are found intracellularly (in neurons and glial cells) and extracellularly, and they serve diverse functions. The ratio of glutamate in the metabolic vs. neurotransmitter pools is critically important to our analysis, but there is a paucity of information on this topic. Even the notion of separate compartments of glutamate in these pools is controversial [83] and further studies are needed to settle this debate. Therefore, MRS measures of these metabolites cannot be attributed directly to one specific function. However, MRS-visible glutamate and glutamine are in fact likely to be related to glutamatergic neurotransmission for several reasons: First, glutamate does not readily pass blood-brain barrier and most brain glutamate is synthesized from glucose within the CNS [84] although some may be synthesized from other amino acids or 3-hydroxybutyrate. Second, although glutamate and glutamine are amino acids and building blocks of proteins glutamate and glutamine bound in macromolecular assemblies do not contribute to the spectroscopic measures [85,86]. Third, ^{13}C NMR studies of the glutamatergic system indicate a close coupling of overall neuronal activity and glutamate-glutamine fluxes. In the cerebral cortex synaptic glutamate release and glutamate-glutamine cycling consumes approximately 60–80% of the energy produced by oxidative metabolism of glucose. With raises in glutamate-glutamine cycling beyond the resting state, glucose oxidation increases to meet the rise in energy demand with a 1:1 stochiometry. In contrast with earlier conceptualizations, this evidence suggests that synaptic glutamate-glutamine cycling cannot be differentiated from overall glutamate metabolism [83]. Broadly speaking, Glx reflects the total glutamatergic pool available for synaptic/metabolic activity in the form of glutamate or glutamine. This pool can expand via replenishment from the TCA or contract via incomplete reuptake/cycling or degradation. On the other hand, glutamate and glutamine levels reflect neuronal and glial distribution of glutamatergic metabolites, respectively. This framework is certainly over-simplistic and will need to be revised, but it is a good starting point for interpreting the existing literature.

Synthesis of Findings

In our review of the current ^{1}H MRS literature, we found clear patterns in Glx levels in major depressive disorder and bipolar disorder. Glx consists mostly of glutamate and glutamine although there are minor contributions from GABA, aspartate, and other metabolites. The preponderance of evidence indicates that Glx levels are reduced in major depressive disorder (Table 1) and elevated in bipolar disorder (Table 2), although these statements only apply to the relatively limited neuroanatomical regions studied thus far. In addition, there are exceptions to each of these statements in the literature: most studies of acutely ill patients report reductions in Glx in major depressive disorder but studies of remitted patients find no change [71] or elevation [72]. In bipolar disorder, almost all studies report elevated Glx independent of disease state, with one negative study and one study finding Glx reduction in one of several brain regions studied - the lentiform nucleus where spectral quality is often poor [81]. Given the multiple sources of variance among studies (in patient selection, clinical and demographic characteristics, and technical differences), the consistency of the literature across most studies is compelling.

Relatively few studies have quantified glutamate and glutamine separately in mood disorders. In major depressive disorder, three out of four studies have reported results consistent with a reduction in glutamine, and the fourth reported normal glutamine but elevated glutamate. Data

on bipolar depression are thin, but one study [76] found elevated glutamate and normal glutamine levels, and glutamine levels increased with lamotrigine administration. The common theme across major depressive disorder and bipolar depression appears to be a reduction of glutamine ***relative to*** glutamate (either reduced glutamine or elevated glutamate). In this context, the finding of elevated glutamine with normal glutamate in mania [73] is interesting and complementary, suggesting that the relative level of cortical glutamine may be a marker differentiating depression from mania. Euthymic subjects with either major depressive disorder or bipolar disorder did not show a clear pattern of glutamate or glutamine changes.

Implications and Interpretations

Glutamatergic neurotransmission is abnormal in both major depressive disorder and bipolar disorder but the two disorders are differentiated by the magnitude of the glutamatergic pool (Glx). The finding of increased Glx in all mood states in bipolar disorder may reflect an underlying predisposition to bipolar disorder. Given the relationship between Glx and glycemic control such a predisposition may be related to abnormalities in systemic metabolism and/or brain bioenergetics. On a pragmatic note, depressive episodes due to bipolar disorder or major depressive disorder may be differentiated from one another using proton MRS, which if confirmed could have implications for diagnostic imaging.

In addition to diagnosis-driven abnormalities in the glutamate system, we also found episode-driven ones. In depressive episodes, both unipolar and bipolar, one sees a relative reduction in glutamine compared with glutamate. This pattern appears to be reversed in mania with an increased glutamine/glutamate ratio [73]. Elevated glutamine/glutamate ratio in mania is in line with findings in other conditions with putatively elevated glutamatergic neurotransmission: first episode schizophrenia [87], administration of the psychotomimetic compound phencyclidine in animals [88], and experimental ischemia [89]. Indeed, synaptic glutamate taken up by glial cells is the major substrate for glutamine synthesis [90,91] and glutamine levels may be an indicator of glutamatergic neurotransmitter activity in humans [87,92] and in animals [93], and even relevant to glutamatergic excitotoxicity [94]. Based on this, glutamatergic neurotransmitter flux may be decreased during depression (both in major depressive disorder and bipolar disorder) and increased during mania. This speculation is consistent with differential regulation of glucose metabolism - closely coupled to glutamatergic neurotransmission- demonstrated in PET studies in mood disorders [95,96].

Finally, the divergence in Glx findings across bipolar disorder and major depressive disorder and in glutamate/glutamine findings across mania and depression are intriguing because glial cell deficits have been reported in both conditions [47]. Given the central role of glial cells in glutamate and glutamine maintenance/recycling, the reported glial abnormalities seem closely relevant to the MRS findings in mood disorders. This dynamic pattern may arise as a result of changes in circuit activity, cerebral metabolism and other factors acting on the background of fixed abnormalities in glial cells. Animal models of impaired glial cell function will be particularly helpful in dissecting which factors may lead to the abnormalities seen in mood disorders. Moreover, a vast body of evidence implicates cellular and structural brain changes in addition to glutamatergic neurotransmission in mood disorders [97]. It is likely that these two sets of changes are interrelated. E.g. abnormalities in glial cell number and function directly impact Glu handling in the brain. Likewise, abnormalities in neuronal packing density, dendritic arborization, and synapse density may underlie impoverishment of glutamatergic neurotransmission. Additional studies focusing on these relationships (e.g. between grey matter density and glutamate-related metabolite levels) would be valuable in addressing this issue.

To summarize, we have reviewed the ^{1}H MRS literature focusing on glutamate-related metabolites in major depressive disorder and bipolar disorder. We conclude that there are robust Glx differences between the two conditions and that there is a weaker but suggestive literature

on the relative levels of Gln and Glu coupled to mood states across the two conditions. While this pattern of findings focuses attention on glutamatergic mechanisms with potential pathophysiological significance, more work is needed to fully understand the nature of these abnormalities and to develop effective treatment strategies to address them.

The current MRS literature on mood disorders should be evaluated in the context of differences in sample characteristics and MRS methodologies that may affect the level of glutamate-related metabolites. No power analysis was reported in any study but small sample sizes were noted to be a limitation in several reports. Short washout periods and/or inclusion of medicated subjects were other common limitations, as the glutamate-related metabolite levels are known to be affected by medications used in mood disorders.

Although our review on the relation of methodological factors with the direction of findings did not reveal any specific patterns, this review likely does not have adequate power to detect patterns if they exist due to the number of studies and the quality of data available. Thus, these confounders cannot be excluded at the level of individual studies. Furthermore, the current literature does not highlight any systematic differences between brain regions examined, but this does not rule out such differences and additional studies may uncover region-specific alterations for glutamate-related measures in mood disorders. One region where the pattern of findings may diverge is the OCC; as reviewed above some studies report Glx elevations in OCC even in MDD. Finally, our conclusions are preliminary and given the many potential confounds (in MRS methods, brain regions studied, the challenge of measuring Gln, the potential disconnect between in vivo MRS and postmortem studies) additional definitive studies are needed to substantiate these conclusions and confirm their significance.

MRS holds substantial promise to advance our insight into glutamatergic pathology in mood disorders. Additional studies quantifying glutamate and glutamine separately and comparing with healthy controls are needed to confirm the patterns of these metabolites both in major depressive disorder and bipolar disorder. Furthermore, comparison of glutamate-related measures in depressed and manic episodes and in euthymia -ideally in the same patient group- is needed. In addition, quantification of glutamate-related metabolites in non-affected relatives is of interest to assess abnormalities associated with susceptibility to the disorder. The possible clinical utility of MRS for the differentiation of bipolar and unipolar depression needs to be explored further in adequately powered MRS studies where head-to-head comparisons can be carried out. Finally, ^{13}C-MRS, a technique based on measuring the flow of ^{13}C-labeled molecules through MRS-visible metabolites has the unique potential to provide detailed information about the reaction rates of glutamatergic metabolism steps and thus reveal the specific processes which are disturbed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

^{1}H MRS Studies Reporting Glutamatergic Findings in Major Depressive Disorder

Study/State	Subjects	Medication status	Field strength	MRS sequence	Voxel size	ROI(s)	Quantification	Glx	Glutamate	Glutamine
MDD										
Auer et al. (2000)	18 MDD, 1 BD-depressed 18 NC	7 Mf, 12 M	1.5 T	PRESS	7.5–12 ml	ACC	I.U.	Decreased	Not significant	N/A
Michael et al. (2003b)	13 MDD, 15 BD-depressed (7 BD-I, 7 BD-II, 1 BD-NOS) (treatment resistant) 28 NC	All Mf (3–8 days washout)	1.5 T	STEAM	3.375 cm3	L Amygdala	I.U.	Decreased (for unipolar patients only)	N/A	N/A
Michael et al. (2003a)	12 MDD (recurrent, treatment resistant) 12 NC	All Mf (3–8 days washout)	1.5 T	STEAM	3.375 cm3	L DLPFC	I.U.	Decreased Not significant after successful ECT treatment	N/A	N/A
Pfleiderer et al. (2003)	17 MDD (recurrent) 17 NC	16 Mf (3–8 days washout), 1 M	1.5 T	STEAM	3.375 cm^3	L ACC	I.U.	Decreased Not significant after successful ECT treatment	N/A	N/A
Sanacora et al. (2004)	33 MDD 38 NC	All Mf (at least for two weeks)	2.1 T	J-editing	3×3×1.5 cm	OCC	Cr ratio	N/A	Increased	Not significant
Binesh et al. (2004)	12 female MDD (>60 yo) 12 NC	All Mf (at least for two weeks)	1.5 T	L-COSY	3×3×3 cm	DLPFC	Cr ratio	Not significant Trend for increase	N/A	N/A
Hasler et al. (2007)	20 MDD 20 NC	All Mf (at least for four weeks)	3 T	PRESS-based J-editing	5×3×2 cm, 3×3×2 cm	DM/DAPFC VMPFC	Cr ratio	Decreased in both ROIs	N/A	N/A
Block et al. (2008)	18 MDD (14 first episode, 4 recurrent) 10 NC	All Mf (at least for eight weeks)	3 T	PRESS	6 ml	L Hippocampus	Cr ratio	Decreased	N/A	Decreased
Price et al. (2008)	15 MDD (treatment resistant), 18 MDD 24 NC	All Mf (at least for two weeks)	3 T	PRESS-based J-editing	2×3×3 cm, 2.5×2.5×3 cm	OCC, ACC	H_2O ratio	Not significant in either ROI	N/A	N/A
Milne et al. (2009)	14 MDD (first episode), 14 MDD (multiple episodes) 27 NC	17 Mf, 11 M	3 T	PRESS	2×2×2 cm	L Hippocampus	Absolute concentrations	Not significant	N/A	N/A

Study/State	Subjects	Medication status	Field strength	MRS sequence	Voxel size	ROI(s)	Quantification	Glx	Glutamate	Glutamine
Walter et al. (2009)	19 MDD 24 NC	All Mf (at least for one week)	3 T	JPRESS	2×2.5 ×3.5 cm	R pgACC	Cr ratio	N/A	Not significant	Not significant Decreased in highly anhedonic patients
MDD-Remission										
Hasler et al. (2005)	16 MDD-remitted (recurrent and first episode patients) 15 NC	All Mf	3 T	PRESS-based J-editing	5×3×2 cm 3×3×2 cm	DM/DAPFC VMPFC	Cr ratio	Not significant in either ROI	N/A	N/A
Bhagwagar et al. (2007)	15 MDD-remitted 16 BD-euthymic (BD-I) 18 NC	All Mf (at least for three months)	3 T	PRESS based J-editing	3×3×2 cm	OCC	Cr ratio	Increased (Glu+Gln)	N/A	N/A

Studies are categorized according to the disease state of the subjects participated and listed chronologically. Disease subtypes and the duration of medication-free periods are stated if specified in the manuscript.

Abbreviations: ACC, anterior cingulate cortex; A.U., arbitrary units; BD, bipolar disorder; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; DM/DAPFC, dorsomedial/dorsal anterolateral prefrontal cortex; ECT, electroconvulsive treatment; Gln, glutamine; Glu, glutamate; I.U., instutional units; L, left; Li,lithium; M, medicated; MDD, major depressive disorder; Mf, medication-free; mPFC, medial prefrontal cortex; MRSI, magnetic resonance spectroscopic imaging; N/A, not applicable; NC, normal controls; NOS, not otherwise specified; OCC, occipital cortex; OFC, orbitofrontal cortex; pg, pregenual; POC, parieto-occipital cortex; R, right; ROI, region of interest; T, teslas; VMPFC, ventromedial prefrontal cortex; yo, years old.

Table 2

^{1}H MRS Studies Reporting Glutamatergic Findings in Bipolar Disorder

Study/State	Subjects	Medication status	Field strength	MRS sequence	Voxel size	ROI(s)	Quantification	Glx	Glutamate	Glutamine
BD-Depression										
Michael et al. (2003b)	13 MDD, 15 BD-depressed (7 BD-I, 7 BD-II, 1 BD-NOS) (treatment resistant) 28NC	Mf (3–8 days washout)	1.5 T	STEAM	3.375 cm3	L Amygdala	I.U.	Not significant (for bipolar patients only)	N/A	N/A
Dager et al. (2004)	28 BD-depressed or mixed (11 BD-I, 17 BD-II) 26 NC	All Mf (at least for eight weeks)	1.5 T	PEPSI	1 cm^3 (MRSI)	Total gray matter and bilateral cingulate cortex, OCC, insula, putamen, caudate, thalamus	H_2O ratio	Increased in gray matter Increased in left insula Non-significant increase in left cingulate cortex	N/A	N/A
Frye et al. (2007)	23 BD-depressed 12 NC	M	1.5 T	PRESS	3×3×3 cm	ACC/mPFC	Absolute concentrations and Cr ratio	Increased	Increased	Not significant Lamotrigine led to elevation
BD-Mania										
Michael et al. (2003c)	8 BD-manic 8 NC	6 Mf, 1 Li, 1 post-ECT	1.5 T	STEAM	3.375 cm^3	L DLPFC	I.U.	Increased	N/A	N/A
Öngür et al. (2008)	15 BD-manic (BD-I) 21 NC	M	4 T	PRESS	2×2×2 cm	ACC, POC	A.U.	Increased in both ROIs	Not significant	Increased
BD-Various states										
Frey et al. (2007)	17 BD-depressed, 7 BD-hypomanic, 1 BD-mixed, 7 BD-euthymic (20 BD-I, 17 BD-II) 32 NC	All Mf (at least for two weeks)	1.5 T	PRESS	2×2×2 cm	L DLPFC	Absolute concentrations	N/A	Not significant	N/A
Port et al. (2008)	10 BD-manic, 5 BD-depressed, 6 BD-euthymic (8 BD-I, 9 BD-II, 4 BD-NOS) 12 NC	All Mf (washout for four times the half-life of the medication)	3 T	PRESSCI	2.02 cm3 (MRSI)	Bilateral ACC, OCC, caudate, lentiform nucleus, thalamus	I.U.	Not significant in ACC, OCC, thalamus, left lentiform and caudate nuclei Decreased in right lentiform nucleus	N/A	N/A

Study/State	Subjects	Medication status	Field strength	MRS sequence	Voxel size	ROI(s)	Quantification	Glx	Glutamate	Glutamine
Michael et al. (2009)	6 BD- various states (rapid cycling, BD-II), 6 BD-depressed (non-rapid cycling) 6 NC	9 M, 3 Mf	1.5	STEAM	3.375 cm3	L DLPFC	I.U.	Increased in rapid cycling group Not significant in non-rapid cyclers	N/A	N/A
BD-Euthymia										
Bhagwagar et al. (2007)	15 MDD-remitted 16 BD-euthymic (BD-I) 18 NC	All Mf (at least for three months)	3 T	PRESS based J-editing	3×3×2 cm	OCC	Cr ratio	Increased (Glu+Gln)	N/A	N/A
Colla et al. (2008)	21 BD-euthymic (BD-I) 19 NC	Li therapy (minimum for 3 years)	3 T	PRESS	2×3×2 cm	R/L Hippocampus	Absolute concentrations	N/A	Increased in L hippocampus	N/A
Senaratne et al. (2009)	12 BD-euthymic 12 NC	M	3 T	PRESS	2×2×2 cm	L Hippocampus, L OFC, L OCC	Absolute concentrations	Increased in OCC Not significant in L OFC and L hippocampus	N/A	N/A
BD-Postmortem										
Lan et al. (2008)	10 BD-postmortem sample (8 BD-I, 1 BD-II, 1 BD-NOS) 10 NC-postmortem sample	5M, 5Mf at death	N/A	NMR	N/A	DLPFC	Absolute concentrations via NMR spectroscopy	N/A	Increased	N/A

Studies are categorized according to the disease state of the subjects participated and listed chronologically. Disease subtypes and the duration of medication-free periods are stated if specified in the manuscript.

Abbreviations: as in Table 1.