A meta-analysis of ultra-high field glutamate, glutamine, GABA and glutathione in psychosis: Implications for studies of psychosis risk

Valerie J. Sydnor[1], **David R. Roalf, PhD**[1,2,*]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, 19104

[2]Lifespan Brain Institute at the Children's Hospital of Philadelphia & the University of Pennsylvania, Philadelphia, PA, 19104

Abstract

Ultra-high field proton magnetic resonance spectroscopy (^{1}HMRS) offers a unique opportunity to measure the concentration of neurometabolites implicated in psychosis (PSY). The extant 7T ^{1}HMRS literature measuring glutamate-associated neurometabolites in the brain in PSY *in vivo* is small, but a comprehensive, quantitative summary of these data can offer insight and guidance to this emerging field. This meta-analysis examines proton spectroscopy (^{1}HMRS) measures of glutamate (Glu), glutamine (Gln), glutamate+glutamine (Glx), gamma aminobutyric acid (GABA), and glutathione (GSH) across 255 individuals with PSY (121 first episode) and 293 healthy comparison participants (HC). While all five neurometabolites were lower in PSY as compared to HC, only Glu (Cohen's d = −0.18) and GSH (Cohen's d = −0.21) concentrations were significantly lower in PSY, whereas concentrations of Gln, Glx, and GABA did not significantly differ between groups. Notably, ^{1}HMRS methodological choices and sample demographic characteristics did not impact study-specific effect sizes for PSY-related Glu or GSH differences. This review thus provides further evidence of neurometabolite dysfunction in first episode and chronic PSY, and thereby suggests that Glu and GSH abnormalities may additionally play a role in more incipient stages of the disorder: in clinical high risk stages. Additional 7T neurochemical imaging studies in larger, longitudinal, and unmedicated samples and in youth at risk for developing psychosis are needed. Such studies are critical for elucidating the neurodevelopmental

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and clinical time course of PSY-related neurometabolite alterations, and for assessing the potential for implicated metabolites to serve as druggable targets for decreasing PSY risk.

1.0 Introduction

Psychosis (PSY) is a complex brain disorder that typically presents in adolescence or early adulthood (Casey et al., 2014; Insel, 2010; Rapoport et al., 2012) that has a devastating impact on social, occupational, and daily functioning and large health costs (Wu et al., 2005; Zeidler et al., 2012). PSY is associated with progressive gray matter loss (Bora et al., 2011; Gur et al., 2000), reduced cortical neuropil density (Selemon and Goldman-Rakic, 1999), altered dopamine receptor availability (Laruelle et al., 2006; Poels et al., 2014), and abnormal excitatory and inhibitory neurotransmitter functioning (Coyle, 2006; Lewis and Moghaddam, 2006; Marsman et al., 2013; Moghaddam, 2004; Remington et al., 2011). Hence, neural circuit architecture and neurotransmission appear to be abnormal in PSY. Structural and neurochemical alterations have also been found, to a lesser extent, in youth at clinical high risk for PSY (CHR) (Allen et al., 2015; Egerton et al., 2014; Roalf et al., 2017, p. 201; Satterthwaite et al., 2016). CHR individuals exhibit brief or attenuated psychotic symptoms, which evolve into frank PSY in approximately 15–20% of individuals at one year (Fusar-Poli et al., 2016, 2012), 20–30% of individuals at two years (Fusar-Poli et al., 2016, 2012), and 35% of individuals at three to ten years following initial presentation to clinical services (Fusar-Poli et al., 2012; Nelson et al., 2013), with greatest transition risk occurring within the first two years (Fusar-Poli et al., 2016; Kempton et al., 2015; Nelson et al., 2013). There is evidence that the neuroetiological mechanisms associated with both PSY and CHR begin to emerge during early development, leading to the appearance of more apparent symptoms in the context of adolescent neuromaturation (Chung and Cannon, 2015; McGlashan and Hoffman, 2000). Mitigating PSY-related dysfunction while the brain is still developing may thus help to reduce the number of CHR individuals who convert to PSY, making identification of neural targets and corresponding interventions paramount.

There is a significant literature supporting the dopamine hypothesis of PSY, which was first proposed over 40 years ago (Howes and Kapur, 2009). Contemporary evidence furthermore indicates that dysregulation of the dopamine system in PSY and CHR may occur secondarily to deficits in glutamate (Glu) function (Poels et al., 2014). Interest in elucidating the role of Glu in the pathogenesis of PSY first emerged due to findings that phencyclidine (NMDA receptor antagonist), ketamine (NMDA receptor antagonist), and −9-THC (transiently disturbs Glu and gamma aminobutyric acid (GABA)) have psychotomimetic properties, inducing both positive and negative symptoms similar to those seen in PSY (Bossong and Niesink, 2010, p. 20210; D'Souza et al., 2004; Frohlich and Van Horn, 2014; Kraguljac et al., 2017; Krystal et al., 1994; Tsai and Coyle, 2002).

Glu is the main excitatory neurotransmitter in the brain, present at approximately 80% of synapses, and it is additionally essential for cellular energy metabolism (Coyle, 2006; Curtis and Johnston, 1974; Ereci ska et al., 1990; McEntee and Crook, 1993; Robbins and Murphy, 2006). Glu metabolism dynamically influences other neurochemicals, including glutamine (Gln), GABA, and glutathione (GSH). Glu released into the synapse and extrasynaptic space is taken up into astrocytes and converted to Gln, preventing excitotoxic cell death due to excess synaptic Glu. Gln is then converted back to Glu in both excitatory and inhibitory neuron presynaptic terminals. In inhibitory terminals, the predominant inhibitory neurotransmitter GABA is produced from Glu by the enzyme glutamate decarboxylase; GABA plays an integral role in maintaining the balance of excitation-inhibition throughout the brain. Finally, Glu is additionally incorporated into glutathione (GSH), an important antioxidant that protects the brain from oxidative stress. Alterations in Glu levels in the brain, such as those proposed to occur in PSY, may therefore co-occur with changes in GABA, Gln, and GSH, leading to multifaceted and detrimental neurobiological effects. Systematic investigation of this entire group of neurochemicals in prodromal and early PSY may therefore provide important and complimentary information.

Proton magnetic resonance spectroscopy (^{1}HMRS) techniques can be used to quantify Glu, GABA, and related neurometabolite levels *in vivo*. While a number of studies have applied ^{1}HMRS to study Glu-related metabolites in PSY (and some in CHR), results are somewhat heterogeneous (Merritt et al., 2016), and the vast majority of studies have been conducted at 3T. Recent improvements in MRI technology, particularly the use of ultra-high field (UHF, 7Tesla) magnets, has expanded and enhanced *in vivo* application of ^{1}HMRS techniques. As reviewed in Godlewska et al. (Godlewska et al., 2017), 7T ^{1}HMRS offers enhanced spectral resolution, thereby producing more specific and reliable metabolite measurements than can be resolved at lower magnetic fields (Godlewska et al., 2017; Terpstra et al., 2016). Moreover, 7T ^{1}HMRS allows for increased metabolite sensitivity, improved image resolution, and approximately 1.6 times higher signal-to-noise ratio (SNR) compared to 3T (Godlewska et al., 2017). Critically, these improvements in specificity, sensitivity, and SNR at 7T are particularly significant for Glu, Gln, GABA, and GSH. For example, Glu, Gln, and GABA resonances can be more reliably distinguished at 7T, preventing the need for one combined measurement of Glu+Gln (i.e., "GLX"), and facilitating accurate measurement of GABA. Promisingly, studies harnessing UHF imaging to investigate PSY have begun to emerge over the past few years (Brandt et al., 2016, p. 20; Kumar et al., 2018; Marsman et al., 2014; Overbeek et al., 2019; Posporelis et al., 2018; Reid et al., 2018; Roalf et al., 2017; Rowland et al., 2016; Taylor et al., 2015; Thakkar et al., 2017; Wang et al., 2019). Here, we review these studies in order to provide insight into whether concentrations of the brain's main excitatory and inhibitory neurotransmitters and associated neurometabolites are altered in PSY.

This review takes the form of a quantitative meta-analysis of existing 7T ^{1}HMRS studies examining Glu-related neurometabolites in PSY. This is a relatively small, evolving, but important area of research. By consolidating early results across studies, this meta-analysis aims to provide a more comprehensive estimate of neurochemical differences between healthy individuals and those with PSY. We believe this will provide insight into the

potential utility of UHF ^{1}HMRS for understanding CHR and psychosis onset, while simultaneously shedding light on possible neurochemical targets for intervention.

2.0   Material and Methods

The report and extraction of relevant articles and accompanying data followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting standards (Supplemental Figure 1) (Stroup et al., 2000). The search strategy included an initial broad search in PubMed, MEDLINE, PsychINFO, and Google Scholar databases using the following search criteria: "psychosis/schizophrenia/clinical high risk for psychosis" AND "7T/UHF" AND "glutamate (Glu)/glutamine (Gln)/Glutamate+Glutamine (Glx)/GABA" OR "spectroscopy (HMRS)", OR "brain". The search was limited to articles published or in press prior to January 31, 2020 that were written in English and that enrolled human participants. A manual review of articles was additionally performed utilizing cross-references from identified original articles and reviews.

Studies included in this meta-analysis contained the following data: 1) experimental ^{1}HMRS measurement of Glu, Gln, Glx (i.e. Glu+Gln), GABA, or GSH in PSY; 2) corresponding ^{1}HMRS measurement in a healthy comparison (HC) group of unrelated participants with no history of major medical, neurological, or psychiatric conditions, and 3) statistical information for calculating effect sizes. DRR reviewed potential publications for inclusion based on the aforementioned criteria. Consensus of both authors was needed to exclude an article. We identified nine (n = 9) publications (Table 1) for inclusion that reported group comparisons (PSY v. HC) of Glu, Gln, Glx, GABA, and/or GSH ^{1}HMRS measurements. One additional article was considered (Overbeek et al., 2019) but ultimately excluded given that the data overlapped almost entirely with an included manuscript (Reid et al., 2018). Across all nine included publications, there was a combined total of 61 effects (k). Examination of all 61 effects revealed that 59 effects utilized absolute neurometabolite concentrations, while 2 effects from Marsman et al. (2014) utilized creatine-normalized ratios (i.e. GABA/Creatine ratio). To ensure data type homogeneity in our meta-analysis, we conducted analyses using absolute concentration effects only (k = 59). DRR initially extracted relevant data from publications, and VJS quality checked all extracted data for accuracy. Variables extracted for meta-analytic analysis included ^{1}HMRS concentration values and standard deviations, neurometabolite measured, ^{1}HMRS sequence type, ^{1}HMRS voxel size, brain region of interest (ROI), mean age of the PSY and HC samples, and sample sex distribution. Data used in this meta-analysis are available in the Supplemental Materials.

2.1   Statistical Analyses

An initial meta-analysis was conducted that included all 9 studies and all 5 neurometabolites to determine an overall effect, followed by meta-regression and analyses of publication bias. All analyses were carried out in Comprehensive Meta-Analysis version 2.21.064 (Biostat, 2005) with standard random-effects models. Neurometabolite concentration differences between PSY and HC participants were standardized using Cohen's d effect sizes (calculated as the difference between the two raw mean scores divided by the pooled standard deviation). Confidence intervals (CI) were additionally calculated for each effect

size. Studies were weighted according to their inverse variance estimates when calculating effect sizes to control for study sample size. Effect sizes can be classified as small (d = ±0.2), medium (d = ±0.5), or large (d ±0.8) (Cohen, 1988). Here, a negative effect size denotes lower neurometabolite level in PSY relative to HC. Homogeneity of effect sizes across studies was assessed using the Cochran Q-statistic (Hedges and Olkin, 1985).

2.1.1   Moderator Variables and Meta-regression—Meta-regression was used to investigate potential moderating variables, given that substantial heterogeneity was observed in the initial meta-analytic result. The following moderator variables were assessed via meta-regression: (1) neurometabolite studied (Glu, Gln, Glx, GABA, GSH), (2) ^{1}HMRS protocol, (3) brain ROI, (4) ^{1}HMRS acquisition voxel size (mm^3), (5) echo time, (6) age, and (7) sex.

2.1.2   Analysis of Publication Bias—Meta-analytic results are susceptible to influence from publication bias (i.e. bias that arises when studies with large effects are overrepresented in the literature compared to similar studies with small or null effects). Publication bias was evaluated using complimentary methods: (1) funnel plot: an asymmetric scatterplot of effect size vs. study precision is indicative of publication bias; (2) adjusted rank-correlation (i.e. Spearman) test according to the methods of Begg and Mazumdar (Begg and Mazumdar, 1994), Egger et al. (Egger et al., 1997), and Duval and Tweedie (Duval and Tweedie, 2000): a high correlation between the effect size and corresponding sampling variances is indicative of publication bias; and (3) a post-hoc trim-and-fill method including calculation of a fail-safe N (Duval and Tweedie, 2000). The trim-and-fill method is a funnel plot-based approach that "trims" outlier studies from the plot and "fills" in potentially missing studies, allowing for estimation of a publication bias-adjusted meta-analytic effect size. This method controls for the possibility that certain studies are outliers, while additionally considering potentially unpublished data (i.e. "file drawer" studies).

3.0   Results

3.1   Summary of Extant Literature

Nine 7T studies comparing neurometabolite concentrations between HC and PSY groups were included in this meta-analysis. Study details including participant demographics, patient characteristics, and ^{1}HMRS acquisition parameters are presented by study in Table 1. Data from 293 HC and 255 PSY participants (including 121 first episode patients within 24 months of PSY onset) were combined for the overall meta-analysis; this analysis does not contain data from CHR individuals due to lack of availability. The vast majority of PSY participants included in this meta-analysis were being treated with antipsychotic medications (both typical and atypical), with reported antipsychotic treatment rates ranging from 80–100% across studies.

The average age of HC and PSY individuals was 27.7 and 28.4 years, respectively. Most available studies were relatively small (< 30 individuals per group), however the most recently published study had a robust (n = 172) sample size (Wang et al., 2019). ^{1}HMRS data was most frequently collected from the anterior cingulate cortex (ACC; 7/9 studies); no other ROI was reported in more than three studies. Average ROI size for ^{1}HMRS acquisition was 11,269 mm^3. Stimulated echo acquisition mode (STEAM) protocols with a short echo

time (< 20 ms) were most commonly used to acquire data (7/9 studies). Glu concentration was reported in all studies, Gln in 7/9, GABA in 5/9, Glx in 2/9, and GSH in 5/9.

3.2 Overall Meta-analysis

The overall meta-analysis investigating differences between HC and PSY participants across all five neurometabolites (Glu, Gln, Glx, GABA, and GSH) revealed an overall significant but small meta-analytic effect size (k = 59, d = −0.13, 95% CI = −0.21 < δ < −0.06; z = 3.64, p < 0.001), indicating that metabolite levels were lower in PSY patients. However, an analysis of effect size homogeneity indicated that study-specific effect sizes were significantly heterogeneous ($Q_B[58]$ = 84.4, p = 0.013).

3.3 Moderator Analyses

Given that variability in study-specific effect sizes across all neurometabolites differed more than would be expected from sampling error alone, a moderator analysis was performed that accounted for neurometabolite type. Effects sizes by study and neurometabolite are shown in Figure 1. Effect sizes for each neurometabolite were homogeneous in direction, as all five neurometabolites were lower in PSY as compared to HC ($Q_B[4]$ = 5.01, p = 0.29). Only Glu (d = −0.18, 95% CI = −0.32 < δ < −0.04, k = 18; Z = 2.59, p = 0.010) and GSH (d = −0.21, 95% CI = −0.36 < δ < −0.06, k = 11; Z = 2.75, p = 0.006), however, were significantly lower in PSY (HC > PSY, Figure 2), i.e., GABA, Glx, and Gln concentrations did not significantly different between groups. Effects sizes for all neurometabolites are shown in Supplemental Table 1. Given these results, additional moderator analyses were performed for both Glu and GSH.

No additional moderator analyses were significant, indicating that meta-analytical effect sizes for Glu and GSH were not significantly influenced by ^{1}HMRS protocol (e.g. STEAM versus sLASER), brain ROI, ^{1}HMRS acquisition voxel size, echo time, sample sex, or sample age. Given minimal variability in the percentage of patients prescribed antipsychotics across studies as well as missing medication data (Table 1), we were unable to examine whether neurometabolite effect sizes differed as a function of antipsychotic treatment rate.

3.4 Publication Bias

Investigations were undertaken to gauge publication bias. The resulting funnel plots for Glu and GSH were symmetric (Supplemental Figures 2 and 3) and Begg (Glu p = 0.64; GSH p = 0.93) and Egger (Glu p = 0.99; GSH p = 0.71) tests of potential bias were non-significant. Trim-and-fill analyses identified no putative outlier effects for Glu or GSH. Calculation of a fail-safe N suggested that to negate the total meta-analytic effect observed across all five neurometabolites, 128 null studies would need to be incorporated into the primary analysis. Furthermore, to negative observed effects for Glu and GSH, 28 and 22 null studies would be needed, respectively. These results indicate that the current results are representative of the extant 7T literature in PSY.

4.0 Discussion

Results from the present 7T ^{1}HMRS meta-analysis indicate that concentrations of brain Glu and GSH are significantly lower in patients with psychosis. Most, albeit not all, examined studies reported at least a trend towards lower brain Glu and GSH in PSY, thus the resulting meta-analytically derived summary effect sizes observed were small but significant. Meta-analytic summary effect sizes for GABA and Glx additionally indicated that levels may be lower in PSY as compared to HC, however summary effects for these metabolites were not significant. Assessments of publication bias indicated that the extant data is likely representative of the field (e.g., a large number of null studies would be needed to negate observed effects), though to date there are only nine independent ^{1}HMRS studies of PSY at 7T. Interestingly, ^{1}HMRS protocol, ^{1}HMRS acquisition voxel size, protocol echo time, brain region studied, sample sex composition, and sample age were not found to systematically affect study-specific effect sizes, though the number of studies available may have been too small to detect subtle moderating effects. Altogether, this meta-analysis supports that 7T ^{1}HMRS can offer promising insight into specific neurochemical disruptions in PSY, and further implicates Glu and GSH in the disorder. Nevertheless, additional data acquired from larger, younger, and unmedicated longitudinal samples is needed to elucidate the developmental time course of neurochemical alterations, the interplay between neurochemical alterations and changes in brain structure and function, and the relationship between such alterations and clinical and cognitive phenotypes that predict transition to PSY.

4.1 The Significance of Lower Brain Glu and GSH in Psychosis at 7T

The present meta-analytic findings add to a growing body of research implicating Glu dysfunction in PSY. Convergent evidence from animal models (Balla et al., 2001; Duncan et al., 2004; Javitt, 2004; Jentsch et al., 1997; Mohn et al., 1999), post-mortem tissue (Beneyto et al., 2007; Goff and Coyle, 2001; Hu et al., 2015), genetics studies (Harrison and Weinberger, 2005; Moghaddam, 2003; Rubio et al., 2013; Stefansson et al., 2002), peripheral markers (Palomino et al., 2007), and *in vivo* spectroscopy (Allen et al., 2015; Baiano et al., 2007) suggests that PSY involves significant abnormalities in the Glu system. Yet notably, the current 7T ^{1}HMRS meta-analytic findings appear to contradict those reported in a large 3T ^{1}HMRS meta-analysis of PSY, in which glutamate-related metabolites (Gln and Glx) were found to be, on average, higher in patients compared to controls (Merritt et al., 2016). Careful consideration of region-specific Glu effects within Merritt et al. (2016) reveals, however, that when Glu was analyzed and reported alone, levels indeed tended to be lower in individuals with PSY. Specifically, region-specific meta-analytic summary effect sizes indicated that Glu levels were lower in PSY patients than HC in the medial prefrontal cortex, frontal white matter, the medial temporal lobe, and the thalamus (though higher in PSY in the basal ganglia) (Merritt et al., 2016). This 7T meta-analysis thus corroborates these findings, as 72% (13/18, Figure 1) of the 7T Glu effects revealed lower Glu in PSY patients across a number of brain regions.

Lower levels of brain Glu may be indicative of a lower density of glutamatergic synapses (Olney and Farber, 1995), reduced excitatory neurotransmission, and/or disrupted glutamate metabolism in PSY. Though the mechanisms underlying putative glutamate dysfunction in

PSY remain unknown, one model posits that a loss of inhibitory control due to NMDA-mediated interneuron dysfunction leads to elevated glutamate levels initially, glutamate-induced excitotoxicity, and an eventual loss of glutamatergic connections (Moghaddam and Javitt, 2012). If, as supported by the present meta-analysis, Glu levels are reduced in individuals diagnosed with PSY, this would suggest that disorder pathomechanisms (such as initially increased Glu) begin prior to when PSY is diagnosed.

GSH, the major intracellular antioxidant in the brain, plays a critical role in maintaining neuronal health. Lower levels of GSH have been found in the periphery in PSY (Raffa et al., 2009), as well as in the brain in post-mortem studies (Gawryluk et al., 2011; Yao et al., 2006). Further, a recent 3T meta-analysis assessing *in vivo* brain GSH in over 500 patients found lower GSH concentrations (effect size = −0.26) within the ACC in PSY (Das et al., 2019). The magnitude of the GSH meta-analytic summary effect size was similar in this 7T meta-analysis (effect size = −0.21) across fewer individuals, corroborating the 3T result and suggesting sensitivity improvements at UHF. GSH, which is synthesized from glutamate, cysteine, and glycine, detoxifies reactive oxygen species and potentiates the NMDA receptor response to glutamate (Do et al., 2009). Interestingly, animal studies have demonstrated that oxidative stress and NMDA receptor hypofunction are reciprocally linked, suggesting that the observed Glu and GSH reductions may be inter-dependent, though only one study in this review reported a significant positive relationship between Glu and GSH (Kumar et al., 2018).

4.2 Interactions Between Antipsychotic Medications and Glutamate Neurometabolites

The effects of antipsychotic psychotropics on neurometabolite levels remain poorly understood. This represents a significant limitation of the extant ^{1}HMRS data to date. While changes in Glu metabolites appear related to the course of psychosis (Merritt et al., 2016), the presence and magnitude of these changes likely depend on stage of illness and pharmacological treatment status. A comprehensive meta-analysis of pharmacological treatment-associated changes in ^{1}HMRS signals found that, across a number of psychotropic classes (antipsychotics and others), pharmacotherapy was linked to a significant decrease in frontal Glx levels in both first episode and chronic PSY patients (Kubota et al., 2020), with a more pronounced decline in first episode (effect size = −0.57) as compared to chronic PSY (effect size = −0.33). This meta-analytic pattern of medication-related neurometabolite reductions has also been observed in individual studies of unmedicated PSY patients and CHR individuals who transitioned to PSY. More specifically, antipsychotic treatment in these groups has been shown to result in lower levels of both Glu and GABA in the brain (de la Fuente-Sandoval et al., 2013b; Fuente-Sandoval et al., 2018), although these findings could be confounded by factors such as illness severity. Altogether, the literature offers evidence that reductions in Glu-related neurometabolites in PSY may be driven, influenced, and/or confounded by treatment with antipsychotics, however the nature and timing of treatment-metabolite relationships have not been fully elucidated, and analyses related to specific antipsychotic medication types are not available. Ultimately, more comprehensive data is needed to disambiguate endogenous disease-related alterations from treatment-induced effects (including effects during initial phases of treatment and after long-term use).

This disambiguation will facilitate more direct interpretations of ^{1}HMRS findings in PSY such as those reviewed in this meta-analysis.

4.3 Challenges and Complementary Approaches to UHF Neurochemical Imaging

^{1}HMRS is a tremendously valuable tool for the *in vivo* study of brain neurochemicals. However, there are inherent methodological limitations, many which are more prominent at 3T. A primary limitation is the sensitivity of ^{1}HMRS, given that the concentration of neurochemicals of interest is very low compared to the concentration of water in the brain. This can make neurometabolite detection difficult, necessitating long acquisitions and many averages to achieve sufficient SNR. An additional limitation comes from spectral overlap of signals from nuclei in different molecules, for example overlap of Glu, Gln, and GABA resonances. Ultra-high field 7T ^{1}HMRS offers both improved sensitivity and specificity for quantifying brain neurochemistry (Choi et al., 2010), especially when shorter TEs are used, which may contribute to the significant effects we report in this meta-analysis across only a few studies. In fact, a direct comparison of brain metabolite quantification at 3T and 7T found that precision was higher for 12 brain metabolites using the 7T spectra (Mekle et al., 2009), despite a reduction in scan time by a factor of two. For Glu specifically, this increase in precision at 7T involves a 50% improvement in signal variability, and increased reliability for measuring coupled metabolites (e.g. Gln and Glu) (Terpstra et al., 2016). Continued implementation of 7T ^{1}HMRS at diverse developmental and disease stages will thus likely result in a refined understanding of neurochemical alterations in attenuated psychosis syndrome and PSY.

Despite the advantages of 7T, there are still limitations of ^{1}HMRS at UHF. Limitations include partial volume effects, susceptibility artifacts, persisting spectral overlap, and limited spatial coverage, given that most ^{1}HMRS acquisitions are single-voxel based, with voxel sizes between 8–25 cm^3 used in most 7T human studies (Table 1). Fortunately, a number of these limitations are overcome by Chemical Exchange Saturation Transfer (CEST) imaging techniques, which are complimentary approaches available only at 7T. By exploiting saturation exchange properties intrinsic to certain metabolites, CEST allows for metabolite detection with at least two orders of magnitude increased sensitivity as compared to ^{1}HMRS (Cai et al., 2013, 2012). Specifically, CEST imaging uses water pool-dependent contrasts produced by endogenous compounds containing exchangeable protons (e.g. -OH, -NH$_2$, -NH groups) (Henkelman et al., 2001; Kogan et al., 2013; Sherry and Woods, 2008; van Zijl and Yadav, 2011; Zhou and van Zijl, 2006), thus CEST is not as constrained by the concentration limitations of ^{1}HMRS. Moreover, CEST is based on magnetization-transfer imaging sequences, and can therefore benefit from well-known fast acquisition strategies while both offering improved spatial coverage and resolution and facilitating multi-modal imaging analyses. To our knowledge, only glutamate CEST (GluCEST) has been applied to the study of PSY, revealing *in vivo* Glu hypofunction in youth on the PSY spectrum, including both PSY and CHR patients (Roalf et al., 2017). However CEST techniques capable of measuring creatine, myo-inositol (Haris et al., 2011), glutamine, and GABA (Lee et al., 2016) have been developed (Oh et al., 2017), and may provide new perspectives on PSY and PSY risk. Still, whether implementing ^{1}HMRS or CEST techniques, multiple

technical and practical challenges remain at 7T that must be considered, which have been comprehensively reviewed (Godlewska et al., 2017).

4.4 Implications for the Study of Clinical High Risk for Psychosis

There is an ample literature examining attenuated PSY and predictors of conversion from CHR to PSY (Lieberman et al., 2019). Indeed, individualized PSY risk calculators using data obtainable in clinical settings have demonstrated utility for predicting risk of conversion in CHR populations (Cannon et al., 2016; Carrión et al., 2016; Ciarleglio et al., 2019). Nonetheless, as supported by published risk calculators as well as by a recent meta-analysis of over 17,000 CHR individuals (Oliver et al., 2020), the most reliable non-biological predictors of PSY onset appear to be currently limited to more severe positive and negative psychotic symptoms and poorer neurocognitive and global functioning (Cannon et al., 2016; Oliver et al., 2020), i.e., attenuated symptoms of PSY itself. We believe that this underscores the need to identify sensitive, specific biological predictors that mediate the association between attenuated symptoms in CHR and transition to PSY, and that can thereby improve our understanding of what constitutes a high-risk state. This idea is supported by the fact that models predicting CHR outcomes are improved when neuroimaging and blood-derived measures are included in addition to clinical symptoms (Chan et al., 2015; Gschwandtner et al., 2009; Koutsouleris et al., 2018). We propose that 7T neurometabolite imaging represents one critical avenue for future investigation into mediators of CHR transition risk, given that these imaging techniques 1) produce quantifiable metrics that can be incorporated into risk calculators, and 2) inherently investigate druggable chemicals that could be targeted by early interventions. Yet, there is currently little available 7T ^{1}HMRS neurometabolite data in CHR individuals, and CHR findings at 3T are even less consistent than those reported in PSY (Merritt et al., 2016; Treen et al., 2016; Wenneberg et al., 2019). Studies have found lower (Allen et al., 2015; Egerton et al., 2014; Keshavan et al., 2009; Uhl et al., 2011), higher (de la Fuente-Sandoval et al., 2013, 2011; Fusar-Poli et al., 2012; Stone et al., 2009; Tandon et al., 2013; Tibbo et al., 2004), and no difference (Natsubori et al., 2014; Purdon et al., 2008, p. 2; Yoo et al., 2009) in Glu (or Glu, Gln, Glx) concentrations between controls and CHR or genetic high risk individuals. It is unclear whether this is due to neurobiological factors (e.g., illness stage or disease heterogeneity), methodological factors (e.g. sensitivity, specificity and SNR limitations), or both. Intriguingly, a number of studies have found that Glu levels, particularly within the striatum, are associated with the transition to PSY (Allen et al., 2015; de la Fuente-Sandoval et al., 2013a; Egerton et al., 2014; Uhl et al., 2011). Additional studies are clearly needed that study Glu and Glu-related metabolites in CHR individuals.

Disruptions in Glu, GSH, and other neurochemicals are undoubtedly only one component of the complex, multi-faceted, and heterogeneous syndrome of PSY. Future efforts should aim to 1) uncover how brain neurochemistry interacts with structural and functional brain changes to increase risk of developing PSY, and to 2) integrate the study of neurochemicals with other genetic, biological, and clinical factors when evaluating Attenuated Psychosis Syndrome and CHR transition risk. As such, comprehensive, multimodal UHF neuroimaging approaches that include measures of neurochemistry are recommended. As 7T MRI becomes more common and is utilized within at-risk populations, the field should consider establishing UHF consortia with standardized acquisition and analysis guidelines,

similar to the European Ultrahigh-Field Imaging Network for Neurodegenerative Diseases (EUFIND) (Düzel et al., 2019). This will be a vital step toward reducing methodological heterogeneity in ^{1}HMRS acquisition protocols and improving our understanding of neurochemical disruptions in PSY and attenuated PSY syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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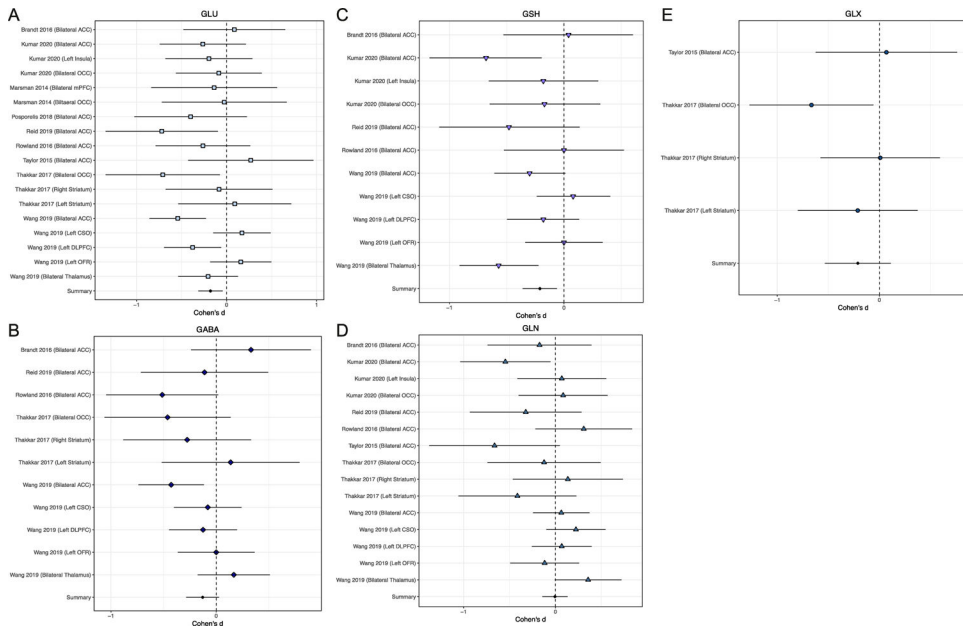
Figure 1.
Study specific effect sizes (Cohen's D +/− 95% CI) for each neurometabolite: **A**. Glutamate (Glu), **B**. Gamma aminobutyric acid (GABA), **C**. Glutathione (GSH), **D**. Glutamine (Gln) and **E**. Glutamate+Glutamine (Glx). Each forest plot displays the study and ROI in which the neurometabolite was measured. A summary effect size is provided for each neurometabolite. Negative effect sizes indicate lower concentration in PSY as compared to HC.
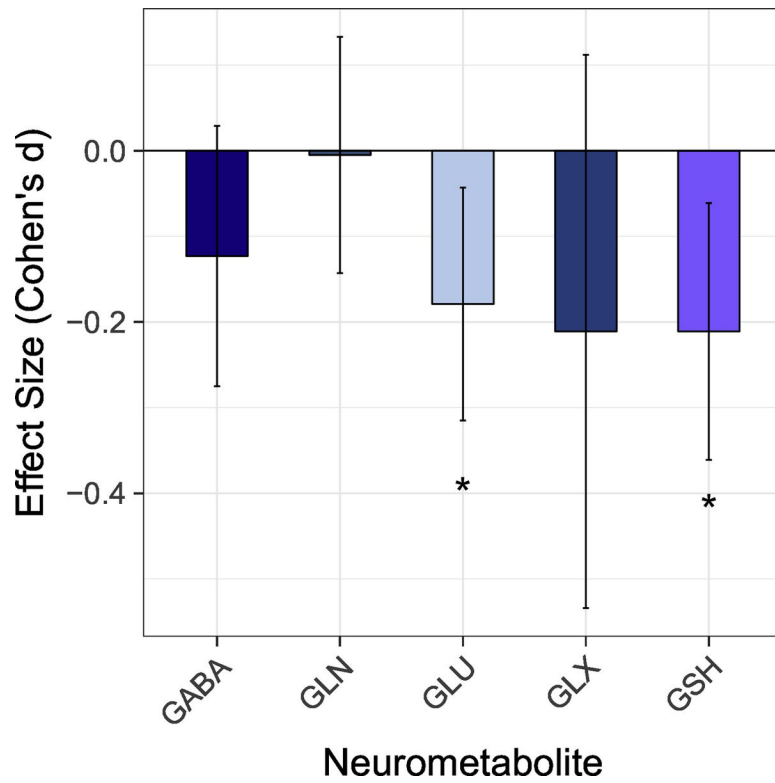
Figure 2.
The meta-analytic derived average effect size (+/ 95% CI) for each neurometabolite. Gamma aminobutyric acid (GABA); Glutamine (Gln); Glutamate (Glu); Glutamate+Glutamine (Glx); Glutathione (GSH).

Table 1.

Summary of Patient Characteristics, Sample Demographics, and 1HMRS Acquisition Parameters for Studies Included in the Present Meta-Analysis.

HC = healthy comparison; PSY = psychosis. *PSY Type Abbreviations:* FEP-SZ = first episode schizophrenia; SAD = schizoaffective disorder; SZ = schizophrenia. *Sex Abbreviations:* %F = percent female; *Region of Interest (ROI) Abbreviations:* ACC = anterior cingulate cortex; B = bilateral; CSO = centrum semiovale; DLPFC = dorsolateral prefrontal cortex; L = left hemisphere; mPFC = medial prefrontal cortex; OCC = occipital cortex; OFR = orbitofrontal cortex. [1] *HMRS Sequence Abbreviations:* MEGA = Mescher-Garwood; sLASER = semi-localized by adiabatic selective refocusing; STEAM = stimulated echo acquisition mode; *Neurometabolite Abbreviations:* GABA = gamma aminobutyric acid; Gln = glutamine; Glu = glutamate; Glx = glutamate+glutamine; GSH = glutathione.

STUDY INFORMATION		PATIENT CHARACTERISTICS			SAMPLE DEMOGRAPHICS				1HMRS ACQUISITION PARAMETERS				
Study	Sample Size Total (HC/PSY)	PSY Type	Patients on Antipsychotics (%)	Class of Antipsychotics Reported	Mean Age HC	Mean Age PSY	Sex (%F) HC	Sex (%F) PSY	ROIs	1HMRS Sequence	Echo Time (ms)	Neurometabolites Measured	ROI Size (mm³)
Brandt 2016	48 (24/24)	SZ, SAD	100	Typical and atypical	36.6	37.5	17	21	B ACC	STEAM	14	Glu, Gln, GABA, GSH	7200
Kumar 2018	73 (45/28)	SZ, SAD	Not reported, "most patients"	Not reported	27.9	27.2	36	29	B ACC L Insula B OCC	STEAM	17	Glu, Gln, GSH	9000 8640 8800
Marsman 2014	40 (23/17)	SZ	100	Atypical	27.7	27.6	30	24	B mPFC B OCC	sLASER	28	Glu	8000[f]
Posporelis 2017	40 (20/20)	FEP-SZ[a]	80	Typical and atypical	23.1	24.3	35	35	B ACC	STEAM	15	Glu	27000
Reid 2019	42 (21/21)	FEP-SZ[b]	95	Atypical	23.5	23.2	24	24	B ACC	STEAM	5	Glu, Gln, GABA, GSH	5400
Rowland 2016	56 (29/27)	SZ, SAD	83	Typical and atypical	29.7	34.4	52	37	B ACC	STEAM	14	Glu, Gln, GABA, GSH	12000
Taylor 2015	32 (16/16)	SZ	88	Atypical	23.9	22.7	31	19	B ACC	STEAM	10	Glu, Gln, Glx	8000
Thakkar 2017	45 (24/21)	SZ, SAD	100	Not reported	33.9	36.4	33	29	B OCC B Striatum	sLASER MEGA-sLASER[c]	36[d] 74[e]	Glu, Gln, GABA, Glx	24000

STUDY INFORMATION		PATIENT CHARACTERISTICS			SAMPLE DEMOGRAPHICS						¹HMRS ACQUISITION PARAMETERS			
Study	Sample Size Total (HC/PSY)	PSY Type	Patients on Antipsychotics (%)	Class of Antipsychotics Reported	Mean Age HC	Mean Age PSY	Sex (%F) HC	Sex (%F) PSY	ROIs	¹HMRS Sequence	Echo Time (ms)	Neurometabolites Measured	ROI Size (mm³)
Wang 2019	172 (91/81)	FEP-SZ[a]	Not reported	Not reported	23.3	22.3	54	30	B ACC L CSO L DLPFC L OFR B Thalamus	STEAM	14	Glu, Gln, GABA, GSH	12000 12000 10000 8000 9000

[a] duration of illness 24 months;

[b] duration of illness 24 months in 95% of patients;

[c] used for GABA acquisition;

[d] echo time used for sLASER sequence;

[e] echo time used for MEGA-sLASER GABA sequence;

[f] ROI size used for sLASER sequence (Glu) in both ROIs.

Additional notes: Clozapine is considered an atypical antipsychotic in this Table. ROI size is respective to the ROI listed, unless otherwise noted. Bilateral ROIs include both midline-crossing single voxel ROIs and two independent voxels placed in left and right hemisphere ROIs, depending on the study.