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Glutamatergic Abnormalities In Schizophrenia: a review of proton MRS findings

Eline M.P. Poels[a,b], **Lawrence S. Kegeles, MD, PhD**[a,b,c], **Joshua T. Kantrowitz, MD**[a,b], **Daniel C. Javitt, MD, PhD**[a,b], **Jeffrey A. Lieberman, MD**[a,b], **Anissa Abi-Dargham, MD**[a,b,c], and **Ragy R. Girgis, MD**[a,b,*]

[a]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA

[b]New York State Psychiatric Institute, New York, NY, USA

[c]Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY, USA

Abstract

The last fifteen years have seen a great increase in our understanding of the role of glutamate in schizophrenia (SCZ). The glutamate hypothesis focuses on disturbances in brain glutamatergic pathways and impairment in signaling at glutamate receptors. Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) is an MR-based technique that affords investigators the ability to study glutamate function by measuring *in vivo* glutamatergic indices in the brains of individuals with SCZ. ^{1}H-MRS studies have been performed comparing glutamatergic levels of individuals with SCZ and healthy control subjects or studying the effect of antipsychotic medications on glutamatergic levels. In this article we summarize the results of these studies by brain region. We will review the contribution of ^{1}H-MRS studies to our knowledge about glutamatergic abnormalities in the brains of individuals with SCZ and discuss the implications for future research and clinical care.

*Corresponding author. Address: 1051 Riverside Drive, Unit 31, New York, NY 10032; Tel: +1-212-543-5055; Fax: +1-212-568-6171; rg2290@columbia.edu (R.R. Girgis).

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Keywords

Schizophrenia; Glutamate; Glutamine; Glx; Magnetic Resonance Spectroscopy (MRS); NMDA

1. Introduction

Progress in neuroimaging techniques has contributed significantly to our knowledge about brain abnormalities in schizophrenia (SCZ). Findings from studies with structural Magnetic Resonance Imaging (MRI) have led to important knowledge about structural brain abnormalities in individuals with SCZ (Shenton et al., 2001). Nuclear medicine techniques such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have revealed key information about presynaptic hyperdopaminergia in striatum in SCZ (Howes et al., 2012). Functional MRI (fMRI) studies have identified key circuits involved in executive functioning in SCZ (Minzenberg et al., 2009). Diffusion Tensor Imaging (DTI) studies have identified important white matter abnormalities (Kubicki et al., 2007). Further, effective drug development necessitates the identification of biological markers to measure target engagement (Javitt et al., 2011), a task for which neuroimaging is critical.

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) is an MR-based technique that permits researchers to examine metabolites *in vivo* in the human brain. ^{1}H-MRS can be used to measure glutamate and its metabolites. The glutamate hypothesis of SCZ focuses on disturbances in brain glutamatergic pathways and impairment in signaling at glutamate receptors, including the N-methyl-D-aspartate (NMDA)-type glutamate receptor (NMDAR) and metabotropic glutamate receptors (mGluRs) (Chavez-Noriega et al., 2002; Kantrowitz and Javitt, 2010) and provides an alternative or complementary theory to the dopamine hypothesis (Davis et al., 1991; Weinberger, 1987) for the pathophysiology in SCZ. Evidence for this theory originates from studies with PCP and ketamine in the early 1960's. Both agents block the NMDAR and produce what would now be considered positive, negative and cognitive symptoms of SCZ (Javitt and Zukin, 1991; Luby et al., 1962). MRS affords investigators the ability to study the NMDAR by measuring *in vivo* glutamatergic indices in the brains of individuals with SCZ.

The objective of this article is to comprehensively review the findings from ^{1}H-MRS studies that measured glutamatergic indices in the brains of individuals with SCZ. To do so we searched the PubMed database using the following search term: (mrs OR spectroscopy OR mri) and (schizophrenia OR schizoaffective OR schizophreniform OR psychosis OR psychotic) and (glutamate OR glutamine OR glx) and included all original investigations that used ^{1}H-MRS to measure glutamatergic levels in individuals with SCZ. We also reviewed the bibliographies of the chosen articles and included any studies that were not included in our search. We focused our review on the glutamatergic indices glutamate (Glu), glutamine (Gln) and Glu+Gln (Glx). Notably, Glx refers to Glu plus Gln, except for those studies where we specifically note that it indicates Glu plus Gln plus GABA. All findings are summarized below by brain region. The results of some these studies are included in Table 1. We restricted our table to the regions of medial prefrontal cortex (MPFC), hippocampus, basal ganglia and thalamus as these are the regions in which studies have been consistent in showing differences between patients and controls.

2. Findings from MRS studies

2. 1 Frontal lobe

2.1.1 Dorsolateral prefrontal cortex—Studies performed with medicated patients show discrepant results. The majority of studies reported no differences between medicated patients and healthy control subjects whether measuring Glu, Gln or Glx in first-episode (FE) (Galinska et al., 2009; Goto et al., 2012), chronic (Block et al., 2000; da Silva Alves et al., 2011; Ohrmann et al., 2008; Rowland et al., 2009; Szulc et al., 2011) or childhood populations (Seese et al., 2011) in the dorsolateral prefrontal cortex (DLPFC) or the adjacent white matter (Ota et al., 2012). Other studies report increased levels of Glu and Gln in FE patients (Olbrich et al., 2008), chronic patients (Stanley et al., 1996; van Elst et al., 2005) and a patient group comprised of individuals at different stages of the illness (Rusch et al., 2008). Decreased levels of Glx were observed in a group of chronic medicated patients (Ohrmann et al., 2007; Ohrmann et al., 2005). One study reported elevated levels of Glx in elderly chronic medicated patients in the left frontal white matter (Chang et al., 2007). A twin study showed no difference in Glu levels in the DLPFC between probands (patients), co-twins and healthy control subjects (Lutkenhoff et al., 2010).

Studies with drug naïve patients consistently show no difference in glutamatergic levels between patients and healthy control subjects whether measuring Gln or Glx in FE patients (Ohrmann et al., 2007; Ohrmann et al., 2005; Stanley et al., 1996) or high risk subjects (Yoo et al., 2009). Kegeles et al. investigated the Glx concentrations in medicated patients, unmedicated patients, and healthy controls subjects, and found no differences in Glx concentrations between the three groups (Kegeles et al., 2012).

Three groups studied the direct effect of antipsychotic medications on glutamatergic levels in the DLPFC by measuring glutamatergic levels in the same patient group before and after treatment. Stanley et al. reported a decrease in Gln levels in FE patients after receiving antipsychotic medication for approximately 14 weeks (Stanley et al., 1996). Decreased Glx levels were observed in FE patients after 6 months of treatment with second generation antipsychotics (Goto et al., 2012). Szulc et al. reported no change in Glx levels of chronic patients between baseline scans and after 40 days of individually based antipsychotic treatment. When they divided the patient group into responders and non-responders, based on their clinical symptoms, they found lower Glx levels at baseline in the group of responders when compared to non-responders. (Szulc et al., 2011; Szulc et al., 2013).

Potential relationships between glutamatergic levels in the DLPFC and clinical/behavioral symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) (Kegeles et al., 2012; Ohrmann et al., 2005; Szulc et al., 2011; Szulc et al., 2012; Yoo et al., 2009), Brief Psychiatric Rating Scale (BPRS) (Olbrich et al., 2008; Rowland et al., 2009; Yoo et al., 2009), Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS) (Olbrich et al., 2008; Stanley et al., 1996) have been investigated. Most of these studies failed to find significant clinical correlations.

Negative correlations were observed in FE medicated patients between Glu levels and BPRS and SANS scores (Olbrich et al., 2008) and in chronic patients between Glu levels and Global Assessment Scale scores over 2 years (GAS2) (van Elst et al., 2005). Positive correlations were observed between the Auditory-Verbal Learning Test immediate recall scores and Glx levels in another sample when both chronic medicated and drug naïve FE patients were combined (Ohrmann et al., 2007) and between PANSS scores and Glx levels in chronic, medicated patients (Szulc et al., 2011).

In summary, there does not seem to be a clear pattern of glutamatergic abnormalities in the DLPFC of medicated patients with SCZ, while studies with unmedicated patients consistently show no difference in glutamatergic levels between patients and healthy control subjects. Clinical correlations were also either negative or inconsistent. There is a suggestion that medication treatment decreases glutamatergic indices, although further investigation is needed to confirm these findings.

2.1.2 Medial prefrontal cortex including anterior cingulate cortex—MRS voxels labeled as being placed in either the MPFC or anterior cingulate cortex (ACC) often overlap with the other region. Therefore, for this review, we have summarized the results of both regions together.

Elevated glutamatergic levels were observed in several studies performed in unmedicated patients. These studies reported elevated levels of Gln in FE drug naïve patients (Aoyama et al., 2011; Bartha et al., 1997; Theberge et al., 2002; Theberge et al., 2007) in this region, as well as increased GABA+Glu levels in chronic patients (Choe et al., 1994; Choe et al., 1996) in the adjacent white matter. However, one study reported no difference in Glu or Gln levels between FE drug naïve patients and healthy control subjects (Aoyama et al., 2011).

The majority of studies performed with chronic medicated patients (Bustillo et al., 2011; Kraguljac et al., 2012; Ohrmann et al., 2008; Ongur et al., 2008; Reid et al., 2010; Rowland et al., 2013; Shirayama et al., 2010; Wood et al., 2007) and one with FE medicated subjects (Bustillo et al., 2010) reported no differences in Glu, Gln or Glx levels between patients and healthy control subjects or decreased Glu levels in patients compared with healthy control subjects (Tayoshi et al., 2009; Theberge et al., 2004; Theberge et al., 2003). Kegeles et al. investigated the effect of medication status on Glx levels in the MPFC and compared medicated with unmedicated patients and healthy control subjects (Kegeles et al., 2012). Elevated Glx levels were found in unmedicated patients when compared to healthy control subjects, but no difference in Glx levels was found in medicated patients when compared to healthy control subjects.

Several studies measured glutamatergic levels in subjects at high risk of developing SCZ. Although most studies reported no differences in glutamatergic levels between high risk subjects and healthy controls whether measuring Glx (Keshavan et al., 2009; Purdon et al., 2008; Yoo et al., 2009) or Glu (Fusar-Poli et al., 2011; Valli et al., 2011), two studies reported increased Gln levels (Stone et al., 2009) and an increased Glu/Gln ratio (Tibbo et al., 2004) in high-risk, unmedicated subjects. A twin study showed lower Glu levels in probands (patients) and co-twins when compared to healthy controls (Lutkenhoff et al., 2010). Glx levels in individuals with childhood SCZ, some of whom were taking medications, were similar to those in healthy control subjects (Thomas et al., 1998).

An increased Gln/Glu ratio was observed in individuals with SCZ (Bustillo et al., 2011; Shirayama et al., 2010) compared with healthy control subjects, while others reported no difference in Gln/Glu ratio between patients and healthy control subjects (Bustillo et al., 2010; Ongur et al., 2008).

The direct effect of medication use on glutamatergic levels in the MPFC and ACC has also been examined. One study reported a decrease in GABA+Glu levels after four weeks to six months of treatment with typical or atypical antipsychotics in chronic patients (Choe et al., 1996). However, other studies reported no change in glutamatergic levels of chronic drug free patients after four weeks of treatment with risperidone (Szulc et al., 2005), in FE patients who were minimally medicated at baseline after 12 weeks of antipsychotic treamtent (Bustillo et al., 2010), or in drug naïve FE patients after 30 (Theberge et al., 2007)

or 80 (Aoyama et al., 2011) months of treatment with a variety of antipsychotic medications. Goff et al. studied the effect of switching from first generation antipsychotic medications to olanzapine in chronic patients and reported no difference in Glx levels after 8 weeks of treatment with olanzapine, with the exception of increased levels of Glx in a subgroup of responders (Goff et al., 2002). Egerton et al. investigated Glu levels in a group of FE patients after at least one course of treatment with antipsychotic medication (Egerton et al., 2012). The group was divided into patients in remission and patients who remained symptomatic. The non-remitted patients had higher levels of Glu in the ACC.

Several studies investigated potential relationships between glutamatergic levels in the MPFC and clinical/behavioral symptoms, as measured by the PANSS (Goto et al., 2012; Kegeles et al., 2012; Ota et al., 2012; Szulc et al., 2005; Tayoshi et al., 2009; Wood et al., 2007; Yoo et al., 2009), SANS and SAPS (Aoyama et al., 2011; Bartha et al., 1997; Bustillo et al., 2010; Goff et al., 2002; Shirayama et al., 2010; Theberge et al., 2002; Theberge et al., 2007), BPRS (Choe et al., 1996; Reid et al., 2010; Yoo et al., 2009) and the N-back working memory test (Kegeles et al., 2012). Most of these studies failed to find significant clinical correlations. Positive correlations were observed between glutamatergic levels and positive (Kegeles et al., 2012) and negative (Egerton et al., 2012) symptoms measured by the PANSS, a composite measure of cognition (Bustillo et al., 2011), symptoms measured by the BPRS total (Choe et al., 1996) and negative subscales (Reid et al., 2010), and score on the Wisconsin Card Sorting Test (WCST) (Ohrmann et al., 2008; Shirayama et al., 2010). A negative correlation was observed between Glu levels and the level of global functioning measured by the Global Assessment of Functioning (GAF) scale (Egerton et al., 2012).

In summary, it has consistently been reported that unmedicated patients have elevated glutamatergic levels in the MPFC compared with healthy control subjects. The pattern in medicated patients is less clear, although the majority of studies suggest that glutamatergic levels in medicated patients are similar to those in healthy control subjects. These observations suggest that medication treatment may decrease glutamatergic levels in the MPFC, or that higher glutamatergic levels are observed in individuals with greater levels of psychopathology. However, studies that have examined either phenomenon directly through longitudinal imaging of subjects in unmedicated and medicated states are few in number and do not consistently support either. Clinical correlations have been mostly negative.

2.2 Parietal & Occipital Lobe

Three studies examined glutamatergic levels in the parietal occipital cortex (POC) as one combined region of interest. One study reported increased Glx levels in a group of high risk adolescents without an Axis 1 diagnosis when compared to healthy control subjects (Keshavan et al., 2009). Other studies have reported no differences in Glx levels between FE patients and healthy control subjects (Goto et al., 2012) and no difference in Glu or Gln levels between chronic medicated patients and healthy control subjects (Ongur et al., 2008). Studies that investigated the occipital lobe as a separate region observed decreased Glx levels in adolescents with childhood SCZ (Thomas et al., 1998) and increased Glx levels in chronic medicated patients (Chang et al., 2007), when compared to healthy control subjects. Studies that focused on the parietal cortex as a separate region reported elevated (Ota et al., 2012) or normal Glx levels (Bustillo et al., 2011; Rowland et al., 2009) in chronic medicated patients compared to healthy control subjects. Bustillo et al. reported an increased Gln/Glu ratio in the parietal gray matter of chronic medicated patients (Bustillo et al., 2011).

To study the direct effect of second generation antipsychotics on Glx levels in the parietal occipital lobe Goto et al. scanned FE patients before and after six months of treatment (Goto et al., 2012). The authors observed no difference in Glx levels before and after treatment in

this region, although some patients who participated in this study were already medicated at the time of their first scan.

Relationships between glutamatergic levels in the POC and clinical/behavioral symptoms as measured by the PANSS (Goto et al., 2012; Ota et al., 2012), a composite measure of global cognition (Bustillo et al., 2011) and BPRS and SANS (Rowland et al., 2009) were investigated. Positive correlations were observed between Glx levels and a composite measure of cognition (Bustillo et al., 2011) and positive symptoms as measured by the PANSS (Ota et al., 2012).

In summary, there is no clear pattern of glutamatergic abnormalities in the parietal and occipital cortex.

2.3 Temporal lobe

Two studies measured glutamatergic levels of patients with SCZ in the superior or lateral temporal lobe. Both studies reported no differences in Glx levels between chronic unmedicated patients (Szulc et al., 2011) or childhood populations (Seese et al., 2011) and healthy control subjects.

Szulc et al. directly studied the effects of antipsychotic medications on glutamatergic levels in the infero-lateral region of the temporal lobe of chronic patients (Szulc et al., 2011). MRS was performed after a 7–14 day medication washout and again after 40 days of treatment with antipsychotic medication. This study reported decreased levels of Glx after treatment. When the same group divided patients into responders and non-responders, based on their clinical symptoms, they found no difference in baseline Glx concentrations between responders and non-responders (Szulc et al., 2013). They also observed no correlations between Glx levels and clinical symptoms measured by PANSS (Szulc et al., 2012).

In summary, there are no patterns of glutamatergic abnormalities in the temporal lobe of patients with SCZ. However, there is some evidence to suggest that treatment with antipsychotic medications may decrease levels of Glx.

2.4 Hippocampus/Medial Temporal Lobe

Several studies measured glutamatergic levels in the hippocampus or in temporal lobe regions that primarily include hippocampus and/or medial temporal lobe. Most studies reported no differences in glutamatergic levels between medicated chronic patients (Hutcheson et al., 2012; Kraguljac et al., 2012; Rusch et al., 2008), medicated (Olbrich et al., 2008) and drug naïve FE patients (Bartha et al., 1999), or between drug naïve (Fusar-Poli et al., 2011; Valli et al., 2011) or partly medicated high risk populations (Stone et al., 2009) and healthy control subjects, in either Glu or Gln. A twin study showed no differences in hippocampal Glu levels between probands (patients), co-twins and healthy control subjects (Lutkenhoff et al., 2010). Galinska et al. combined the hippocampus and temporal cortex in one region of interest and reported no differences in Glx levels between FE medicated patients and healthy control subjects (Galinska et al., 2009).

In contrast, three studies have reported increased Glu (van Elst et al., 2005) and Glx (Chang et al., 2007; da Silva Alves et al., 2011) levels in chronic medicated patients. Another recently published study reported increased Glx levels in unmedicated patients, as well as an important negative correlation between Glx and hippocampal volume (Kraguljac et al., 2013).

Kegeles et al. investigated the laterality index of the Glx to Choline (Cho) ratio in chronic patients (Kegeles et al., 2000). Glx was a combined measure of Glu, Gln and γ-aminobutyric

acid (GABA). The Glx/Cho laterality index showed a right-sided excess in the hippocampus of patients compared to healthy control subjects.

Two studies investigated the direct effect of medication on glutamatergic levels in the hippocampus and temporal lobe as one combined region. Szulc et al. scanned chronic patients twice-once after 7 days of medication wash-out and a second time after at least four weeks of treatment with risperidone (Szulc et al., 2005). They observed no change in Glx (a combined measure of Glu, Gln and GABA) levels after treatment in this study. Another group studied the effect of 12 weeks of Ethyl-eicosapentaenoic acid (E-EPA), an omega-3 fatty acid, on glutamatergic levels in FE atypical medicated patients (Berger et al., 2008). They observed an increase in Glx levels after treatment in the left hippocampus and temporal lobe of patients.

Several studies investigated possible relationships between glutamatergic levels in the hippocampus and clinical/behavioral symptoms. Rusch et al. reported both negative correlations between Glu levels and the number of completed categories and the percentage of conceptual level responses on the WCST and positive correlations between perseverative errors on the WCST and Glu levels (Rusch et al., 2008). A positive correlation was observed between Glx levels and symptoms as measured by the PANSS negative subscale (Szulc et al., 2005), while a negative correlation was observed between Glu levels and GAS2 score (van Elst et al., 2005). No significant correlations were observed between BPRS or SANS scores and Glu levels (Olbrich et al., 2008), the ratio of Glu/Cho and symptoms as measured by the PANSS (Kegeles et al., 2000) or Glx levels and BPRS and RBANS scores (Kraguljac et al., 2013).

In summary, studies of glutamatergic levels in hippocampus are mostly negative although one recent study showed increased Glx in unmedicated patients as well as a negative correlation between Glx and hippocampal volume. Several reports suggest greater levels of glutamatergic indices in chronic medicated patients, although one longitudinal study reported no effect of medication in this population. Additionally, some investigations suggest relationships between elevated glutamate levels and worse executive functioning and global clinical state, although these findings need to be replicated.

2.5 Centrum Semiovale

Rowland et al. measured Glx levels in the Centrum Semiovale (CSO) region of chronic medicated patients and healthy control subjects and reported no difference in Glx concentration between the two groups. This study did report lower Glx concentrations in patients when Glx concentrations were averaged across the CSO and the ACC (Rowland et al., 2013).

2.6 Thalamus

The majority of studies measuring glutamatergic levels in thalamus reported no differences between patients and control subjects whether measuring Glu, Gln or Glx in chronic drug free patients (Szulc et al., 2011), FE medicated patients (Galinska et al., 2009), FE drug naïve patients (Bustillo et al., 2010) or high risk populations (Keshavan et al., 2009; Valli et al., 2011; Yoo et al., 2009). Increased levels of Gln were found in FE drug naïve patients (Aoyama et al., 2011; Theberge et al., 2002; Theberge et al., 2007) and chronic medicated patients (Theberge et al., 2003) compared with healthy control subjects. Decreased levels of Glu and Glx (Stone et al., 2009) and Glu (Fusar-Poli et al., 2011) were reported in high risk populations.

Egerton et al. compared groups of remitted FE patients and non-remitted FE patients and reported no difference in Glu levels between these groups in the thalamus (Egerton et al., 2012).

The direct effect of medication on glutamatergic levels in the thalamus has also been investigated. Szulc et al. scanned chronic patients before and after at least 4 weeks of treatment with risperidone and reported no change in Glx (which included GABA) levels (Szulc et al., 2005). Two other studies also reported no change in glutamatergic levels of FE patients after treatment with a variety of antipsychotic medications, whether measuring Glu or Gln (Aoyama et al., 2011) or the Gln/Glu ratio (Bustillo et al., 2010), while one study did report a decrease in thalamic Gln levels after 30 months of treatment with antipsychotics (Theberge et al., 2007). One group measured Glx concentrations in chronic patients before and after 40 days of treatment with antipsychotic medication and reported no difference in Glx concentrations (Szulc et al., 2011). The same group divided patients into responders and non-responders, based on their clinical symptoms, and reported no difference in Glx levels between these two patient groups (Szulc et al., 2013).

Several studies investigated the possible relationships between glutamatergic levels in the thalamus and clinical/behavioral symptoms as measured by the SANS and SAPS (Aoyama et al., 2011; Bustillo et al., 2010; Theberge et al., 2002; Theberge et al., 2007), PANSS (Szulc et al., 2005; Szulc et al., 2011; Szulc et al., 2012; Yoo et al., 2009) and GAF scale (Egerton et al., 2012). No significant correlations were reported.

In summary, the majority of studies show no difference in glutamatergic levels in thalamus between patients and control subjects. Similarly, while there do not appear to be relationships between glutamatergic levels and symptomatology in the thalamus, additional studies need to be performed before stronger conclusions can be made.

2.7 Cerebellum

One study measured Glu and Glx levels in the cerebellum of a group of drug naïve prodromal and FE patients (de la Fuente-Sandoval et al., 2011) and reported no difference in Glu or Glx levels between patients and healthy control subjects in this region. The same study observed no relationships between Glu or Glx levels and clinical symptoms measured by PANSS and the Structured Interview for Prodromal Syndromes (SIPS). The same group measured Glu and Glx levels in cerebellum in a group of drug naïve FE patients and reported elevated Glu, but not Glx, levels in patients compared with healthy control subjects, as well as a decrease in Glu levels after four weeks of treatment with risperidone (de la Fuente-Sandoval et al., 2013b). No significant correlations were observed between Glu levels and PANSS scores (de la Fuente-Sandoval et al., 2013b).

2.8 Basal Ganglia and Substantia Nigra

Studies with chronic medicated patients report no differences in Glx (Block et al., 2000) or Glu and Gln levels (Tayoshi et al., 2009) between patients and healthy control subjects in basal ganglia. A study with FE patients reported higher levels of Glx in patients compared with healthy control subjects (Goto et al., 2012). Some but not all of these patients were medicated. Two studies specifically investigated the caudate region and reported higher levels of Glu in the dorsal caudate of high risk and prodromal drug naïve patients (de la Fuente-Sandoval et al., 2011) but no difference in Glx levels between a group of high risk subjects and healthy control subjects (Keshavan et al., 2009). Two studies focused on the putamen (Yamasue et al., 2003) and the substantia nigra (Reid et al., 2013) and reported no difference in Glx concentrations between chronic medicated patients and healthy control subjects. One longitudinal study of antipsychotic-naïve individuals with FE psychosis

demonstrated that Glu and Glx levels in associative striatum were elevated at baseline and that Glu levels decreased after four weeks of treatment with risperidone (de la Fuente-Sandoval et al., 2013b).

A follow-up study was done with high risk patients to determine whether or not they would transition to a psychotic disorder (de la Fuente-Sandoval et al., 2013a). Glutamatergic levels were measured again after two years and higher levels of Glu were observed in the psychosis transition group when compared to the non-transition group and healthy control subjects.

Goto et al. observed no direct effect of treatment with second generation antipsychotics on glutamatergic levels in the basal ganglia of FE patients when measuring Glx levels in this region before and after 6 months of treatment (Goto et al., 2012), although some patients who already receiving medications when they obtained their baseline scans.

Some studies investigated possible relationships between glutamatergic levels and clinical/behavioral symptoms as measured by PANSS (de la Fuente-Sandoval et al., 2013b; de la Fuente-Sandoval et al., 2011; Goto et al., 2012; Tayoshi et al., 2009), SIPS (de la Fuente-Sandoval et al., 2013a; de la Fuente-Sandoval et al., 2011), BPRS and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Reid et al., 2013). Most studies failed to find significant correlations. Reid et al. found a significant correlation between the Glx/creatine ratio and the RBANS total score in healthy control subjects, while the same correlation was not found in individuals with SCZ. de la Fuente-Sandoval reported negative correlations (i.e., opposite) between changes in PANSS General Psychopathology scores and changes in both Glu and Glx levels in associative striatum of FE subjects after four weeks of treatment with risperidone (de la Fuente-Sandoval et al., 2013b). They also reported a correlation trend between Glu in the associative striatum at 4 weeks and the PANSS positive subscale score at 4 weeks.

In summary, there is the suggestion that glutamatergic levels in the basal ganglia are elevated in high risk and drug free FE patients, and that these levels may decrease with antipsychotic treatment, although these findings warrant replication.

3. Discussion

The data reviewed herein support findings of regional glutamatergic abnormalities in SCZ. Namely, they suggest elevated levels of glutamatergic indices in MPFC and basal ganglia (especially associative striatum) in medication-naïve or medication free patients, and a possible relationship between elevated Glx in hippocampus of unmedicated patients and decreased hippocampal volume. Clinical and neuropsychological correlations have been widely performed but are generally negative, except for in hippocampus/medial temporal lobe in which elevated glutamate levels are related to worse executive functioning and global clinical state.

Such findings may have important implications for both research and clinical practice. For example, elevated glutamate in the MPFC or hippocampus in medication free individuals may identify those who are more likely to respond to antipsychotic medications, while elevated glutamate in associative striatum may identify high risk individuals who are more likely to progress to psychosis. Such findings also have implications for future research and drug development. For example, studies showing changes in glutamatergic indices after treatment with antipsychotic medications suggest that ^{1}H-MRS can be used to measure target engagement of novel, putative glutamatergic agents. In particular, the results of several investigations suggest that treatment with antipsychotic medications decreases levels of glutamatergic indices (de la Fuente-Sandoval et al., 2013b; Kegeles et al., 2012), the

implication of which may be that in the future researchers and clinicians will be able to utilize non-invasive brain imaging such as ^{1}H-MRS to assess treatment response rather than rely solely on clinical assessment. Additionally, some putatively glutamatergic agents such as N-acetylcysteine (Berk et al., 2008) and bitopertin (Umbricht et al., 2010) have shown early promise in clinical trials. The success of these and other experimental agents will depend, in part, on the ability of researchers to demonstrate that these agents engage the glutamate system and identify subgroups of patients for whom agents that engage the glutamate system are most likely to be effective. However, these implications remain speculative and before further work is done, many of the findings reported above will require replication and extension.

In addition, numerous limitations are present which constrain our ability to interpret these findings. For example, ^{1}H-MRS has limited spatial resolution, and presents a whole tissue measure of neurochemical, rather than distinguishing between intrasynaptic, extrasynaptic, or intracellular compartments. In addition, studies used differing field strengths, spectral fitting methods, and glutamatergic indices.

Despite these limitations, ^{1}H-MRS has much to offer for understanding the role of glutamate in SCZ, and future research will benefit from numerous technological innovations, including stronger magnets and more sophisticated methods, such as [^{13}C] MRS in which anaplerotic mechanisms and the glutamate-glutamine cycle can be measured (Mason et al., 2007). Future studies will also need to include more longitudinal assessment of subjects in the drug naïve FE state and in the high risk or prodromal state, and follow them to conversion to psychosis. Moreover, multimodal approaches (i.e., combining ^{1}H-MRS with PET and/or fMRI etc.) would help elucidate the relationships between neurochemical and functional deficits and patterns (Demjaha et al., 2013). Finally, as glutamatergic neurotransmission is genetically linked to SCZ (Harrison and Weinberger, 2005), an additional strength of MRS could be as a method to determine how alterations in specific genetic risk factors may be linked to glutamatergic dysfunction. Imaging genetics has been shown to be an effective and productive methodology for functional imaging (Egan et al., 2001; Meyer-Lindenberg et al., 2006), and its role in ^{1}H-MRS imaging in SCZ remains to be determined. However, the great variability in results reported in ^{1}H-MRS studies suggests a potentially important contribution from imaging genetics to the explanation of this heterogeneity. Therefore, despite the limitations of ^{1}H-MRS, we remain in the infancy of glutamatergic ^{1}H-MR and can predict that it will provide a greater understanding of glutamatergic function in SCZ.

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Table 1

Summary of cross-sectional studies measuring Glutamatergic levels in the MPFC (including ACC), Hippocampus, Basal Ganglia, and Thalamus.

Source	Field strength	Number PN/PF/PM/HC	Results Glu/Gln/Glx			
			MPFC	Hipp	Tha	BG
Aoyama 2011	4.0 T	17/0/0/17	-/-/na		-/↑/na	
Bartha 1997	1.5 T	10/0/0/10	-/↑/n.a.			
Bartha 1999	1.5 T	11/0/0/11		-/-/na		
Block 2000	1.5 T	0/0/25/19				na/na/-
Bustillo 2010	4.0 T	14/0/0/10	-/-/na		-/-/na	
Bustillo 2011	4.0 T	0/0/30/28	na/na/-			
Chang 2007	4.0 T	0/2/21/22		na/na/↑[a]		
Choe 1994[b]	1.5 T	23/0/010	↑/na/na			
Choe 1996[b]	1.5 T	37/18/0/20	↑/na/na.			
de la Fuente Sandoval 2011	3.0 T	36[c]/0/0/40				↑/na/-
de la Fuente Sandoval 2013	3.0 T	24/0/0/18				↑/na/↑
Fusar-Poli 2011[d]	3.0 T	24/0/0/17	-/na/na	-/na/na	↓/na/na	
Galinska 2009	1.5 T	1/0/29/19		na/na/-	na/na/-	
Goto 2012	3.0 T	16[e]/18				na/na/↑
Hutcheson 2012	3.0 T	0/0/28/28		na/na/-		
Kegeles 2012[f]	3.0 T	9/7/16/22	na/na/↑			
Keshavan 2009[d]	1.5 T	40/0/0/46	na/na/-		na/na/-	na/na/-
Kraguljac 2012	3.0 T	0/0/48/46	na/na/-	na/na/-		
Kraguljac 2013	3.0 T	11/16/0/27		na/na/↑		
Lutkenhoff 2010	3.0 T	0/0/9/21	↓/na/na	-/na/na		
Ohrmann 2008	1.5 T	0/0/43/37	na/na/-			
Olbrich 2008	2.0 T	0/0/7/16		-/-/na		
Öngür 2008	4.0 T	0/017/21	-/-/na			
Purdon 2008[d]	3.0 T	15/0/0/14	-/na/-			
Reid 2010	3.0 T	0/0/26/23	na/na/-			
Reid 2013	3.0 T	0/0/35/22				na/na/-

Source	Field strength	Number PN/PF/PM/HC	Results Glu/Gln/Glx			
			MPFC	Hipp	Tha	BG
Rowland 2012	3.0 T	0/0/21/20	na/na/-[g]			
Shirayama 2010	3.0 T	0/1/18/18	-/-/na			
da Silva Alves 2011[h]	3.0 T	0/0/9/16		-/-/↑		
Stone 2009[d]	3.0 T	19/6/2/27	-/↑/-	-/-/-	↓/-/↓	
Szulc 2011	1.5 T	0/0/42/26			na/na/-	
Tayoshi 2009	3.0 T	0/0/30/25	↓/-/na			-/-/na
Tebartz van Elst 2005	2.0 T	0/0/18/28[i]		↑/-/na		
Théberge 2002	4.0 T	21/0/0/21	-/↑/na		-/↑/na	
Théberge 2003	4.0 T	0/0/21/21	↓/↓/na		-/↑/na	
Thomas 1998[j]	1.5 T	3/7/3/12	na/na/-			
Valli 2011[d]	3.0 T	22/0/0/14	-/na/na	-/na/na	-/na/na	
Wood 2007	3.0 T	0/2/13/14	na/na/-			
Yamasue 2003	1.5 T	0/0/16/15				na/na/-
Yoo 2009[d]	1.5 T	22/0/0/22	na/na/-		na/na/-	

PN = number of drug naïve patients

PF = number of drug free patients

PM = number of medicated patients

HC = number of healthy control subjects

MPFC = Medial Prefrontal Cortex including the Anterior Cingulate Cortex, Hipp = Hippocampus, Tha = Thalamus, BG = Basal Ganglia

Glu = Glutamate, Gln = Glutamine, Glx = Glu + Gln

- = no difference

na = not analyzed

↑ = higher levels

↓ = lower levels

[a] Significant higher Glx levels only in left hippocampus, not in right hippocampus

[b] Glutamatergic levels including GABA

[c] Subject group of 18 drug naïve FEP and 18 drug naïve high risk subjects with prodromal symptoms

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[d] Study with high-risk patients

[e] The number of medicated vs. unmedicated patients is not clearly described in this paper. In addition, the specific number of patients in general is not clearly described in this paper.

[f] Results are seen only in unmedicated patients, not in medicated patients

[g] Decreased Glx levels were observed in patients when concentrations were averaged over the CSO and ACC

[h] Results of comparison between SCZ patients with 22q11 deletion syndrome and healthy control subjects

[i] Smaller numbers of subjects were used for specific neurochemical analyses due to several scans not meeting quality criteria. Analysis for Glu was done with 8 SCZ and 16 healthy controls and analysis for Gln was done with 9 SCZ and 13 healthy controls.

[j] Subjects with childhood schizophrenia