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Using proton magnetic resonance spectroscopic imaging to study glutamatergic alterations in patients with schizophrenia: A systematic review

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ABSTRACT

The glutamate hypothesis of schizophrenia posits aberrant glutamatergic activity in patients with schizophrenia. Levels of glutamate and glutamine can be detected and quantified in vivo by proton magnetic resonance spectroscopy. A related technique, proton magnetic resonance spectroscopic imaging (^{1}H-MRSI), is particularly useful as it simultaneously collects multiple spectra, across multiple voxels, from a single acquisition. The primary aim of this study was to review and discuss the use of ^{1}H-MRSI to measure levels of glutamate and glutamine in patients with schizophrenia. Additionally, the advantages and disadvantages of using ^{1}H-MRSI to examine schizophrenia pathophysiology are discussed. A literature search was conducted through Ovid. English language studies utilizing ^{1}H-MRSI to measure glutamate and glutamine in patients with schizophrenia were identified. Six studies met the inclusion criteria. The included studies provide inconclusive support for glutamatergic elevations within frontal brain regions in patients with schizophrenia. The key benefit of employing ^{1}H-MRSI to examine schizophrenia pathophysiology appears to be its broader spatial coverage. Future ^{1}H-MRSI studies utilizing large sample sizes and longitudinal study designs are necessitated to further our understanding of glutamatergic alterations in patients with schizophrenia.

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1. Introduction

Schizophrenia is often a lifelong illness that carries a poor prognosis, highlighted by multiple recurrences of psychotic episodes and marked progressive functional deterioration (Cechnicki et al., 2014; Karson et al., 2016; Penttilä et al., 2014). The primary treatment is antipsychotic pharmacotherapy; a shared property amongst antipsychotics is dopamine receptor antagonism (Frangou, 2008; Ginovart and Kapur, 2012). This notion, along with evidence from positron emission tomography studies, heavily implicates aberrant dopaminergic activity in the pathophysiology of schizophrenia (Ginovart and Kapur, 2012; Howes et al., 2012). The dopamine hypothesis of schizophrenia suggests striatal hyperdopaminergia and frontal hypodopaminergia in the illness (Howes and Kapur, 2009; Slifstein et al., 2015). Despite the dopamine hypothesis being informative, it fails to account for the heterogeneity observed amongst patients with schizophrenia. Antipsychotic treatment has limited efficacy for a subset (20–35%) of patients with schizophrenia (Meltzer, 1997; Miyamoto et al., 2014). Further, the dopamine hypothesis does not account for negative and cognitive symptomatology (George et al., 2013; Miyamoto et al., 2012).

The glutamate hypothesis of schizophrenia provides another important and complementary perspective, suggesting that disrupted glutamatergic activity is involved in illness pathophysiology (Coyle et al., 2003; Javitt and Zukin, 1991; Kantrowitz and Javitt, 2012; Olney and Farber, 1995). The basis for this hypothesis has been pharmacological studies in which *N*-methyl-D-aspartate receptor (NMDAR) antagonist administration leads to the emergence of schizophrenia symptomatology in healthy controls (Krystal et al., 1994; Lahti et al., 2001), and symptom exacerbation in patients with schizophrenia (Lahti et al., 2001, 1995). Beyond symptomatology, studies administering an NMDAR antagonist to healthy controls or in preclinical models also observe disturbances in levels of neurotransmitters, blood flow, and brain structure, resembling those seen in schizophrenia (Farber et al., 2002; Nagels et al., 2011; Olney and Farber, 1995; Rowland et al., 2005; Stone et al., 2012). Current proponents of the glutamate hypothesis posit that hypofunctioning NMDARs on gamma-Aminobutyric acid-ergic inhibitory interneurons result in the disinhibition of downstream pyramidal neurons and a

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paradoxical increase in glutamatergic activity (Moghaddam et al., 1997; Moghaddam and Krystal, 2012; Nakazawa et al., 2012).

In recent years, the glutamate hypothesis of schizophrenia has also generated strong support from proton magnetic resonance spectroscopy (^{1}H-MRS) studies. ^{1}H-MRS is a magnetic resonance imaging (MRI) technique that permits non-invasive in vivo detection and quantification of various neurometabolites (Juchem and Rothman, 2014; van der Graaf, 2010). As such, ^{1}H-MRS has the capacity to further our understanding of neuropsychiatric illnesses. Its use allows for the assessment of glutamate, its main metabolite glutamine, and glutamate + glutamine (Glx), as well as non-glutamatergic neurometabolites, such as *N*-acetylaspartate, myo-inositol, choline, and creatine (Juchem and Rothman, 2014). Notably, the present study focuses on glutamate and glutamine; more information on the state of the literature for other neurometabolites exists within authoritative reviews (Kraguljac et al., 2012b; Schwerk et al., 2014).

Past ^{1}H-MRS work in patients with schizophrenia suggests elevated levels of glutamate, glutamine, and Glx in antipsychotic-naive or antipsychotic-free states, whereas findings from investigations in medicated patient populations are more variable, with reports of elevated, similar, and decreased levels compared to those of healthy controls (Bustillo, 2013; Chang et al., 2007; de la Fuente-Sandoval et al., 2013; Egerton et al., 2017; Kegeles et al., 2012; Plitman et al., 2018, 2016a; Poels et al., 2014; van Elst et al., 2005). The elevated levels of these neurometabolites observed in untreated patients may be linked with certain alterations in brain structure as well as symptom severity, although these relationships require further investigation (Merritt et al., 2013; Plitman et al., 2016b, 2014). Moreover, a recent meta-analysis considering those within high-risk, first-episode of psychosis (FEP), and schizophrenia stages of illness found evidence for aberrant glutamatergic signalling, such as increased glutamate within the basal ganglia, increased glutamine within the thalamus, and increased Glx within the basal ganglia and medial temporal lobe compared to healthy controls (Merritt et al., 2016). Evidently, in addition to several other possible confounding factors (e.g. ^{1}H-MRS methods, concomitant medications), the brain region within which levels of neurometabolites are being investigated is an important consideration.

It is noteworthy that the majority of ^{1}H-MRS work uses single-voxel spectroscopy (SVS). In SVS, a single volume element ("voxel") is placed within a particular region of interest (ROI) (Juchem and Rothman, 2014); this approach is particularly useful for the study of neuropsychiatric illnesses where hypotheses guide the investigation of a particular region (Bustillo, 2013; Wijtenburg et al., 2015). However, it might be challenging to define a predetermined ROI in illnesses which are not known to have a clearly delineated area of pathology, or when it is unknown whether neurometabolite abnormalities are indeed region-specific or actually global (Boer and Klomp, 2014). The multiple-voxel technique referred to as proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) or chemical shift imaging is a particularly useful solution in this regard as it permits the simultaneous collection of multiple spectra, across an array of voxels, from a single acquisition (Boer and Klomp, 2014). ^{1}H-MRSI can be collected in a 1D, 2D, or 3D fashion and, akin to standard imaging techniques, phase encoding gradients are utilized for spatial localization (Dale et al., 2015), thereby allowing the study of spatial distribution of various neurometabolites (van der Graaf, 2010).

The present work aimed to review and discuss existing studies that utilized ^{1}H-MRSI to measure levels of glutamate and glutamine in patients with schizophrenia. In doing so, the advantages and disadvantages of using ^{1}H-MRSI over SVS for such research questions are considered.

2. Methods and materials

2.1. Literature search

A search was conducted to identify published English language human studies utilizing ^{1}H-MRSI to measure glutamate, glutamine, or Glx in patients with schizophrenia using Embase, Medline, and PsycINFO. The Ovid search was performed utilizing the following search terms: (CSI OR HMRSI OR MRSI OR MRS-I OR "chemical shift imaging" OR "MRS imaging" OR "spectroscopic imaging") AND ("high risk" or psychosis or schizophreni*). Two authors (E.P., E.G.) independently performed the search (last search: September 2018) and assessed eligibility by reviewing titles and abstracts. The reference sections of major review articles were additionally searched.

2.2. Inclusion criteria

Full-length English language articles were included if: (1) a group of patients with schizophrenia or related disorders were included into the study and (2) glutamate, glutamine, or Glx was measured using ^{1}H-MRSI.

2.3. Exclusion criteria

No additional exclusion criteria were applied to assess study eligibility.

3. Results

3.1. Search results and general descriptions of reviewed studies

The initial Ovid search yielded 581 publications. Following the removal of duplicates, 375 publications remained. Screening of titles and abstracts by two authors rendered 43 articles to undergo full-text assessment for eligibility. Six studies were deemed eligible for inclusion (Bustillo et al., 2017, 2016, 2011; Homan et al., 2014; Seese et al., 2011; Smesny et al., 2015) and were consequently reviewed. Despite also searching for studies that included high-risk participants or patients with psychosis, the only studies that met inclusion criteria included patients with schizophrenia. The characteristics of these studies are summarized in Table 1. Generally, 4 studies examined patients within a chronic stage of illness (Bustillo et al., 2017, 2016, 2011; Homan et al., 2014), 1 study examined patients within their first episode of schizophrenia (FES) (Smesny et al., 2015), and 1 study examined comparably young patients with childhood-onset schizophrenia (Seese et al., 2011). In 5 of the studies, the majority or all of the patients were treated with antipsychotic medication; 1 study examined antipsychotic-naive patients (Smesny et al., 2015). Four studies were carried out at 3 T (Bustillo et al., 2017, 2016; Homan et al., 2014; Smesny et al., 2015), 1 was carried out at 4 T (Bustillo et al., 2011), and 1 was carried out at 1.5 T (Seese et al., 2011). All but 1 study (Bustillo et al., 2011), which utilized Proton Echo-Planar Spectroscopic Imaging (PEPSI), employed a Point RESolved Spectroscopy (PRESS) sequence for ^{1}H-MRSI data collection. TEs of 15 ms (Bustillo et al., 2011), 30 ms (Homan et al., 2014; Seese et al., 2011; Smesny et al., 2015), and 40 ms (Bustillo et al., 2017, 2016) were employed. All but 1 study (Homan et al., 2014), which used jMRUI, utilized LCModel. All 6 studies measured Glx levels, 2 concomitantly measured glutamate levels (Bustillo et al., 2011; Smesny et al., 2015), and 1 concomitantly measured glutamine levels (Bustillo et al., 2011). The investigated brain regions differed across studies, and included grey matter (GM) and white matter (WM) areas within frontal, temporal, parietal, and cingulate regions. Collectively, the main glutamatergic findings of the included studies suggest that levels of glutamate and Glx might be increased within frontal brain regions. A more detailed analysis of the included studies is found below.

3.2. Detailed analysis of reviewed studies

3.2.1. Group differences between patients with chronic schizophrenia and healthy controls

Four of the reviewed studies examined group differences involving levels of glutamate, glutamine, or Glx between patients with schizophrenia in chronic stages of illness and healthy controls. A detailed discussion of these 4 studies follows.

Table 1
Summary of studies that met inclusion criteria ($n = 6$).

Authors, year, journal	*n*	Mean age (SD)	Gender	Illness stage	AP Tx	Tesla	^{1}H-MRSI parameters	Metabolite[a]	QC cutoffs	Correction	Analysis software	Regions of interest	Key findings[a] [effect sizes[b]]
Bustillo et al. (2017), Front Psychiatry	58 SCZ; 67 HC	SCZ: 38 (14); HC: 36 (12)	SCZ: 46 M, 12 F; HC: 49 M, 18 F	Chronic	All med	3	Sequence: PRESS, TE: 40 ms, TR: 1500 ms, FOV: 220 × 220 mm, Cartesian k-space size: 32 × 32, circular k-space sampling (radius: 12), slice thickness: 15 mm, nominal voxel size: 0.71 cm^3, effective voxel volume: 2.4 cm^3, averages: 1, scan time: 582 s	Glx	%SD ≤20%	Partial volume and relaxation effects	LCModel	Supraventricular frontal medial GM, left and right frontal WM, parietal medial GM, and left and right parietal WM	Glx levels in GM positively correlated with glutamate-related genetic risk score in young (≤36 years) SCZ. GM and WM Glx was higher in SCZ regardless of age
Bustillo et al. (2016), Schizophr Bull	104 SCZ; 97 HC	SCZ: 36.3 (13.8); HC: 37.1 (12.3)	SCZ: 89 M, 15 F; HC: 69 M, 28 F	Chronic	97 med	3	Sequence: PRESS, TE: 40 ms, TR: 1500 ms, FOV: 220 × 220 mm, Cartesian k-space size: 32 × 32, circular k-space sampling (radius: 12), slice thickness: 15 mm, nominal voxel size: 0.71 cm^3, effective voxel volume: 2.4 cm^3, averages: 1, scan time: 582 s	Glx	%SD ≤20%	Partial volume and relaxation effects	LCModel	Supraventricular frontal medial GM, left and right frontal WM, parietal medial GM, and left and right parietal WM	Glx was increased in medial frontal and medial parietal GM and right frontal WM in SCZ [young GM: 0.11; young WM: 0.14; old GM: 0.22; old WM: 0.03]. WM Glx levels were positively correlated with positive symptoms in older SCZ
Smesny et al. (2015), Schizophr Res	31 FES; 31 HC	FES: 25.97 (4.95); HC: 25.42 (5.18)	FES: 16 M, 15 F; HC: 15 M, 16 F	First-episode	All naive	3	Sequence: PRESS, TE: 30 ms, TR: 2000 ms, FOV: 24 × 24 cm2, voI: 15 × 9 × 1.5 cm^3, nominal voxel size: 15 × 15 × 15 mm^3, 16 × 16 phase encoding steps, scan time: 15 min	Glu (Glx)	N/A	Partial volume effects	LCModel	Frontal, prefrontal, and ACC	Bilaterally increased Glu levels in frontal/prefrontal cortex and ACC[c] [right frontal/prefrontal cortex + adjacent WM: 1.10; right ACC: 1.06; left ACC: 0.76; left frontal/prefrontal cortex + adjacent WM: 0.79; right DLPFC + frontal WM: 0.59; right ACC + adjacent WM: 0.50; left ACC and cerebral WM: 0.17; left DLPFC + adjacent frontal WM: 0.63]
Homan et al. (2014), NeuroImage	12 SCZ (AH); 8 SCZ (NH); 11 HC	SCZ (AH): 42.3 (9.7); SCZ (NH): 41.2 (14.7); HC: 43.1 (10.4)	SCZ (AH): 7 M, 5 F; SCZ (NH): 7 M, 1 F; HC: 6 M, 5 F	Chronic	All med	3	Sequence: PRESS, TE: 30 ms, TR: 1.7 s, FOV: 160 mm, matrix size: 20 × 20, circular k-space sampling, thickness: 15 mm, averages: 4	Glx/Cr	N/A	N/A	jMRUI	Wernicke's area, and left and right Heschl's gyri	No identified group differences
Bustillo et al. (2011), Biol Psychiatry	30 SCZ (12 Young); 28 HC (10 Young)	Young SCZ: 23.5 (3.2); Old SCZ: 49.4 (9.6); Young HC: 22.2 (4.4); Old HC: 49.5 (9.2)	Young SCZ: 9 M, 3 F; Old SCZ: 15 M, 3 F; Young HC: 8 M, 2 F; Old HC: 10 M, 8 F	Chronic	All med	4	Sequence: PEPSI, TE: 15 ms, TR: 2 s, FOV: 256 mm, matrix size: 32 × 32, slice thickness: 15 mm, nominal voxel size: 1 cc, averages: 8 water suppressed and 1 nonwater suppressed, scan time: 10 min	Glu, Gln, Glx	FWHM <0.06 ppm, % SD <20%, and SNR >5	Partial volume and relaxation effects	LCModel	Supraventricular left and right frontal lateral GM, frontal medial GM, left and right frontal WM, left and right parietal lateral GM, parietal medial GM, and left and right parietal WM	No diagnosis by age group by fractional GM interaction and no main effect of diagnosis. No interactions for Glx involving ROIs. Gln/Glu higher in medial-frontal/parietal GM in young SCZ compared to young HC, not in old SCZ. Glx positively correlated with overall cognitive performance in SCZ [young GM: 0.27; young WM: 0.43; old GM: 0.08; old WM: 0.12]
Seese et al. (2011), Schizophr Res	28 COS; 34 HC	SCZ: 14.1 (3.0); HC: 11.5 (2.9)	SCZ: 15 M, 13 F; HC: 15 M, 19 F	COS	21 med	1.5	Sequence: PRESS, TE: 30 ms, TR: 1500 ms, in-plane resolution: 11 × 11mm^2, slab thickness: 9 mm, NEX: 4	Glx	FWHM ≤0.1 ppm, % SD ≤20%, and SNR ≥3	CSF	LCModel	Bilateral inferior frontal, middle frontal, and superior temporal gyri	No identified group differences [inferior frontal gyrus: left = 0.09, right = 0.04; middle frontal gyrus: left = 0.00, right = 0.06; superior temporal gyrus: left = 0.21, right = 0.05]

Abbreviations: ACC: anterior cingulate cortex; AH: with auditory verbal hallucinations, AP Tx: antipsychotic treatment, COS: childhood-onset schizophrenia, Cr: creatine, CSF: cerebrospinal fluid, DLPFC: dorsolateral prefrontal cortex; F: female, FES: first-episode schizophrenia, FOV: field of view, FWHM: full-width at half maximum, Gln: glutamine, Glu: glutamate, Glx: glutamate+glutamine, GM: grey matter, HC: healthy control, ^{1}H-MRSI: proton magnetic resonance spectroscopic imaging, M: male, med: medicated, NH: without auditory verbal hallucinations, PEPSI: Proton Echo-Planar Spectroscopic Imaging, PRESS: Point RESolved Spectroscopy, QC: quality control, SCZ: schizophrenia, SD: standard deviation, SNR: signal-to-noise ratio, TE: echo time, TR: repetition time, WM: white matter.

[a] Only details related to the primary aims of this work are included within this table.

[b] Effect sizes calculated in cases where means and standard deviation were provided.

[c] Glx findings were not accessible.

Bustillo et al. (2016) used the largest sample of schizophrenia subjects ($n = 104$) and healthy controls ($n = 97$) to date to measure Glx levels from an axial supraventricular tissue slab. The included sample was in the chronic stage of illness and mostly medicated with antipsychotics. Participants underwent ^{1}H-MRSI scans at 3 T using a TE of 40 ms. LCModel was utilized for data fitting, and results were corrected for both partial volume and relaxation effects. In addition, a %SD cutoff of 20% was employed. Voxels were classified as being either "predominantly" GM, "predominantly" WM, or mixed. Regions of interest were selected in each hemisphere from "predominantly" GM and WM voxels, anterior (frontal) and posterior (parietal) to the central sulcus. As a result, 6 ROIs were chosen: frontal medial GM, left and right frontal WM, parietal medial GM, and left and right parietal WM. In terms of Glx, the authors found a group-by-tissue interaction. Post-hoc analyses showed that Glx was increased in the patient group compared to the control group in both GM and WM. In GM, Glx increases were present within medial frontal and marginally in medial parietal regions. In WM, Glx increases were present within the right frontal region. The authors also investigated *N*-acetylaspartate, myo-inositol, choline, and creatine levels within this study, reporting a group-by-age-by-tissue interaction for *N*-acetylaspartate and a group-by-age^{2}-by tissue interaction for creatine. Post-hoc analyses for *N*-acetylaspartate revealed increased levels in GM but reduced levels in WM within older schizophrenia patients; these effects were further localized to medial frontal GM, and frontal left and right and parietal left and right WM ROIs. Further, in younger schizophrenia patients, *N*-acetylaspartate levels were also reduced in WM, localized to the right frontal WM ROI. Post-hoc analyses for creatine revealed WM reductions in older schizophrenia patients, localized to the right parietal WM ROI. No interactions or main effects were identified for myo-inositol or choline levels.

In a follow-up study, Bustillo et al. (2017) examined a subset of the same participant sample ($n = 58$ antipsychotic-treated patients with chronic schizophrenia and 67 healthy controls). ^{1}H-MRSI data was carried over from the previous study, and consistent with the previous report, GM and WM Glx levels within the subset of patients were higher than in the subset of healthy controls.

In another study, Homan et al. (2014) included 3 groups: 12 patients with schizophrenia with auditory verbal hallucinations (AVH), 8 patients with schizophrenia without AVH for the last 12 months, and 11 healthy controls. Notably, both patient groups consisted of antipsychotic-treated patients with chronic schizophrenia. The authors utilized ^{1}H-MRSI to obtain spectra from Wernicke's area, and left and right Heschl's gyri. ^{1}H-MRSI scanning was performed at 3 T, using a TE of 30 ms. Spectra were processed using jMRUI (Stefan et al., 2009) and no group effects were detected for Glx levels expressed as ratios to creatine levels. In this study, *N*-acetylaspartate, myo-inositol, and choline levels were additionally investigated. For each of these neurometabolites, no group effect was identified.

Finally, Bustillo et al. (2011) measured Glx levels from a location including GM and WM in bilateral frontal and parietal brain areas of 30 antipsychotic-treated patients with chronic schizophrenia and 28 healthy controls. Participants underwent ^{1}H-MRSI scans at 4 T using a TE of 15 ms. LCModel was utilized for data fitting, and results were corrected for both partial volume and relaxation effects. Of note, full-width at half maximum (FWHM), signal-to-noise ratio (SNR), and %SD cutoffs of <.06 ppm, >5, and < 20%, respectively, were implemented. Also, as above, voxels were classified as being either "predominantly" GM, "predominantly" WM, or mixed. Ten ROIs were selected in each hemisphere from "predominantly" GM and WM voxels, anterior (frontal) and posterior (parietal) to the central sulcus: the left and right frontal lateral GM, frontal medial GM, left and right frontal WM, left and right parietal lateral GM, parietal medial GM, and left and right parietal WM. With respect to Glx, there was no diagnosis by age group by fractional GM interaction, or main effect of diagnosis. Further, no significant interactions were identified for Glx in ROI analyses. However, an exploratory ROI investigation using a less stringent Cramer-Rao lower bound cut-off of 30 identified higher glutamine to glutamate ratio in medial-frontal/parietal GM in young patients with schizophrenia (<30 years) compared to young healthy controls, although results did not survive correction for multiple comparisons. Additionally, the authors examined *N*-acetylaspartate, myo-inositol, creatine, and choline levels, reporting diagnosis by age group by fractional GM interactions for each. Post-hoc analyses demonstrated lower *N*-acetylaspartate in GM in the young schizophrenia group, a trend towards lower *N*-acetylaspartate in WM in the older schizophrenia group, increased myo-inositol in both GM and WM in the older schizophrenia group, and increased creatine levels in GM in the older schizophrenia group. Notably, no interaction effects were identified for *N*-acetylaspartate, myo-inositol, creatine, or choline levels in ROIs.

3.2.2. Group differences between patients within early stages of schizophrenia and healthy controls

Two of the reviewed studies examined patients within early stages of schizophrenia. A detailed discussion of these 2 studies is presented below.

In the study by Smesny et al. (2015), 31 antipsychotic-naive patients experiencing their FES and 31 healthy controls were investigated. ^{1}H-MRSI was acquired at 3 T, using a TE of 30 ms, from an ROI encompassing voxels within the frontal, prefrontal, and anterior cingulate cortex. Data were quantified with LCModel and controlled for partial volume effects. This study found increases in glutamate levels within voxels encompassing the right and left frontal/prefrontal cortex and adjacent WM, and the right and left anterior cingulate cortex within the patient group.

In 28 youth with childhood-onset schizophrenia and 34 healthy controls, Seese et al. (2011) measured Glx levels acquired by ^{1}H-MRSI bilaterally from inferior frontal, middle frontal, and superior temporal gyri. Participants underwent MRI scans at 1.5 T and a TE of 30 ms was utilized to acquire ^{1}H-MRSI from 3 slabs: 2 sampled the left and right peri-Sylvian region, including inferior frontal, superior temporal, and other nearby cortex, and 1 sampled bilateral middle frontal cortex, mesial prefrontal cortex, and prefrontal WM positioned in between. Further, ROIs were sketched manually for bilateral inferior frontal, middle frontal, and superior temporal gyri. Each ROI was then divided into its GM, WM, and CSF components. ^{1}H-MRSI data were processed using LCModel and corrected for CSF. ROI averages were created using voxels containing at least 75% by volume GM + WM, a SNR ≥3, and a FWHM ≤0.1 ppm. In addition, a %SD cutoff of 20% was employed. The authors found no significant differences between groups in terms of Glx levels. Also, *N*-acetylaspartate, myo-inositol, choline, and creatine levels were examined in this study; no group differences were identified for these neurometabolites.

3.2.3. Relationships between neurometabolite levels and symptomatology or genotype

Three of the reviewed studies found relationships between levels of Glx and other measures of interest. These studies are discussed below.

With respect to symptomatology, Bustillo et al. (2016) found that WM Glx levels were positively correlated with positive symptoms in older schizophrenia patients (>35 years). The same study found that positive symptoms negatively correlated with WM *N*-acetylaspartate levels in older schizophrenia patients, and that cognitive score correlated positively with WM *N*-acetylaspartate and creatine levels in controls but negatively in patients with schizophrenia; for creatine, this finding was only in the younger group. In addition, while not reporting upon relationships between symptom scores and Glx levels, Homan et al. (2014) observed a positive association between left Heschl's gyrus NAA levels with total PANSS scores and negative PANSS scores. Further, Bustillo et al. (2011) found that Glx levels were positively correlated with overall cognitive performance only in the schizophrenia group, accounting for about 36% of the variance. Lastly, Seese et al. (2011) reported that formal thought disorder scores in the schizophrenia group were positively correlated with superior temporal and inferior frontal gyri *N*-acetylaspartate levels as well as superior temporal gyrus creatine levels.

In another investigation, Bustillo et al. (2017) examined whether 3 of the 6 glutamate-related risk-conferring single-nucleotide polymorphisms (SNPs) identified by the Psychiatric Genetics Consortium to confer risk for schizophrenia and to involve genes implicated in brain glutamate function were related to Glx levels. To ensure specificity of any identified relationships, the authors also explored the relationships between 3 calcium signalling SNPs and Glx levels. The authors found that GM Glx levels were positively correlated with summary risk scores for the 3 glutamate polymorphisms only in the younger schizophrenia group (≤36 years). No relationships were identified between Glx levels and summary risk scores for the 3 calcium polymorphisms.

4. Discussion

4.1. Collective interpretation of reviewed studies

Overall, our search to identify studies assessing levels of glutamate and glutamine in patients with schizophrenia using ^{1}H-MRSI unexpectedly yielded only 6 studies, which are notably diverse in terms of ^{1}H-MRSI parameters, the brain regions investigated, and the characteristics of participants, including age, sex, and stage of illness. Thus, additional work is undoubtedly necessitated to draw stronger conclusions. However, on the basis of the existing ^{1}H-MRSI studies investigating glutamatergic alterations in patients with schizophrenia, there appears to be elevated glutamatergic activity within frontal brain regions of patients with this illness.

As mentioned above, previous SVS findings suggest elevated levels of glutamate, glutamine, and Glx in patients with limited antipsychotic exposure (Bustillo, 2013; de la Fuente-Sandoval et al., 2013; Kegeles et al., 2012; Plitman et al., 2016a; Poels et al., 2014). In the present review, only Smesny et al. (2015) included unmedicated patients and akin to SVS studies, found elevated levels of glutamate. By contrast, a diverse literature base of SVS studies investigating medicated patients with schizophrenia contributes heterogeneous findings with respect to glutamate, glutamine, and Glx, ranging from elevated, similar, and decreased levels compared to those of healthy controls (Chang et al., 2007; Kraguljac et al., 2012a; Poels et al., 2014; Rowland et al., 2013; Théberge et al., 2003; van Elst et al., 2005). The studies in the present review that included medicated patients with schizophrenia were also variable, albeit to a lesser extent, with respect to their findings, with some reporting elevated Glx levels and others not identifying group differences. That being said, our review sample was small and the included studies omitted many ventral brain regions; this is noteworthy in that future ^{1}H-MRSI studies might render similar variability to SVS work, especially within medicated patients.

The purported elevated frontal glutamatergic activity in patients with schizophrenia is in line with a previous SVS study that included a large sample of patients with chronic schizophrenia and found glutamine elevations in the dorsal anterior cingulate within the patient group (Bustillo et al., 2014). By comparison, a previous meta-analysis examining SVS studies reported increased medial frontal glutamine and decreased medial frontal glutamate in patients with schizophrenia (Marsman et al., 2013). In contrast, the most recent meta-analysis on this topic (Merritt et al., 2016) failed to find differences in levels of glutamate, glutamine, and Glx within the medial frontal cortex, dorsolateral prefrontal cortex (DLPFC), or frontal WM, considering all clinical groups (i.e. high-risk, FEP, schizophrenia). However, the same study reported increases in medial frontal Glx levels in high-risk individuals and frontal WM Glx levels in patients with schizophrenia. When analyses were extended to include studies that measured glutamine at <4 T and glutamate at <3 T, the authors found elevated medial frontal glutamine levels in cases (consisting of all clinical groups) and in the FEP group, and elevated DLPFC glutamine levels in the schizophrenia group (the latter result was no longer significant after the exclusion of 1 study examining patients with a 22q11 deletion) (Merritt et al., 2016). Interestingly, longitudinal SVS studies have suggested that elevated glutamate and Glx levels may resolve following antipsychotic treatment (de la Fuente-Sandoval et al., 2013; Egerton et al., 2017; Kegeles et al., 2012). In light of this, the findings from the present review might be interpreted to suggest that frontal glutamatergic elevations may persist in patients with schizophrenia even following antipsychotic treatment. However, of particular relevance to this discussion is a recent SVS study at 7 T examining medicated patients with FEP, which measured glutamate and glutamine in five brain regions: the dorsal anterior cingulate, DLPFC, orbital frontal cortex, thalamus, and centrum semiovale (Wang et al., 2019). Notably, the authors found reduced anterior cingulate glutamate in the FEP group and did not identify group differences in glutamate or glutamine in other investigated areas. This finding is consistent with other recent studies performed at 7 T (Kumar et al., 2018; Reid et al., 2019).

While the novelty of the present review is its specific examination of ^{1}H-MRSI studies, it is unclear to what extent the utilization of ^{1}H-MRSI instead of SVS impacts the observed elevations in frontal glutamate and Glx within the patient group. It is possible that the limited spatial coverage offered by SVS may explain why some SVS studies have failed to find differences in these neurometabolites within frontal brain regions, although other factors such as sample size and age likely carry influence as well. For instance, the included studies speak to the importance of having sufficient sample sizes, as the 3 studies that detected differences in a glutamatergic neurometabolite (Bustillo et al., 2017, 2016; Smesny et al., 2015) used amongst the largest sample sizes in the present review. Based on the largest effect sizes in Table 1, proposed sample thresholds for future work are roughly 86 participants in each group (i.e. patients, controls) for studies investigating patients with chronic schizophrenia, and approximately 15 participants in each group for studies investigating antipsychotic-naive patients with FES (alpha probability: 0.05, power: 0.8, allocation ratio: 1; two-tailed; two independent means).

4.2. Limitations of reviewed studies

The studies reviewed here are not without limitations. First, although glutamatergic dysregulation in subcortical regions is regularly described within existing SVS literature, none of the included studies investigated a subcortical region. Second, all but 1 study (Smesny et al., 2015) focused their investigation on Glx, which is a summed measure of glutamate and glutamine that provides somewhat limited insight into glutamatergic metabolism. However, it is important to mention that the separation of glutamate and glutamine at field strengths <7 T is difficult. Third, while 1 study included antipsychotic-naive patients (Smesny et al., 2015), all others may have been influenced by antipsychotic treatment. Antipsychotics have been previously shown to decrease levels of glutamate and Glx, and thus their influence on study findings cannot be discounted. Fourth, all of the included studies employed cross-sectional study designs, limiting interpretations of their results. A better alternative would be a study wherein participants at-risk for psychosis are assessed longitudinally, capturing their progression throughout various stages of illness. However, given that only a portion of individuals transition to a subsequent stage of illness, it is undoubtedly more logistically challenging to carry out this study design. Fifth, some of the included studies may have been limited by their sample sizes, which may have not allowed for sufficient power to detect group differences. Finally, heterogeneity within each study is an important consideration; participant factors such as age, sex, and stage of illness, as well as antipsychotic treatment status may particularly play a role.

4.3. Considerations of using ^{1}H-MRSI to study glutamatergic alterations in patients with schizophrenia

In this section, the advantages and disadvantages of using ^{1}H-MRSI in patients with schizophrenia are discussed in the context of the work presented above. One of the main advantages of utilizing ^{1}H-MRSI to study glutamatergic alterations in patients with schizophrenia is its capacity for broader spatial coverage in comparison to SVS. There are several reasons why this advantage is particularly important when

studying schizophrenia pathophysiology. First, the precise location(s) of glutamatergic dysregulation in patients with schizophrenia remains elusive. As noted above, a recent meta-analysis identified differences in levels of glutamate, glutamine, and Glx between patients with schizophrenia spanning various brain regions (i.e. basal ganglia, thalamus, medial temporal lobe, frontal WM) (Merritt et al., 2016). The ability of ^{1}H-MRSI to collect information from a broad spatial area was taken advantage of by most of the included studies discussed above, which sought to examine a larger brain region than that covered in most SVS investigations. Second, the larger total coverage provided by ^{1}H-MRSI is useful for studying illnesses that influence several areas of the brain (Dale et al., 2015). Schizophrenia is an illness in which existing evidence implicates multiple brain regions, and both GM and WM involvement (Haijma et al., 2013; Kelly et al., 2018; Najjar and Pearlman, 2015; Samartzis et al., 2014; van Erp et al., 2018). SVS is inherently limited in its brain coverage, and results in poor detection of tissue composition effects, while ^{1}H-MRSI permits the assessment of GM and WM regions. This is especially important because tissue compartment has been shown to have an influential effect on neurometabolite levels; it was previously observed that GM Glx levels are twice as high as WM Glx levels (Bustillo et al., 2016). This feature of ^{1}H-MRSI was capitalized upon by 3 manuscripts above, which characterized voxels as being "predominantly" GM or WM voxels (Bustillo et al., 2017, 2016, 2011). Third, schizophrenia is characterized by vast and widespread structural compromise, and SVS techniques are highly impacted by alterations in participants' brain tissue morphology. Thus, the utilization of ^{1}H-MRSI contributes towards mitigating biases introduced by voxel selection during SVS (Dale et al., 2015).

Other advantages of using ^{1}H-MRSI that are not specific to the study of schizophrenia include its higher spatial resolution compared with SVS (Zhang et al., 2018). Additionally, unlike SVS, ^{1}H-MRSI voxels can be repositioned during post-processing stages by grid shifting (Dale et al., 2015; van der Graaf, 2010) and pixels can also be summed together (Juchem and Rothman, 2014).

There are a few noteworthy disadvantages of ^{1}H-MRSI that should be highlighted. First, ^{1}H-MRSI may require a longer scanning time, as well as more time during the post-processing stage, as voxels need to be analyzed individually (Dale et al., 2015; Zhu and Barker, 2011). Relatedly, as a result of its long acquisition time, ^{1}H-MRSI is limited by its inability to assess task-related changes in glutamate, glutamine, and Glx. Second, voxels may experience significant spectral contamination by signals from adjacent voxels (i.e. "voxel bleed" or "point spread function" effects) (Kreis, 2004; van der Graaf, 2010). Third, spectral quality is typically higher in SVS than ^{1}H-MRSI; thus, it is generally possible to quantify more neurometabolites with the former (Bertholdo et al., 2013). Compared with SVS, it is generally more difficult to obtain a uniformly homogeneous magnetic field over the large ROI in ^{1}H-MRSI, resulting in relatively poorer spectral quality (Juchem and Rothman, 2014). As a result, the reliability of quantification of weaker metabolites, including glutamine, is likely compromised in ^{1}H-MRSI.

In light of the above-mentioned advantages and disadvantages of using ^{1}H-MRSI compared to SVS, an important utility of the former appears to be its ability to identify ROIs wherein glutamatergic alterations might appear for ensuing SVS work to target. This approach, whether adopted within the same sample or across samples, might lead to better characterization of glutamatergic disruptions in patients with schizophrenia.

4.4. Limitations of present review

The present review should also be considered in light of its limitations. First, the principal aim may have been too specific, resulting in the sole investigation of glutamate, glutamine, and Glx, and no other neurometabolites. Since glutamate and glutamine were the primary focus of the present work, the only results concerning other neurometabolites that were considered in this study were those of the included studies. Thus, this review does not encompass the entire existing literature surrounding these neurometabolites. Second, the employed search terms may have resulted in the omission of relevant articles from the Ovid search. Third, the present review is limited by the vast heterogeneity that exists across included studies, especially in terms of ^{1}H-MRSI parameters and the brain region investigated.

4.5. Future directions

Going forward, studies should employ a longitudinal study design to investigate glutamatergic alterations in patients with schizophrenia using ^{1}H-MRSI. It would be particularly useful to confirm and regionally isolate previously shown decreases in levels of glutamate and Glx following antipsychotic treatment with ^{1}H-MRSI. Also, longitudinal ^{1}H-MRSI studies should track patients with schizophrenia along various stages of illness (e.g. high-risk, FEP, chronic) and across the spectrum of antipsychotic treatment response. That being said, it is noteworthy that the need for additional longitudinal studies is not exclusive to ^{1}H-MRSI; rather, this is independent of technique and concomitantly applies to SVS studies and neuroimaging work as a whole. In addition, future work should investigate subcortical regions within which glutamatergic elevations have been previously shown (de la Fuente-Sandoval et al., 2011; Kraguljac et al., 2013; Plitman et al., 2016a). Importantly, the authors of 1 study included in this review have stated that they are currently implementing a whole-brain ^{1}H-MRSI sequence (Bustillo et al., 2016). Of relevance, recent work demonstrates whole-brain ^{1}H-MRSI using rapid k-space acquisition techniques and higher field strengths (i.e. 7 T) (Chiew et al., 2018; Hingerl et al., 2018; Maudsley et al., 2009); whole brain ^{1}H-MRSI should be considered in study designs going forward. Furthermore, the utilization of ^{1}H-MRSI results for the identification of ROIs to target for subsequent SVS work deserves consideration and testing. Finally, future studies should continue to consider the influence of tissue compartments by examining GM and WM voxels, as several included studies observed notable differences in this regard.

4.6. Conclusions

In the present work, existing studies assessing levels of glutamate, glutamine, and Glx using ^{1}H-MRSI in schizophrenia were reviewed and discussed. The findings of these studies generally suggest that glutamatergic elevations exist within frontal brain regions in patients with schizophrenia. Furthermore, the elevations in levels of glutamate, glutamine, and Glx that are frequently identified in early stages of illness, when patients' antipsychotic exposure is limited, appear to persist (to a lesser extent) in medicated patients with schizophrenia. This notion of persistent glutamatergic elevations in medicated patients provides support for their role as a trait marker of illness. Notably, the findings from the current review also shine light upon the importance of sufficient sample size.

There are noteworthy advantages and disadvantages of utilizing ^{1}H-MRSI instead of SVS to study glutamatergic activity in patients with schizophrenia. The key benefit of employing ^{1}H-MRSI is its broader spatial coverage, which is particularly advantageous in studying schizophrenia due to the many brain regions within which glutamatergic alterations have been previously identified, the involvement of both GM and WM in the illness pathophysiology, and the vast structural compromise that exists.

The employment of ^{1}H-MRSI may further improve our understanding of glutamatergic dysregulation in schizophrenia and its role within illness pathophysiology. This might contribute to the development of novel treatments seeking to modify the glutamatergic system; despite significant promise from the glutamate hypothesis of schizophrenia, limited effective glutamatergic therapeutic alternatives currently exist (Fusar-Poli et al., 2015; Iwata et al., 2015; Tiihonen and Wahlbeck, 2006). An improved understanding of glutamatergic disruptions utilizing ^{1}H-MRSI might also contribute towards improving selection of the

subset of patients for whom glutamatergic agents might be effective. Overall, there is a pressing need for additional ^{1}H-MRSI work to complement existing SVS studies; emphasis should particularly be placed towards utilizing longitudinal study designs, replicating existing results, and investigating subcortical regions.

Contributors

E.P. performed the literature search and analysis, and wrote the manuscript. E.G. also contributed to the literature search and analysis, contributed to writing, and critically reviewed and approved the final manuscript. M.L. contributed to writing, and critically reviewed and approved the final manuscript. J.N. contributed to writing, and critically reviewed and approved the final manuscript. M.M.C. supervised the work, contributed to writing, and critically reviewed and approved the final manuscript.

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