HHS Public Access

Author manuscript

Schizophr Res. Author manuscript; available in PMC 2021 August 24.

Published in final edited form as:

Schizophr Res. 2022 November ; 249: 74–84. doi:10.1016/j.schres.2020.02.001.

The Role of Glutamate and GABA in Cognitive Dysfunction in Schizophrenia and Mood Disorders – A Systematic Review of Magnetic Resonance Spectroscopy Studies

Mounica Reddy-Thootkur[1], **Nina Vanessa Kraguljac**[1], **Adrienne Carol Lahti**[1,*]

[1]Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Abstract

Epidemiologic, genetic, and neurobiological studies suggest considerable overlap between schizophrenia and mood disorders. Importantly, both disorders are associated with a broad range of cognitive deficits as well as altered glutamatergic and GABAergic neurometabolism. We conducted a systematic review of magnetic resonance spectroscopy (MRS) studies investigating the relationship between glutamatergic and GABAergic neurometabolites and cognition in schizophrenia spectrum disorders and mood disorders. A literature search in Pubmed of studies published before April 15th 2019 was conducted and 37 studies were deemed eligible for systematic review. We found that alterations in glutamatergic and GABAergic neurotransmission have been identified relatively consistently in both schizophrenia and mood disorders. However, because of the vast heterogeneity of published studies in terms of illness stage, medication exposure, MRS acquisition parameters and data post-processing strategies, we still do not understand the relationship between those neurotransmitters and cognitive dysfunction in mental illness, which is a critical initial step for rational drug development. Our findings emphasize the need for coordinated multi-center studies that characterize cognitive function and its biological substrates in large and well-defined clinical populations, using harmonized imaging sequences and analytical methods with the goal to elucidate the underlying pathophysiological mechanisms and to inform future clinical trials.

Keywords

Psychosis; Bipolar disorder; major depressive disorder; glx; fMRI; multimodal neuroimaging

*Corresponding Author: Adrienne C. Lahti, MD, Department of Psychiatry and Behavioral Neurobiology, The University of Alabama at Birmingham, SC 501, 1720 7th Ave S, Birmingham, AL 35294-0017, 205-996-6776, alahti@uabmc.edu.

5.2. Contributors

ACL designed the project. MRT and NVK collected the data, all authors contributed to interpretation of the data. MRT and NVK wrote the first draft of the manuscript. All authors critically revised and approved the final manuscript.

5.3. Conflict of interest

All authors declare no potential conflict of interest.

1. INTRODUCTION

Epidemiologic, genetic, and neurobiological studies suggest considerable overlap between schizophrenia and mood disorders (International Schizophrenia et al., 2009). Importantly, both disorders are associated with a broad range of cognitive deficits (Bora et al., 2010), although important clinical differences also exist. It is well established that cognitive deficits are already evident in first-episode psychosis (FEP) patients (Mesholam-Gately et al., 2009) and in youth at high risk to develop psychosis (Bora et al., 2014). While there now is evidence for the presence of cognitive impairment in first-episode bipolar disorder (Bora and Pantelis, 2015), impairment is more severe in FEP than in first episode bipolar disorder. In addition, there is also evidence for cognitive deficits in subjects at-risk to develop bipolar disorder (Olvet et al., 2010). Cluster analysis studies based on cognitive performance in schizophrenia (Hill et al., 2002) and in bipolar disorder (Burdick et al., 2014) have demonstrated the presence of several clusters, including a cluster characterized by global deficits, clusters characterized by more modest and specific deficits, and a cluster with preserved cognition. Finally, cross-diagnostic samples (schizophrenia and bipolar disorder) have demonstrated that patients with schizophrenia were more likely to be represented in the global impairment cluster and less likely to be represented in the preserved cognition cluster than bipolar subjects (Lewandowski et al., 2014).

Second generation antipsychotic medications improve cognition with small effect sizes that are not clinically relevant (Hill et al., 2010; Thornton et al., 2006; Woodward et al., 2005). In addition, the results of clinical trials of potential cognitive-enhancing drugs have been vastly negative, despite the fact that these compounds were chosen based on pharmacological models of cognitive impairment (Hurford et al., 2011). Brain imaging techniques, such as functional MRI and diffusion weighted imaging, have been used to uncover neural abnormalities underlying cognitive dysfunction. For example, a systematic review of resting-state functional connectivity in schizophrenia suggests that cognitive dysfunction stems from an alteration of the dynamic between task-positive and task-negative networks, as well as diffuse abnormalities in cortico-subcortical regions (Sheffield and Barch, 2016). Importantly, researchers have used MR Spectroscopy (MRS), a technique that allows for the *in vivo* measurement of neurometabolites, including the excitatory neurotransmitter glutamate and inhibitory neurotransmitter γ-Aminobutyric acid (GABA), to investigate the correlates of mental illness.

Abnormalities in the excitation/inhibition (E/I) balance because of N-methyl-D-aspartate (NMDA) receptor hypofunction on GABA interneurons are implicated in the pathophysiology of schizophrenia (Javitt, 2012; Kraguljac et al., 2017; Moghaddam and Javitt, 2012; Olney and Farber, 1995). In humans, NMDA receptor antagonists induce a behavioral phenotype that mirrors the symptoms of schizophrenia (Lahti et al., 1995), including cognitive impairments (Kraguljac et al., 2018; Lahti et al., 2001; Parwani et al., 2005). Likewise, there is mounting evidence suggesting that glutamate and GABA have a central role in mood disorders. Abnormal levels of glutamate collected in both plasma and cerebrospinal fluid have been reported (Sanacora et al., 2012) and NMDA antagonist agents, like ketamine, are now used for the fast relief of depressive symptoms. Microdialysis research in humans (Buchanan et al., 2016) and rodents (Jett et al., 2017) has

linked increased release of glutamate and GABA to improved cognition. MRS studies have detected altered levels of these amino acid neurotransmitters, as well as alterations in the relationship between these metabolites and cognitive function (Li et al., 2018; Maddock and Buonocore, 2012).

Here, we performed a systematic literature review of MRS studies investigating the relationship between spectroscopic measurements of the major excitatory and inhibitory metabolites glutamate, glutamine and GABA in schizophrenia spectrum disorders, bipolar spectrum disorders and depression with the objective to summarize the progress made in our pathophysiological understanding of the intricate relationships between altered neurotransmission and cognitive deficits across the psychosis/ mood disorder spectrum. We hypothesized that we would observe similar alterations in the relationship between the glutamate and GABA and cognitive function in both subjects with schizophrenia and mood disorder compared to healthy controls.

2. EXPERIMENTAL MATERIALS AND METHODS

2.1. Eligibility criteria

Studies were included if they presented original data published before April 2019 (last search April 15th 2019), examining the relationship between glutamate, glutamine or GABA in patients with a psychosis spectrum disorder or mood disorder. Studies were not included when the healthy control group was genetically related to the patient groups. Studies published in languages other than English, postmortem studies, non-human studies, and review articles were excluded. We only included trials with 10 or more subjects. Studies expressively including subjects with comorbid substance use disorders, neurological or genetic diseases, or intellectual disabilities were not considered. When a single study was published in several papers, the article reporting the largest group was used.

2.2. Literature search

MRT and NVK performed a literature search in PubMed using the following key words: (MRS OR spectroscopy) and (GABA OR glutamate OR glx OR glutamine) AND (schizophrenia OR schizoaffective OR psychosis OR bipolar OR depression OR mania) AND (cognition OR memory OR attention OR executive function OR cognitive control OR RBANS OR MATRICS). The reference lists of included studies, as well as relevant meta-analyses were inspected for additional eligible publications.

2.3. Study selection

After removal of duplicate articles, NVK and MRT screened titles and abstracts retrieved from the search and selected potentially eligible studies for full text review. Both authors applied eligibility criteria, and a list of eligible full text articles was developed through consensus. Full text articles were then downloaded or requested from the university library and assessed for eligibility, relevant data was extracted and tabulated by MRT and double checked by NVK and ACL.

2.4. Data extraction

We extracted the following data from each study: name of first author, year of publication, number of participants per diagnostic category, illness duration, mood state, use of psychotropic medications, data acquisition parameters, magnetic field strength, spectroscopy acquisition sequence, data processing parameters, metabolites investigated, main study outcomes.

3. RESULTS

3.1. Study identification

Figure 1 describes outcomes at each level of our study identification process. Of the 131 potentially relevant articles, we included 37 studies in this systematic review.

3.2. Schizophrenia

3.2.1. Glutamate and cognition in schizophrenia—A total of 19 studies included for systematic review had data on the role of glutamate and cognition in schizophrenia. Six studies reported elevated glutamate metabolites in schizophrenia (Bustillo et al., 2017; Cannon et al., 2015; Huang et al., 2017; Kegeles et al., 2012; Kraguljac et al., 2013). A study with a large cohort found no association between white matter glutamate + glutamine (Glx) and cognition (Bustillo et al., 2017); another study found prefrontal glutamine/glutamate (Gln/Glu) to be negatively associated with cognition in the combined group (schizophrenia and controls) (Shirayama et al., 2010); four studies did not find any association between elevated Glx and cognition in either groups. Six studies failed to find a difference in the glutamate levels (Bustillo et al., 2011; Purdon et al., 2008; Reid et al., 2013; Reid et al., 2010; Rowland et al., 2009; Yoon et al., 2010). A study in siblings of schizophrenia patients found frontal glutamate to be negatively associated with cognition in high risk subjects; this association was not seen in controls (Purdon et al., 2008). A study in a cohort of young and old patients found white matter Glx to be positively associated with cognitive performance in patients, but not in controls (Bustillo et al., 2011). Another study reported substantia nigra Glx to be positively associated with cognition in controls, but not in schizophrenia patients (Reid et al., 2013). Three studies reported no association between glutamate metabolites and cognition in either groups. Lastly, three studies reported reduced glutamate metabolites; two studies found no association between anterior cingulate cortex Glx and cognition in either groups (Rowland et al., 2013b; Rowland et al., 2016b). The third study reported a negative association between anterior cingulate cortex glutamine and a measure of immediate memory in controls, but not in schizophrenia (Reid et al., 2018). For a summary of findings, see Table 1.

3.2.2. GABA and cognition in schizophrenia—Nine studies included for systematic review evaluated the relationship between GABA levels and cognitive assessments in schizophrenia. One of these studies reported increased prefrontal GABA, but found to have no association with cognition in either groups (Kegeles et al., 2012). Four studies reported reduced GABA; one of them is a study in 28 medication-naïve first episode patients that found no association between GABA measured in the occipital cortex and visual contrast sensitivity (Kelemen et al., 2013). A study at 7T reported medial prefrontal

cortex GABA to be negatively associated with cognitive performance in patients, but not in controls (Marsman et al., 2014). Another study found a positive association between anterior cingulate cortex GABA and a measure of attention in the combined group (Rowland et al., 2013b). Four studies did not find difference in GABA levels (Chen et al., 2014; Reid et al., 2018; Rowland et al., 2016a; Rowland et al., 2016b). One of them, a study at 7T, found negative association between anterior cingulate cortex GABA levels and cognition in schizophrenia, but not in controls (Reid et al., 2018). A study in a group of young and old patients reported a positive association between anterior cingulate cortex GABA and working memory in patients (Rowland et al., 2016a), an another study found a positive association between GABA and working memory and processing speed in patients, but not in controls (Rowland et al., 2016b). For a summary of findings, see Table 2.

3.2.3. Combined MRS/ fMRI studies—A total of 8 combined MRS/ fMRI studies were identified as eligible for systematic review. Glutamate and GABA are vital components of the fMRI blood oxygen dependent response, because of their role in neuroenergetics. In schizophrenia, only a few studies have evaluated the relationship between glutamate and the blood oxygen level dependent (BOLD) response. We identified three studies in the at risk mental state (ARMS) populations and five in schizophrenia populations reporting associations between glutamate and the BOLD response (3 in chronic medicated patients, one in medicated FEP and one in chronic unmedicated patients). In overlapping ARMS populations compared to controls, Fusar-Poli (Fusar-Poli et al., 2011) reported opposite associations between thalamic glutamate levels and prefrontal, hippocampal and superior temporal activation during verbal fluency, while Valli (Valli et al., 2011) identified opposite pattern of coupling between medial temporal glutamate and medial temporal activation during episodic memory. ARMS patients followed for 18 months after scanning were categorized into those achieving good versus poor functional outcomes; at baseline, those who subsequently achieved poor outcome showed negative associations between thalamic glutamate and prefrontal striatal activation, patterns that were not seen in the subjects achieving good outcome and the controls (Allen et al., 2015). In healthy controls, a positive correlation was found between hippocampal Glx and inferior frontal activation during a memory task; this association was not seen in patients with schizophrenia (Hutcheson et al., 2012). There were no significant differences in Glx levels between the groups. Another study found an opposite relationship between anterior cingulate cortex glutamate and the BOLD response in the inferior parietal cortex during a cognitive control task (Stroop task) in schizophrenia compared to healthy controls (Falkenberg et al., 2014). Likewise, Overbeek (Overbeek et al., 2019) and Cadena (Cadena et al., 2018) identified an opposite relationship between anterior cingulate cortex glutamate (measured at 7 T in medicated FEP) and anterior cingulate cortex Glx (measured at 3 T in unmedicated schizophrenia patients) respectively, and the BOLD response in the posterior default mode network during cognitive task (Stroop task) performance in schizophrenia compared to healthy controls. Both Falkenberg (Falkenberg et al., 2014) and Overbeek (Overbeek et al., 2019) obtained these results in the context of decreased anterior cingulate cortex glutamate levels in patients, while in the Cadena's study, anterior cingulate cortex Glx levels were not significantly different between the groups. Finally, White (White et al., 2015) reported a positive correlation between Glx in the substantia nigra and BOLD response during

prediction error in healthy controls, but not in schizophrenia. Glx levels were significantly elevated in the patients compared to controls. For a summary of findings, see Table 3.

3.3. Mood Disorders

3.3.1. Glutamate and cognition in mood disorders—Five studies examining glutamatergic metabolites in mood disorders were included in this systematic review. Three studies evaluated the relationship between glutamate metabolites (glu or glx) and cognition in mood disorders. In major depressive disorder, two studies reported unaltered left hippocampal glutamate levels (Jayaweera et al., 2015; Shirayama et al., 2017), the first was performed in chronically ill medicated patients, the second in medication-naïve first episode psychosis patients. Interestingly, both studies reported a correlation between memory performance and hippocampal glutamate levels, the first found this relationship only in healthy controls whereas the second study found it in both groups. The second study also examined glutamate in the medial prefrontal cortex and amygdala. In addition to reductions in glutamate levels in the medial prefrontal cortex in patients compared to controls, they also found a negative relationship between performance on the Trail Making Test and glutamate levels in both brain regions (Jayaweera et al., 2015). Another study recruited a mixed group of patients diagnosed with either major depression or bipolar disorder who met criteria for a depressive episode within the past three months. Here, hippocampal glutamate levels were increased in patients, but no associations between metabolite levels and memory performance were detected (Hermens et al., 2015).

Both studies examining the relationship between glutamatergic metabolites and cognition in youth with severe mood dysregulation failed to detect relationships between these markers (Dickstein et al., 2008; Wozniak et al., 2012), and only the study conducted at 4T reported elevated glutamate levels in the anterior cingulate cortex (Wozniak et al., 2012). For a summary of findings, see Table 4.

3.3.2. GABA and cognition in mood disorders—Finally, only one study examined the GABA levels in mood disorder patients as they relate to cognitive performance. The study found to have better cognitive performance in those with higher anterior cingulate cortex GABA levels in depressed bipolar patients, but not in controls (Huber et al., 2018).

4. DISCUSSION

In schizophrenia and mood disorders, altered glutamatergic/GABA neurotransmission has been identified relatively consistently. Here, we performed a systematic review of the literature to determine whether there are associations between these neurotransmitters and cognitive dysfunction in these disorders, and/or if there are alterations in these relationships in patients compared to healthy controls. We report a numbers of studies evaluating these associations; however, because of the vast heterogeneity in the cognitive domains studied, in voxel location, stage of illness, medication status, magnet strength, sequence acquisitions and data post processing strategies, it is difficult to draw definite conclusions.

4.1. Glutamatergic metabolites in context of cognitive dysfunction

In schizophrenia, more studies reported a lack of association between glutamate and cognition than studies that did; however many of those studies suffered from small sample sizes. The study of Bustillo (Bustillo et al., 2014), which enrolled the largest number of subjects (104 medicated, chronic schizophrenia patients), failed to find an association between Glx measured in a supraventricular slab of white and gray matter and cognition in either schizophrenia or healthy controls. Rowland (Rowland et al., 2016b) who enrolled 45 chronic schizophrenia patients did not find associations between medial prefrontal cortex glutamate and cognition in either schizophrenia or healthy controls; however higher glutamate was associated with more negative auditory mismatch negativity in schizophrenia, but not in healthy controls. In a group of medication-naïve FEP, no associations were found between dorsolateral prefrontal cortex Glx and cognition. On the other hand, Glx measured in the substantia nigra did correlate with cognition in controls, but not in schizophrenia patients. In mood disorders, the only replicated finding thus far is an association between hippocampal glutamate levels and memory performance on the Ray Auditory Verbal Learning Test (RAVLT). One study found this relationship only in healthy controls but not chronically ill medicated patients with major depression (Jayaweera et al., 2015), whereas the second study found it in both healthy controls and medication-naïve patients with a first depressive episode (Wozniak et al., 2012), suggesting that exposure to psychotropic medications or illness chronicity may alter the relationship between glutamate metabolism and cognition in major depression.

4.2. GABA in context of cognitive dysfunction

More studies evaluating GABA reported association between GABA and cognition. One study (Rowland et al., 2016a) which enrolled a large sample (45 schizophrenia subjects) reported a positive correlation between medial prefrontal cortex GABA and both working memory and processing speed in schizophrenia, but not in healthy controls. On the other hand, two studies, with relatively small sample sizes but carried out at 7T, which is associated with a better signal to noise ratio and ability to separate MRS peaks, reported a negative association between GABA and a measurement of IQ and cognitive ability using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), respectively. Similarly, the only mood disorder study meeting inclusion criteria in our study also reported an association between GABA and cognitive performance on the Wisconsin Card Sorting Test (WCST) (Huber et al., 2018).

4.3. Multimodal neuroimaging studies and cognitive dysfunction

Combining MRS with fMRI can shed light into how differences in glutamate/GABA could influence the way the brain implement cognitive processes in a more fine-grained way than behavioral measures. Indeed, the majority of combined MRS/fMRI studies discussed in this paper either have found coupling between glutamate/GABA and BOLD response in controls but not in patients (or the reverse), or have found opposite patterns of coupling between groups. What is not clear is whether these alterations are driven by differences in glutamate/GABA levels, as these different and opposite patterns are seen in the context of altered glutamate levels or not differences. Nevertheless, like the study of Rowland that

combined MRS with EEG (Rowland et al., 2013a), combining MRS with fMRI appears to improve our capacity to detect abnormal patterns of cognitive processes. Interestingly, three studies performed with different patient populations and on different scanners report a similar pattern of opposite coupling in schizophrenia compared to controls between anterior cingulate cortex glutamate and the BOLD response in regions of the posterior default mode network during an inhibitory control task (Cadena et al., 2018; Falkenberg et al., 2014; Overbeek et al., 2019). These findings are in agreement with a recent review of combined MRS/ fMRI studies in controls reporting evidence that glutamate was correlated with the BOLD response within the measured voxels, but also with regions distant from the voxel (Duncan et al., 2014). Thus, in schizophrenia, the relationship between anterior cingulate cortex glutamate and the BOLD response in distant brain regions is impaired. One might speculate that the overall regional ratio of excitation over inhibition, modulated by a number of neurotransmitters including glutamate and GABA, might tune the neuronal projections and thus affect the BOLD signal in distant regions. Unfortunately, it remains unclear how these neurometabolites affect brain cognitive processes in mood disorders due to the paucity of combined MRS/ fMRI studies conducted.

4.4. Limitations

This work needs to be seen in context of several limitations. We did not perform analyses investigating possible confounds of antipsychotic medication exposure or illness chronicity on the relationships between cognition and neurometabolite levels, because only a limited number of studies were conducted in drug naïve patients experiencing their first episode of psychosis or a mood disorder. Additionally, in those with a more chronic illness, medication exposure was, perhaps not surprisingly, heterogeneous ranging from antidepressants to mood stabilizers to antipsychotic drugs or combinations thereof. We also chose not to perform meta-analyses to quantify findings as distinct brain regions have differing relevance for diverse cognitive domains and metabolite alterations are not uniform across brain regions. Unfortunately, with the number of studies published in individual cognitive domains in different brain regions we did not have the statistical power accurately capture this diversity. Finally, it is not possible to equate the glutamate, glutamine and GABA metabolite peaks captured with MRS to neurotransmission.

4.5. Conclusions

In schizophrenia and mood disorders, alterations in glutamatergic and GABAergic neurometabolism have been identified relatively consistently. However, because of the vast heterogeneity of published studies, we still do not understand the relationship between those neurotransmitters and cognitive dysfunction in mental illness, which is a critical initial step for rational drug development. As suggested by our study, it is possible that higher field magnet (7T) is better suited for this kind of research. Our findings emphasize the need for coordinated multi-center studies that characterize cognitive function and its relationship with glutamate and GABA in large and well-defined clinical populations, using harmonized imaging sequences and analytical methods. As an important first step, an international consortium of 24 research sites was created to establish a framework for future methodological standardization of GABA-edited MRS acquisition (Mikkelsen et al., 2017). In addition, there are a number of new imaging techniques that could help with this type

of research, such as functional MRS (fMRS), where changes in glutamate and GABA are measured during task performance, ^{13}Carbon spectroscopy which allows the determination of the in vivo rates of the glutamate-glutamine cycle (Moreno et al., 2001), and glutamate chemical exchange saturation transfer (GluCEST) (Cai et al., 2012; Cai et al., 2013), a MRS technique which allows for the measurement of glutamate across many brain regions.

Funding body

This work was supported by the National Institute of Mental Health (R01MH102951, R01MH113800, ACL; R01118484, K23MH106683, NVK).

6. REFERENCES

Allen P, Chaddock CA, Egerton A, Howes OD, Barker G, Bonoldi I, Fusar-Poli P, Murray R, McGuire P, 2015. Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. Schizophr Bull 41(2), 429–439. [PubMed: 25123110]

Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C, 2014. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr Scand 130(1), 1–15. [PubMed: 24611632]

Bora E, Pantelis C, 2015. Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls. Schizophr Bull 41(5), 1095–1104. [PubMed: 25616505]

Bora E, Yucel M, Pantelis C, 2010. Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond. Schizophr Bull 36(1), 36–42. [PubMed: 19776206]

Buchanan RJ, Gjini K, Modur P, Meier KT, Nadasdy Z, Robinson JL, 2016. In vivo measurements of limbic glutamate and GABA concentrations in epileptic patients during affective and cognitive tasks: A microdialysis study. Hippocampus 26(5), 683–689. [PubMed: 26606278]

Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, Malhotra AK, 2014. Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med 44(14), 3083–3096. [PubMed: 25065409]

Bustillo JR, Chen H, Gasparovic C, Mullins P, Caprihan A, Qualls C, Apfeldorf W, Lauriello J, Posse S, 2011. Glutamate as a marker of cognitive function in schizophrenia: a proton spectroscopic imaging study at 4 Tesla. Biol Psychiatry 69(1), 19–27. [PubMed: 20970118]

Bustillo JR, Chen H, Jones T, Lemke N, Abbott C, Qualls C, Canive J, Gasparovic C, 2014. Increased glutamine in patients undergoing long-term treatment for schizophrenia: a proton magnetic resonance spectroscopy study at 3 T. JAMA Psychiatry 71(3), 265–272. [PubMed: 24402128]

Bustillo JR, Jones T, Chen H, Lemke N, Abbott C, Qualls C, Stromberg S, Canive J, Gasparovic C, 2017. Glutamatergic and Neuronal Dysfunction in Gray and White Matter: A Spectroscopic Imaging Study in a Large Schizophrenia Sample. Schizophr Bull 43(3), 611–619. [PubMed: 27550776]

Cadena EJ, White DM, Kraguljac NV, Reid MA, Maximo JO, Nelson EA, Gawronski BA, Lahti AC, 2018. A Longitudinal Multimodal Neuroimaging Study to Examine Relationships Between Resting State Glutamate and Task Related BOLD Response in Schizophrenia. Front Psychiatry 9, 632. [PubMed: 30555359]

Cai K, Haris M, Singh A, Kogan F, Greenberg JH, Hariharan H, Detre JA, Reddy R, 2012. Magnetic resonance imaging of glutamate. Nat Med 18(2), 302–306. [PubMed: 22270722]

Cai K, Singh A, Roalf DR, Nanga RP, Haris M, Hariharan H, Gur R, Reddy R, 2013. Mapping glutamate in subcortical brain structures using high-resolution GluCEST MRI. NMR Biomed 26(10), 1278–1284. [PubMed: 23553932]

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R, North American Prodrome Longitudinal Study, C., 2015. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal

neuroimaging study of youth at elevated clinical risk. Biol Psychiatry 77(2), 147–157. [PubMed: 25034946]

Chang L, Friedman J, Ernst T, Zhong K, Tsopelas ND, Davis K, 2007. Brain metabolite abnormalities in the white matter of elderly schizophrenic subjects: implication for glial dysfunction. Biol Psychiatry 62(12), 1396–1404. [PubMed: 17693392]

Chen CM, Stanford AD, Mao X, Abi-Dargham A, Shungu DC, Lisanby SH, Schroeder CE, Kegeles LS, 2014. GABA level, gamma oscillation, and working memory performance in schizophrenia. Neuroimage Clin 4, 531–539. [PubMed: 24749063]

Dickstein DP, van der Veen JW, Knopf L, Towbin KE, Pine DS, Leibenluft E, 2008. Proton magnetic resonance spectroscopy in youth with severe mood dysregulation. Psychiatry Res 163(1), 30–39. [PubMed: 18403184]

Duncan NW, Wiebking C, Northoff G, 2014. Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans-a review of multimodal imaging studies. Neurosci Biobehav Rev 47, 36–52. [PubMed: 25066091]

Falkenberg LE, Westerhausen R, Craven AR, Johnsen E, Kroken RA, EM LB, Specht K, Hugdahl K, 2014. Impact of glutamate levels on neuronal response and cognitive abilities in schizophrenia. Neuroimage Clin 4, 576–584. [PubMed: 24749064]

Fusar-Poli P, Stone JM, Broome MR, Valli I, Mechelli A, McLean MA, Lythgoe DJ, O'Gorman RL, Barker GJ, McGuire PK, 2011. Thalamic glutamate levels as a predictor of cortical response during executive functioning in subjects at high risk for psychosis. Arch Gen Psychiatry 68(9), 881–890. [PubMed: 21536967]

Hermens DF, Naismith SL, Chitty KM, Lee RS, Tickell A, Duffy SL, Paquola C, White D, Hickie IB, Lagopoulos J, 2015. Cluster analysis reveals abnormal hippocampal neurometabolic profiles in young people with mood disorders. Eur Neuropsychopharmacol 25(6), 836–845. [PubMed: 25795519]

Hill SK, Bishop JR, Palumbo D, Sweeney JA, 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. Expert Rev Neurother 10(1), 43–57. [PubMed: 20021320]

Hill SK, Ragland JD, Gur RC, Gur RE, 2002. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. J Clin Exp Neuropsychol 24(6), 765–780. [PubMed: 12424651]

Huang ML, Khoh TT, Lu SJ, Pan F, Chen JK, Hu JB, Hu SH, Xu WJ, Zhou WH, Wei N, Qi HL, Shang DS, Xu Y, 2017. Relationships between dorsolateral prefrontal cortex metabolic change and cognitive impairment in first-episode neuroleptic-naive schizophrenia patients. Medicine (Baltimore) 96(25), e7228. [PubMed: 28640119]

Huber RS, Kondo DG, Shi XF, Prescot AP, Clark E, Renshaw PF, Yurgelun-Todd DA, 2018. Relationship of executive functioning deficits to N-acetyl aspartate (NAA) and gamma-aminobutyric acid (GABA) in youth with bipolar disorder. J Affect Disord 225, 71–78. [PubMed: 28800423]

Hurford IM, Marder SR, Keefe RS, Reise SP, Bilder RM, 2011. A brief cognitive assessment tool for schizophrenia: construction of a tool for clinicians. Schizophr Bull 37(3), 538–545. [PubMed: 19776205]

Hutcheson NL, Reid MA, White DM, Kraguljac NV, Avsar KB, Bolding MS, Knowlton RC, den Hollander JA, Lahti AC, 2012. Multimodal analysis of the hippocampus in schizophrenia using proton magnetic resonance spectroscopy and functional magnetic resonance imaging. Schizophr Res 140(1–3), 136–142. [PubMed: 22831772]

International Schizophrenia C, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P, 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460(7256), 748–752. [PubMed: 19571811]

Javitt DC, 2012. Twenty-five years of glutamate in schizophrenia: are we there yet? Schizophr Bull 38(5), 911–913. [PubMed: 22987849]

Jayaweera HK, Lagopoulos J, Duffy SL, Lewis SJ, Hermens DF, Norrie L, Hickie IB, Naismith SL, 2015. Spectroscopic markers of memory impairment, symptom severity and age of onset in

older people with lifetime depression: Discrete roles of N-acetyl aspartate and glutamate. J Affect Disord 183, 31–38. [PubMed: 26000754]

Jett JD, Bulin SE, Hatherall LC, McCartney CM, Morilak DA, 2017. Deficits in cognitive flexibility induced by chronic unpredictable stress are associated with impaired glutamate neurotransmission in the rat medial prefrontal cortex. Neuroscience 346, 284–297. [PubMed: 28131625]

Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC, 2012. Elevated prefrontal cortex gamma-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Arch Gen Psychiatry 69(5), 449–459. [PubMed: 22213769]

Kelemen O, Kiss I, Benedek G, Keri S, 2013. Perceptual and cognitive effects of antipsychotics in first-episode schizophrenia: the potential impact of GABA concentration in the visual cortex. Prog Neuropsychopharmacol Biol Psychiatry 47, 13–19. [PubMed: 23954737]

Kraguljac NV, Carle M, Frolich MA, Tran S, Yassa MA, White DM, Reddy A, Lahti AC, 2018. Mnemonic Discrimination Deficits in First-Episode Psychosis and a Ketamine Model Suggests Dentate Gyrus Pathology Linked to N-Methyl-D-Aspartate Receptor Hypofunction. Biol Psychiatry Cogn Neurosci Neuroimaging 3(3), 231–238. [PubMed: 29486864]

Kraguljac NV, Frolich MA, Tran S, White DM, Nichols N, Barton-McArdle A, Reid MA, Bolding MS, Lahti AC, 2017. Ketamine modulates hippocampal neurochemistry and functional connectivity: a combined magnetic resonance spectroscopy and resting-state fMRI study in healthy volunteers. Mol Psychiatry 22(4), 562–569. [PubMed: 27480494]

Kraguljac NV, White DM, Reid MA, Lahti AC, 2013. Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. JAMA Psychiatry 70(12), 1294–1302. [PubMed: 24108440]

Lahti AC, Koffel B, LaPorte D, Tamminga CA, 1995. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13(1), 9–19. [PubMed: 8526975]

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA, 2001. Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25(4), 455–467. [PubMed: 11557159]

Lewandowski KE, Sperry SH, Cohen BM, Ongur D, 2014. Cognitive variability in psychotic disorders: a cross-diagnostic cluster analysis. Psychol Med 44(15), 3239–3248. [PubMed: 25066202]

Li CT, Yang KC, Lin WC, 2018. Glutamatergic Dysfunction and Glutamatergic Compounds for Major Psychiatric Disorders: Evidence From Clinical Neuroimaging Studies. Front Psychiatry 9, 767. [PubMed: 30733690]

Maddock RJ, Buonocore MH, 2012. MR spectroscopic studies of the brain in psychiatric disorders. Curr Top Behav Neurosci 11, 199–251. [PubMed: 22294088]

Marsman A, Mandl RC, Klomp DW, Bohlken MM, Boer VO, Andreychenko A, Cahn W, Kahn RS, Luijten PR, Hulshoff Pol HE, 2014. GABA and glutamate in schizophrenia: a 7 T (1)H-MRS study. Neuroimage Clin 6, 398–407. [PubMed: 25379453]

Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ, 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23(3), 315–336. [PubMed: 19413446]

Mikkelsen M, Barker PB, Bhattacharyya PK, Brix MK, Buur PF, Cecil KM, Chan KL, Chen DY, Craven AR, Cuypers K, Dacko M, Duncan NW, Dydak U, Edmondson DA, Ende G, Ersland L, Gao F, Greenhouse I, Harris AD, He N, Heba S, Hoggard N, Hsu TW, Jansen JFA, Kangarlu A, Lange T, Lebel RM, Li Y, Lin CE, Liou JK, Lirng JF, Liu F, Ma R, Maes C, Moreno-Ortega M, Murray SO, Noah S, Noeske R, Noseworthy MD, Oeltzschner G, Prisciandaro JJ, Puts NAJ, Roberts TPL, Sack M, Sailasuta N, Saleh MG, Schallmo MP, Simard N, Swinnen SP, Tegenthoff M, Truong P, Wang G, Wilkinson ID, Wittsack HJ, Xu H, Yan F, Zhang C, Zipunnikov V, Zollner HJ, Edden RAE, 2017. Big GABA: Edited MR spectroscopy at 24 research sites. Neuroimage 159, 32–45. [PubMed: 28716717]

Moghaddam B, Javitt D, 2012. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 37(1), 4–15. [PubMed: 21956446]

Moreno A, Ross BD, Bluml S, 2001. Direct determination of the N-acetyl-L-aspartate synthesis rate in the human brain by (13)C MRS and [1-(13)C]glucose infusion. J Neurochem 77(1), 347–350. [PubMed: 11279290]

Ohrmann P, Siegmund A, Suslow T, Pedersen A, Spitzberg K, Kersting A, Rothermundt M, Arolt V, Heindel W, Pfleiderer B, 2007. Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. J Psychiatr Res 41(8), 625–634. [PubMed: 16949099]

Olney JW, Farber NB, 1995. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52(12), 998–1007. [PubMed: 7492260]

Olvet DM, Stearns WH, McLaughlin D, Auther AM, Correll CU, Cornblatt BA, 2010. Comparing clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome. Schizophr Res 123(1), 59–63. [PubMed: 20716479]

Overbeek G, Gawne TJ, Reid MA, Salibi N, Kraguljac NV, White DM, Lahti AC, 2019. Relationship Between Cortical Excitation and Inhibition and Task-Induced Activation and Deactivation: A Combined Magnetic Resonance Spectroscopy and Functional Magnetic Resonance Imaging Study at 7T in First-Episode Psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging 4(2), 121–130. [PubMed: 30470582]

Parwani A, Weiler MA, Blaxton TA, Warfel D, Hardin M, Frey K, Lahti AC, 2005. The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl) 183(3), 265–274. [PubMed: 16220331]

Purdon SE, Valiakalayil A, Hanstock CC, Seres P, Tibbo P, 2008. Elevated 3T proton MRS glutamate levels associated with poor Continuous Performance Test (CPT-0X) scores and genetic risk for schizophrenia. Schizophr Res 99(1–3), 218–224. [PubMed: 18248960]

Reid MA, Kraguljac NV, Avsar KB, White DM, den Hollander JA, Lahti AC, 2013. Proton magnetic resonance spectroscopy of the substantia nigra in schizophrenia. Schizophr Res 147(2–3), 348–354. [PubMed: 23706412]

Reid MA, Salibi N, White DM, Gawne TJ, Denney TS, Lahti AC, 2018. 7T Proton Magnetic Resonance Spectroscopy of the Anterior Cingulate Cortex in First-Episode Schizophrenia. Schizophr Bull.

Reid MA, Stoeckel LE, White DM, Avsar KB, Bolding MS, Akella NS, Knowlton RC, den Hollander JA, Lahti AC, 2010. Assessments of function and biochemistry of the anterior cingulate cortex in schizophrenia. Biol Psychiatry 68(7), 625–633. [PubMed: 20570244]

Rowland LM, Edden RA, Kontson K, Zhu H, Barker PB, Hong LE, 2013a. GABA predicts inhibition of frequency-specific oscillations in schizophrenia. J Neuropsychiatry Clin Neurosci 25(1), 83–87. [PubMed: 23487198]

Rowland LM, Kontson K, West J, Edden RA, Zhu H, Wijtenburg SA, Holcomb HH, Barker PB, 2013b. In vivo measurements of glutamate, GABA, and NAAG in schizophrenia. Schizophr Bull 39(5), 1096–1104. [PubMed: 23081992]

Rowland LM, Krause BW, Wijtenburg SA, McMahon RP, Chiappelli J, Nugent KL, Nisonger SJ, Korenic SA, Kochunov P, Hong LE, 2016a. Medial frontal GABA is lower in older schizophrenia: a MEGA-PRESS with macromolecule suppression study. Mol Psychiatry 21(2), 198–204. [PubMed: 25824298]

Rowland LM, Spieker EA, Francis A, Barker PB, Carpenter WT, Buchanan RW, 2009. White matter alterations in deficit schizophrenia. Neuropsychopharmacology 34(6), 1514–1522. [PubMed: 19052539]

Rowland LM, Summerfelt A, Wijtenburg SA, Du X, Chiappelli JJ, Krishna N, West J, Muellerklein F, Kochunov P, Hong LE, 2016b. Frontal Glutamate and gamma-Aminobutyric Acid Levels and Their Associations With Mismatch Negativity and Digit Sequencing Task Performance in Schizophrenia. JAMA Psychiatry 73(2), 166–174. [PubMed: 26720179]

Rusch N, Tebartz van Elst L, Valerius G, Buchert M, Thiel T, Ebert D, Hennig J, Olbrich HM, 2008. Neurochemical and structural correlates of executive dysfunction in schizophrenia. Schizophr Res 99(1–3), 155–163. [PubMed: 17616347]

Sanacora G, Treccani G, Popoli M, 2012. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology 62(1), 63–77. [PubMed: 21827775]

Seese RR, O'Neill J, Hudkins M, Siddarth P, Levitt J, Tseng B, Wu KN, Caplan R, 2011. Proton magnetic resonance spectroscopy and thought disorder in childhood schizophrenia. Schizophr Res 133(1–3), 82–90. [PubMed: 21872444]

Sheffield JM, Barch DM, 2016. Cognition and resting-state functional connectivity in schizophrenia. Neurosci Biobehav Rev 61, 108–120. [PubMed: 26698018]

Shirayama Y, Obata T, Matsuzawa D, Nonaka H, Kanazawa Y, Yoshitome E, Ikehira H, Hashimoto K, Iyo M, 2010. Specific metabolites in the medial prefrontal cortex are associated with the neurocognitive deficits in schizophrenia: a preliminary study. Neuroimage 49(3), 2783–2790. [PubMed: 19850131]

Shirayama Y, Takahashi M, Osone F, Hara A, Okubo T, 2017. Myo-inositol, Glutamate, and Glutamine in the Prefrontal Cortex, Hippocampus, and Amygdala in Major Depression. Biol Psychiatry Cogn Neurosci Neuroimaging 2(2), 196–204. [PubMed: 29560915]

Szulc A, Galinska-Skok B, Tarasow E, Konarzewska B, Waszkiewicz N, Hykiel R, Walecki J, 2012. Clinical and cognitive correlates of the proton magnetic resonance spectroscopy measures in chronic schizophrenia. Med Sci Monit 18(6), CR390–398. [PubMed: 22648255]

Thornton AE, Van Snellenberg JX, Sepehry AA, Honer W, 2006. The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review. J Psychopharmacol 20(3), 335–346. [PubMed: 16174678]

Valli I, Stone J, Mechelli A, Bhattacharyya S, Raffin M, Allen P, Fusar-Poli P, Lythgoe D, O'Gorman R, Seal M, McGuire P, 2011. Altered medial temporal activation related to local glutamate levels in subjects with prodromal signs of psychosis. Biol Psychiatry 69(1), 97–99. [PubMed: 21035785]

White DM, Kraguljac NV, Reid MA, Lahti AC, 2015. Contribution of substantia nigra glutamate to prediction error signals in schizophrenia: a combined magnetic resonance spectroscopy/functional imaging study. NPJ Schizophr 1, 14001. [PubMed: 26878032]

Woodward ND, Purdon SE, Meltzer HY, Zald DH, 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol 8(3), 457–472. [PubMed: 15784157]

Wozniak J, Gonenc A, Biederman J, Moore C, Joshi G, Georgiopoulos A, Hammerness P, McKillop H, Lukas SE, Henin A, 2012. A magnetic resonance spectroscopy study of the anterior cingulate cortex in youth with emotional dysregulation. Isr J Psychiatry Relat Sci 49(1), 62–69. [PubMed: 22652930]

Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, Carter CS, 2010. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. J Neurosci 30(10), 3777–3781. [PubMed: 20220012]

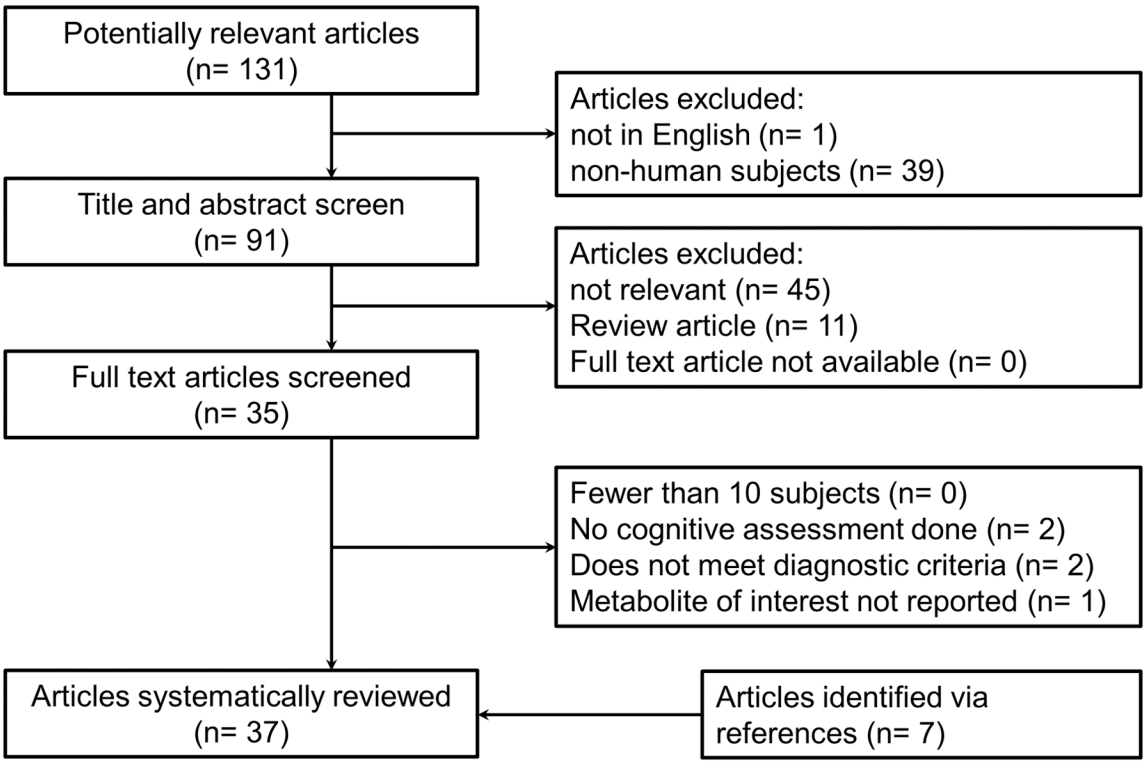

Figure:
Process of study selection

Table 1:

Glutamate metabolites and cognition in schizophrenia

Author Year of publication	n (control/ patient)	Illness stage	Medication status	Cognitive domain	Region	Tesla	Metabolite	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
(Chang et al., 2007)	22/23	Chronic (elderly)	mixed	MMSE	Frontal, temporal, and occipital WM	4	Glx	SV	PRESS	30	W	↑Glx in all regions	No associations
(Ohrmann et al., 2007)	20/35	mixed	mixed	Broad neuropsychological battery	Left DLPFC	1.5	Glx	SV	STEAM	20	W	↓Glx in SZ vs FEP and HC	DLPFC Glx was positively associated with the AVLT immediate in chronic medicated patients, but not FEP or HC
(Purdon et al., 2008)	14/15	Genetic HR (siblings)	Un-medicated	CPT	Frontal cortex	3	Glu	SV	STEAM	20	Cr	-	Higher frontal Glu was associated with lower score on the CPT in high risk subjects, but not HC
(Rusch et al., 2008)	31/29	mixed	Medicated	WCST	Left hippocampus and DLPFC	2	Glu, Gln	SV	PRESS	30	W	↑DLPFC Glu/ Gln	Hippocampal Glu was negatively associated with better performance on the WCST in SZ, but not HC
(Rowland et al., 2009)	11/20	Chronic (10 deficit/ 10 non-deficit)	Medicated	RBANS	Middle frontal, inferior parietal cortex	3	Glx	SV	PRESS	35	W	-	No associations
(Shirayama et al., 2010)	18/19	Chronic	mixed	WCST, TMT, DSDT, Verbal	MPFC	3	Gln, Glu	SV	PRESS	30	W	↑Gln/ Glu	MPFC Gln/Glu was

Author Year of publication	n (control/ patient)	Illness stage	Medication status	Cognitive domain	Region	Tesla	Metabolite	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
				fluency test, Stroop, Iowa gambling test									negatively associated with the WCST and DSDT in the combined SZ and HC group
(Reid et al., 2010)	23/26	Chronic	Medicated	RBANS	ACC	3	Glx	SV	PRESS	80	Cr	-	No associations
(Yoon et al., 2010)	13/13	mixed	mixed	OSSS	Calcarine sulci	3	Glx	SV	MEGA-PRESS	68	Cr	-	No associations
(Bustillo et al., 2011)	28/30	Chronic Young: 10/12; Old: 18/18	Medicated	Broad neuropsychological battery	frontal lobe and parietal lobe	4	Glx	MRSI	PEPSI	15	W	-	WM Glx was positively associated with cognitive performance in SZ, but not HC
(Seese et al., 2011)	34/28	Chronic (Children)	NR	K-FTDS	DLPFC, inferior frontal and superior temporal cortex	1.5	Glx	MRSI	PRESS	30	Cr	-	No associations
(Kegeles et al., 2012)	22/32	Chronic	Mixed	N-Back	MPFC, DLPFC	3	Glx	SV	MEGA-PRESS	68	Cr, W	↑ MPFC Glx in un-medicated SZ	No associations
(Szulc et al., 2012)	0/47	Chronic	Un-medicated	WCST, TMT, Verbal fluency test	Frontal,temporal cortex, thalamus	1.5	Glx	SV	PRESS	35	Cr, W	N/A	No associations
(Reid et al., 2013)	22/35	Chronic	Medicated	RBANS	SN	3	Glx	SV	PRESS	80	Cr	-	SN Glx positively associated with RBANS total score in HC, but not SZ.
(Kraguljac et al., 2013)	27/22	Chronic	Un-medicated	RBANS	Hippocampus	3	Glx	SV	PRESS	80	Cr	↑Glx	No associations
(Rowland et al., 2013b)	20/21	Chronic Young (11/10);	Medicated	RBANS	ACC, CSO	3	Glx	SV	MEGA-PRESS/ PRESS	68/ 35	W	↓Glx in ACC and CSO	No associations

Author Year of publication	n (control/ patient)	Illness stage	Medication status	Cognitive domain	Region	Tesla	Metabolite	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
		old (10/10)											
(Rowland et al., 2016b)	53/45	Chronic	mixed	DST, Digit symbol coding test, auditory MMN (EEG)	ACC	3	Glu, Gln,	SV	PR-STEAM/	6.5	W	↓Glu	No associations *Higher Glu was associated with more negative MMN amplitude in SZ, but not in HC*
(Bustillo et al., 2017)	97/104	Chronic	Medicated	MCCB	Axial supraventricular slab	3	Glx	MRSI				↑Glx in GM and WM	No associations
(Huang et al., 2017)	43/58	FEP	naïve	MCCB	Left DLPFC	3	Glx	SV	Stimulated echo pulse	9.2	Cr	↑Glx	No associations
(Reid et al., 2018)	21/21	FEP	Medicated	RBANS	ACC	7	Glu, Gln	SV	STEAM	5	W	↓Glu	Negative association between Gln and RBANS immediate memory in HC, but not in SZ

↑ Metabolite level is higher in patients than controls; ↓ Metabolite level is lower in patients than controls; - no group differences in metabolite levels

Abbreviations:

n: number of subjects; N/A: not applicable; NR: not reported; FEP: first episode psychosis patients; SZ: patients with schizophrenia; HR: high risk patients; HC: healthy controls

TE: Echo Time; SV: single voxel spectroscopy; MRSI: MR spectroscopic imaging; PRESS: Point Resolved Spectroscopy; MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy; STEAM: STimulated Echo Acquisition Mode; PEPSI: Proton Echoplanar spectroscopic Imaging; W: water; Cr: creatine; Glu: glutamate; Gln: glutamine; Glu/Gln: ratio between glutamate and glutamine; Glx: glutamate+ glutamine

ACC: anterior cingulate cortex; CSO: centrum semiovale; DLPFC: dorsolateral prefrontal cortex; GM: grey matter; MPFC: medial prefrontal cortex; SN: substantia nigra; WM: white matter

AVLT: auditory-verbal learning test, CPT: continuous performance test; DSDT: digit span distraction test; DST: digit sequencing task; EEG: Electroencephalogram; K-FTDS: kiddie formal thought disorder rating scale; MCCB: MATRICS consensus cognitive battery; MMSE: mini-mental state examination; MMN – Mismatch Negativity; OSSS: orientation specific surround suppression; RBANS: repeatable battery for the assessment of neuropsychological status; TMT: trail making test; WCST: wisconsin card sorting test

Table 2:

GABA and cognition in schizophrenia

Author	n (control/ patient)	Illness stage	Medication status	Cognitive domain	Region	Tesla	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
(Yoon et al., 2010)	13/13	mixed	mixed	OSSS	Calcarine sulci	3	SV	MEGA-PRESS	68	Cr	↓GABA	GABA was positively correlated to the magnitude of OSSS in the combined SZ and HC group
(Kegeles et al., 2012)	22/32	Chronic	Mixed	N-Back	MPFC, DLPFC	3	SV	MEGA-PRESS	68	Cr, W	↑GABA in MPFC in unmedicated vs HC; - DLPFC	No associations
(Kelemen et al., 2013)	20/28	FEP	naïve	Visual processing	Occipital cortex	3	SV	MEGA-PRESS	68	Cr	↓GABA	No associations between GABA and visual contrast sensitivity
(Rowland et al., 2013b)	20/21	Chronic young (11/10); old (10/10)	Medicated	RBANS	ACC, CSO	3	SV	MEGA-PRESS	68/ 35	W	Trend for ↓GABA in old SZ vs old HC	ACC GABA was positively correlated with RBANS attention score in the combined SZ and HC group
(Marsman et al., 2014)	23/17	Chronic	Medicated	WAIS	MPFC, POC	7	SV	MEGA-sLASER	74	Cr	↓GABA in MPFC	MPFC GABA negatively associated with WAIS scores in SZ, but not HC
(Chen et al., 2014)	12/12	Chronic	mixed	Modified Sternberg working memory task (EEG)	Left DLPFC	3	SV	MEGA-PRESS	68	W	-	No associations *Left DLPFC GABA was positively correlated with the gamma amplitudes during both the rest and working memory task in the combined SZ and HC group*
(Rowland et al., 2016a)	77/60	Chronic young (40/29); old (37/31)	mixed	Digit symbol coding test, DST and UPSA	ACC	3	SV	MEGA-PRESS	68	W	Age strongly predicted GABA levels in SZ	ACC GABA was positively associated with the DST in SZ, but not HC
(Rowland et al., 2016b)	53/45	Chronic	mixed	DST, auditory MMN (EEG)	ACC	3	SV	MEGA-PRESS	6.5/ 68	W	-	Higher GABA was correlated with better DST working memory and processing speed in SZ, but not HC
(Reid et al., 2018)	21/21	FEP	Medicated	RBANS	ACC	7	SV	STEAM	5	W	-	Negative association between GABA and

Author	n (control/ patient)	Illness stage	Medication status	Cognitive domain	Region	Tesla	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
												RBANS total score, immediate memory and language subscales in SZ, but not HC

↑ Metabolite level is higher in patients than controls; ↓ Metabolite level is lower in patients than controls; - no group differences in metabolite levels

Abbreviations:

n: number of subjects; FEP: first episode psychosis patients; SZ: patients with schizophrenia; HC: healthy controls

TE: Echo Time; SV: single voxel spectroscopy; MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy; MEGA-sLASER: MEGA- semi localization by adiabatic selective refocusing sequence; STEAM: STimulated Echo Acquisition Mode; W: water; Cr: creatine; GABA: γ-aminobutyric acid

ACC: anterior cingulate cortex; CSO: centrum semiovale; DLPFC: dorsolateral prefrontal cortex; MPFC: medial prefrontal cortex; POC: parieto-occipital cortex

DST: digit sequencing task; EEG: Electroencephalogram; MMN – Mismatch Negativity; OSSS: orientation specific surround suppression; RBANS: repeatable battery for the assessment of neuropsychological status; UPSA: UCSD performance based skills assessment; WAIS: wechsler adult intelligence scale

Table 3:

Multimodal imaging, metabolites, and cognition in schizophrenia

Author	n (control/ patient)	Illness stage	Medication status	Cognitive domain (all are fMRI tasks)	Region	Tesla	Metabolite	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and fMRI
(Fusar-Poli et al., 2011)	17/24	ARMS	naïve	Verbal fluency task	ACC, left hippocampus and left thalamus	3	Glu	SV	PRESS	30	W	↓Glu in thalamus	Thalamic Glu levels were negatively associated with activation in the right DLPFC and left orbitofrontal cortex, but positively associated with activation in the right hippocampus and the bilateral temporal cortex in ARMS; opposite pattern seen in HC.
(Valli et al., 2011)	14/22	ARMS	naïve	Verbal episodic memory task	ACC, medial temporal cortex, and thalamus	3	Glu	SV	PRESS	30	W	Not reported	Medial temporal Glu was positively associated with medial temporal activation during the episodic memory task in HC; opposite pattern seen in ARMS.
(Hutcheson et al., 2012)	28/28	Chronic	Medicated	Memory retrieval	Left hippocampus	3	Glx	SV	PRESS	80	Cr	-	Hippocampal Glx was positively correlated with the left IFG BOLD response during memory retrieval in HC, but not SZ
(Falkenberg et al., 2014)	17/17	Chronic	Medicated	Bergen dichotic listening task	dorsal ACC	3	Glu	SV	PRESS	35	Cr	↓Glu	Positive correlations between Glu and BOLD in inferior parietal in SZ; opposite pattern in HC.

Author	n (control/ patient)	Illness stage	Medication status	Cognitive domain (all are fMRI tasks)	Region	Tesla	Metabolite	Acquisition	MRS Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and fMRI
(Allen et al., 2015)	27/33	UHR	mixed	Verbal fluency task	Left thalamus	3	Glu	SV	PRESS	30	W	-	UHR subjects with poor functional outcome showed negative relationship between thalamic glutamate levels and prefrontal striatal activation, pattern not seen in those with good functioning and HC
(Overbeek et al., 2019)	21/17	FEP	Medicated	RBANS, Stroop test	ACC	7	Glu, Gln, GABA	SV	STEAM	5	W	↓Glu	ACC GABA was negatively correlated with Stroop effect reaction time. In FEP, the relationship between ACC Glu and BOLD response in the DMN was opposite to HC
(White et al., 2015)	19/22	Chronic	Medicated	Prediction error task	SN	3	Glx	SV	PRESS	80	Cr	↑Glx	In HC, but not in SZ, prediction error BOLD response was positively associated with SN Glx
(Cadena et al., 2018)	20/22	Chronic	Un-medicated	Stroop task	ACC	3	Glx	SV	PRESS	80	Cr	-	In SZ, the relationship between ACC Glx and BOLD in regions of the salience network and posterior DMN was opposite to HC

↑ Metabolite level is higher in patients than controls; ↓ Metabolite level is lower in patients than controls; - no group differences in metabolite levels

Abbreviations:

n: number of subjects; ARMS: at risk mental state; FEP: first episode psychosis patients; SZ: patients with schizophrenia; UHR: ultra high risk patients; HC: healthy controls

TE: Echo Time; SV: single voxel spectroscopy; PRESS: Point Resolved Spectroscopy; STEAM: STimulated Echo Acquisition Mode; W: water; Cr: creatine; Glu: glutamate; Gln: glutamine; Glx: glutamate+ glutamine; GABA: γ-aminobutyric acid

ACC: anterior cingulate cortex; BOLD: blood oxygen level dependent signal; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; SN: substantia nigra

Table 4:

Glutamate and GABA and cognition in mood disorders

Author	N (HC/BD/MDD)	Diagnosis	Mood Status	Illness stage	Medication status	Cognitive domain	Region	Tesla	Metabolite	Acquisition	Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
(Dickstein et al., 2008)	48/36	Mood dys-regulation	NR	NR	Off meds	WASI	frontal lobe, hippocampus, POC, and parietal lobe	1.5	Glx	SV	PRESS	30	Cr	-	No associations
(Wozniak et al., 2012)	13/24	Mood dys-regulation	NR	NR	Mixed	WASI	ACC	4	Glu	SV	PRESS	30	W	↑Glu	No associations
(Jayaweera et al., 2015)	21/0/35	MDD	Depressed	Chronic	Mixed	WTAR, MMSE, RAVLT	Left hippocampus	3	Glu	SV	PRESS	35	Cr	-	Lower levels of hippocampal Glu are associated with poor memory retention in HC, but not MDD
(Hermens et al., 2015)	40/75/90	BD and MDD	Recently Depressed	Chronic	Mixed	WTAR, RAVLT,TMT	Left hippocampus	3	Glu	SV	PRESS	35	Cr	↑Glu	No associations
(Shirayama et al., 2017)	27/0/22	MDD	Depressed	FE	naïve	TMT, RAVLT, Verbal paired associates test, Stroop, VF	MPFC, right hippocampus and amygdala	3	Glu, Gln, Glx	SV	PRESS	30	Cr	↓Glu in the MPFC	Negative correlation between amygdala and MPFC Glu and TMT and positive correlation between hippocampus Glu and RAVLT in all subjects
(Huber et al., 2018)	10/20/0	BD	Depressed	NR	NR	WCST,TMT, Stroop	ACC, POC	3	GABA	SV	PRESS 2D J-edit	31–229	W	-	Higher ACC GABA is associated with better WCST scores in

Author	N (HC/BD/MDD)	Diagnosis	Mood Status	Illness stage	Medication status	Cognitive domain	Region	Tesla	Metabolite	Acquisition	Sequence	TE (ms)	Reference	Metabolite level group difference	Associations between metabolites and cognition
															BD, but not HC

↑ Metabolite level is higher in patients than controls; ↓ Metabolite level is lower in patients than controls; - no group differences in metabolite levels

Abbreviations:

NR: not reported; n: number of subjects; FE: first episode patient; BD: bipolar disorder; MDD: major depressive disorder; HC: healthy controls

TE: Echo Time; SV: single voxel spectroscopy; PRESS: Point Resolved Spectroscopy W: water; Cr: creatine; Glu: glutamate; Gln: glutamine; Glx: glutamate+ glutamine; GABA: γ-aminobutyric acid

ACC: anterior cingulate cortex; MPFC: medial prefrontal cortex; POC: parieto-occipital cortex

MMSE: mini-mental state examination; RAVLT: rey auditory-verbal learning test; TMT: trail making test; VF: verbal fluency task; WASI: wechsler abbreviated scale for intelligence; WCST: wisconsin card sorting test; WTAR: wechsler test of adult reading