ADMINISTRATIVE INFORMATION

Title

Glutamatergic neurotransmission in schizophrenia: a systematic review protocol of ¹H-MRS studies throughout phenotypic stages of schizophrenia

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Contributions

JJL will develop the protocol draft, identify research questions, perform literature search and stage 1 screening, and data synthesis. Stage 1 screening will consist of removal of duplicates, removal of non-English language and title and abstract screen for acceptance. SPC will complete stage 2 screening with JJL: this will include full text screening to ascertain which articles should be included into the review. JJL will perform the data extraction and risk of bias assessment. The risk of bias assessment will be discussed with SPC and SLR to ensure agreement. All authors will assist with the development of the protocol, refining research questions, and in conducting the final draft of the systematic review.

Amendments

This is the original protocol for this systematic review, created in 2020 in accordance with the PRISMA-P recommendations, where applicable (Moher et al., 2015). Given that the systematic review will comprise non-intervention-based empirical research, PRISMA-P checklist items pertaining to clinical intervention trials have been omitted or substituted with appropriate alternatives. In the event of amendments to the protocol, the date and description of each amendment will be provided along with an update to the review rationale as necessary.

Support Sources

Financial support for salary is provided by the Australian National Health and Medical Research Council Senior Research Fellowship to SLR (GNT1154651).

ABSTRACT

Schizophrenia is a significant mental health condition involving the dysregulation of multiple neurological pathways in its pathophysiology. The glutamate hypothesis for schizophrenia suggests a dysfunctional glutamatergic system throughout the varying phenotypic stages of schizophrenia – i.e. first-episode psychosis, chronic schizophrenia, and treatment-resistant schizophrenia. In this systematic review protocol (based on PRSIMA-P guidelines), we outline an approach to explore the relationship between the levels of glutamate, glutamine, and the glutamate-to-glutamine ratio and the varying phenotypic stages of schizophrenia. Furthermore, the protocol proposes to review the empirical magnetic resonance spectroscopy (^1H -MRS) literature to better understand the association between these changes in the above clinical subgroups and their neuroanatomical correlates.

INTRODUCTION

Rationale

Schizophrenia is a chronic psychiatric condition that, although characterised by a relatively low global lifetime prevalence of ~0.7% (Saha, Chant, Welham, & McGrath, 2005), is one of the leading contributors to the global adult burden of disease (Whiteford, et al., 2013). In Australia, total cost of health and social care for schizophrenia in 2017 alone was ~2.9 billion AUD (Mindgardens Neuroscience Network, 2019). Although usually associated with a lifetime of disability, the significant burden of disease can be reflected upon two main features of schizophrenia: 1) first psychotic features tend to develop in early adolescence or early adulthood, with a peak age of onset for first episode of psychosis (FEP) at mid to late 20s (Lewis & Moghaddam, 2006), and 2) approximately 30% of patients with schizophrenia show poor or partial response to typical antipsychotic medication (Caspi, Davidson, & Tamminga, 2004; Meltzer, 1997; Suzuki, et al., 2011).

Recent studies have evidenced the broad aetiology of schizophrenia, leading to a range of research on the dysregulation of multiple pathways in its pathophysiology (Benes, 2009; Deng & Dean, 2013; Karam, et al., 2010) and, whilst dopaminergic models of the disease are able to account for the positive symptoms of schizophrenia (e.g. delusions and hallucinations), glutamatergic models appear to encompass both negative symptoms (e.g. social withdrawal, anhedonia, amotivation, etc.) and cognitive symptoms (e.g. memory, social cognition, problem solving, etc.; Howes, McCutcheon, & Stone, 2015). The glutamate hypothesis of schizophrenia suggests a dysfunctional glutamatergic system, in which synaptic plasticity and cortical microcircuitry are affected, leading to potential morphological changes in postsynaptic neurons and structural brain changes in schizophrenia (Marsman, et al., 2013; Merritt, Egerton, Kempton, Taylor, & McGuire, 2016).

Recent developments in localised proton magnetic resonance spectroscopy (^1H -MRS) studies have significantly contributed to our current understanding of neurometabolic activity in schizophrenia. A number of studies have reported on the changes in glutamate (Glu), glutamine (Gln), and the combined glutamate and glutamine signal (Glx) – hence addressed as glutamatergic neurometabolites – throughout the multiple phenotypic stages of the disease: prodromal/high risk (Egerton, et al., 2014; Purdon, Valiakalayil, Hanstock, Seres, & Tibbo, 2008; Tandon, et al., 2013), FEP (Bustillo, et al., 2010; de la Fuente-Sandoval, et al., 2011; Egerton, et al., 2018), chronic schizophrenia (Balz, et al., 2018; Bustillo, et al., 2014; Falkenberg, et al., 2014; Theberge, et al., 2003), and patients with schizophrenia resistant to non-clozapine anti-psychotic medications (i.e. treatment-resistant schizophrenia, TRS) and those resistant to clozapine (i.e. ultra-treatment-resistant schizophrenia, uTRS; Demjaha, et al., 2014; Goldstein, Anderson, Pillai, Kydd, & Russell, 2015; Iwata, et al., 2019; Mouchlianitis, et al., 2016).

Studies using ^1H -MRS have shown an elevation of glutamine in the anterior cingulate cortex of high-risk participants (Stone, et al., 2009) and in both the anterior cingulate cortex and thalamus of medication naïve FEP patients (Bartha, et al., 1997; Théberge, et al., 2002; Théberge, et al., 2007). Glutamine has also shown to be elevated in the prefrontal cortex, the hippocampus, and in the anterior cingulate cortex of patients with chronic schizophrenia (Bustillo, et al., 2014; van Elst, et al., 2005). In unmedicated participants with high-risk of schizophrenia and FEP, glutamate has been reported to be both elevated in the dorsal caudate (de la Fuente-Sandoval, et al., 2011) and reduced in the thalamus (Egerton, et al., 2014) and the anterior cingulate cortex (Stone, et al., 2009). In patients with chronic schizophrenia, studies have reported on an increase of glutamate in the superior temporal sulcus, the prefrontal cortex, and the hippocampus (Balz, et al., 2018; van Elst, et al., 2005), as well as on a decrease in glutamate concentrations in the anterior cingulate cortex (Tayoshi, et al., 2009; Theberge, et al., 2003) and the hippocampus (Stan, et al., 2004). ^1H -MRS studies on

patients with TRS have revealed an increase in the concentration of glutamate in the anterior cingulate cortex (Demjaha, et al., 2014; Egerton, et al., 2012). Other studies, using clozapine responsiveness as a benchmark for TRS, have found an increase of combined glutamate and glutamine in the putamen of clozapine-responsive patients (Goldstein, Anderson, Pillai, Kydd, & Russell, 2015), and an increase in both glutamate and combined glutamate and glutamine in the anterior cingulate cortex of patients non-responsive to clozapine (Iwata, et al., 2019; Mouchlianitis, et al., 2016). A focussed review and meta-analysis by Marsman and colleagues (2013) of twenty-four ¹H-MRS studies in a total of 647 patients with schizophrenia revealed decreased levels of glutamate and increased levels of glutamine in the medial frontal region in this cohort when compared with healthy controls, and no differences in neither the hippocampus nor the thalamus; the study also noted a decrease with age of glutamate, glutamine and Glx in the frontal region. On the other hand, when comparing high risk for schizophrenia, FEP, and chronic schizophrenia patient groups against healthy controls, a 2016 meta-analysis found significant elevated levels of glutamate and Glx in the basal ganglia, higher levels of glutamine in the thalamus, and increased levels of Glx in the medial temporal lobe (Merritt, Egerton, Kempton, Taylor, & McGuire, 2016). A systematic review and meta-analysis by Iwata et al. (2018), on antipsychotic-naïve and antipsychotic-free patients with schizophrenia, found a single study reporting higher levels of glutamate in the associative striatum of antipsychotic-naïve patients with FEP, yet no differences for Glx concentrations in the non-medicated cohort.

Not only do many of these results show inconsistent findings amongst themselves, with varied reports of increased, similar, and decreased levels of glutamatergic neurometabolites when compared to healthy controls, but they also vary significantly with their neuroanatomical region of interest for ¹H-MRS voxel placement. Furthermore, due to their similar chemical compositions, glutamate and glutamine have a narrow chemical shift range – i.e. similar resonance frequencies and spectral patterns – that can lead to significant

resonance overlap at standard, short echo timings and clinical field strengths. Given the difficulty in discerning between the two spectra signals using MRS, many studies that report on the combination of glutamate and glutamine (i.e. Glx) rather than on the two metabolites separately. As such, research into the role of glutamate cycling in the pathophysiology of schizophrenia has revealed some curious – yet unclear – working hypotheses for the role played by glutamate and glutamine in schizophrenia. Therefore, while a breadth of research has investigated the implications of glutamatergic neurometabolites in the different phenotypic presentations of schizophrenia throughout the course of the disease and in multiple areas of the human brain, a lack of clarity and consensus remains with regards to the changes in these molecules in both their clinical presentations and their neuroanatomical correlates. This proposed systematic review aims to explore the relationship between the levels of glutamate, glutamine and, where possible, the glutamate-to-glutamine ratio and the varying phenotypic stages of schizophrenia, especially with regards to treatment-resistant schizophrenia, to assess the current body of evidence across the course of the disease and corresponding neuroanatomical correlates, and to offer further clarification and refinement of this field of knowledge. Also, in order to provide a data rich analysis, the proposed systematic review will assess MRS studies with field strengths of 3T or above, which have been marked as appropriate for the estimation of glutamate and glutamine (Snyder & Wilman, 2010), in comparison to the limited resolution at 1.5T.

Objectives

The aim of the systematic review is to provide an updated summary of the current published case-control publications for regional neuroanatomic concentrations of glutamate, glutamine, and, where possible, the ratio of glutamate-to-glutamine using ¹H-MRS at a field strength of 3T or above in FEP, chronic schizophrenia (i.e. non-clozapine antipsychotic pharmacotherapy), and schizophrenic patients undertaking clozapine pharmacotherapy.

Furthermore, the systematic review will evaluate emerging empirical relationships between glutamatergic measures in the above clinical subgroups and their neuroanatomical correlates.

METHODS

Eligibility criteria

Records eligible for inclusion will be established via two stages of screening. Title and abstracts of each record will be screened at stage one. Records will be screened based on full-text read at stage two. The specified eligibility checklists will be completed at each stage.

Records will be eligible at stage one if they meet the following criteria:

1. Written in English.
2. Forming part of an original empirical investigation.
 - a. Empirical investigations in the form of case studies will be excluded.
3. The participant sample consists of an adult human population.
4. Includes one or more participant groups with experience of schizophrenia and schizophrenia related disorders (e.g. schizoaffective disorder) across the multiple stages of illness.
5. Data is collected using ^1H -MRS.

Records will be eligible at stage two if, in addition to stage one criteria, they meet the following criteria:

1. Schizophrenia (as defined in stage one, item 4) must be identified as an independent variable in the investigation of glutamate and glutamine concentrations.

2. The participant sample does not include individuals with an identified neurological disorder; neurodegenerative illness; an acquired or traumatic brain injury; alcohol and substance abuse or dependence.
3. Brain neurometabolite activity and concentration data must include glutamate and/or glutamine.
4. Neurometabolite data is collected using ^1H -MRS at a field strength of 3T or above.
5. Relationships between glutamate and glutamine concentrations and schizophrenia (as defined in stage one, item 4) may be investigated via one of the following methods:
 - a. Between-group comparisons to identify differences in glutamatergic metabolite (as defined in stage two, item 3) concentrations between participants with schizophrenia (as defined in stage one, item 4) and healthy controls;
 - b. Between-group comparisons to identify differences in glutamatergic metabolite (as defined in stage two, item 3) concentrations between participants with differing schizophrenia (as defined in stage one, item 4) stages of illness;
 - c. Correlations between levels of glutamatergic metabolite (as defined in stage two, item 3) concentrations and schizophrenia (as defined in stage one, item 4) stage of illness.
 - d. Within-group comparisons to identify changes in glutamate and glutamine concentrations (as defined in stage two, item 3) over time in individuals with schizophrenia (as defined in stage one, item 4).

Information sources

A search of several electronic databases: Web of Science, PsychNet, EBSCOhost, and PubMed will be conducted to identify relevant literature published from the 1st of January 1980.

Search strategy

The search strategy will be adapted to the technical search requirements of each database. The search will be applied to title, abstract and key terms (where possible), and record type will be specified as published empirical articles. Following data collection of empirical articles, the search strategy will be run separately on review articles, of which the reference lists will be examined to identify any additional empirical articles to be included. Following data collection of all eligible records, the search strategy will be re-run with appropriate date restrictions to identify articles published between the commencement of the initial search and the conclusion of data collection, to capture any articles published within this time. The final search strategy conducted for each online database will be included in the appendix of the final systematic review.

Search terms were selected to represent schizophrenia throughout its phenotypic presentations, glutamate and glutamine, and ¹H-MRS. Both broad and domain-specific search terms for glutamate, glutamine, schizophrenia, and ¹H-MRS will be included, as relevant to the field. The following search will be run in each database, with technical adaptations applied appropriately: (glutamate OR glutamine) AND (schizo* OR psychosis) AND (MRS OR “magnetic resonance spectroscopy”) AND (patient OR participant OR people OR person).

STUDY RECORDS

Data management

Endnote citation management software will be used to store search results such as title, authors, abstract, key words and digital identifying information (DOI, URL) for each empirical record. Full-text articles for relevant reviews will also be saved as attachment to

database listing. Empirical records identified within the reference lists of the review articles will be cross-checked against the main directory of empirical search results and identifying information for each record will be entered into a digital spreadsheet for screening. Records will then be screened against the specified checklist criteria at stage one (title and abstract) and stage two (full text). Full-text articles for records deemed eligible for inclusion at stage one will be sourced and saved within the Endnote directory. Identifying information of records deemed eligible for inclusion at stage two will be exported into a separate digital spreadsheet for data extraction.

Selection process

A two-staged screening process will be employed to determine record eligibility. Pre-determined screening checklists will be applied at stage one and stage two of screening, with record adherence to the criteria documented accordingly. The completed checklists for each stage of screening will be included in the appendix of the final systematic review.

At stage one, JJL will screen the title, abstract and key words of all records returned from the search against the stage one eligibility criteria; completing the relevant screening checklist for each. In the case that a record's adherence to the screening checklist is unclear at stage one, the record will be retained for stage two screening. Full-text articles will be obtained for all records which adhere to the screening criteria at stage one.

At stage two, JJL and SPC will screen the full-text article of each record retained at stage one against the stage two eligibility criteria; completing the relevant screening checklist for each and documenting reasons for record exclusion. Any discrepancies in record adherence to the checklist between the reviewers at stage one will be identified and discussed to obtain a consensus agreement. Any difficulties in reaching a consensus agreement will be

mediated by SLR. The completed checklist at stage two will be reviewed by the collaborative team to confirm record adherence to the eligibility criteria.

Data collection process

A single reviewer (JJL) will conduct data extraction using a pre-determined checklist (see Data Items). A copy of the checklist will be provided in the appendix of the final systematic review. The relevant checklist data items will be completed for each eligible record. The data collection checklist will be reviewed by an additional author for verification of adherence.

Data items

Data items to be extracted from eligible records will comprise three themes: sample characteristics, methodology, and identified relationships between glutamate, glutamine, and glutamate/glutamine ratio, schizophrenia, and ¹H-MRS. See below for specific variables to be extracted where possible.

1. Sample characteristics

Population of sample recruitment; stage of schizophrenia investigated (i.e. FEP, chronic schizophrenia (i.e. non-clozapine antipsychotic pharmacotherapy), clozapine pharmacotherapy); sample size; age; sex; estimated premorbid IQ; handedness; education status; country of residence; clinical status/current psychiatric diagnoses; mental health consumer status; current medications; age of schizophrenia (or related disorders) onset; schizophrenia (or related disorders) duration.

2. Study Characteristics

¹H-MRS characteristics and field strength used (i.e. 3T or greater); investigation of glutamate, glutamine, and glutamate/glutamine ratio; data analysis methods (e.g. between-group comparison, within-group comparisons, correlations, regression); comparator group (e.g. healthy control group, clinical control group); country of data collection.

3. Relationships between glutamate, glutamine, and glutamate/glutamine ratio and schizophrenia

Significance, strength and type of relationships identified, along with relevant statistical data (e.g. group means and standard deviations, t-values, F-values, correlation coefficients, regression coefficients, p-values, and effect sizes, where applicable).

Outcomes and prioritisation

Primary outcomes

- Concentrations of glutamate and glutamine, and glutamate/glutamine ratio associated with schizophrenia stage of illness (or related disorder);

Secondary outcomes

Depending on the themes which emerge from the data, the following secondary outcomes may be addressed:

- Neuroanatomic correlates associated with changes in glutamate, glutamine, and glutamate/glutamine ratio (and their ratio) concentrations;

- Evidence for the effect of antipsychotic medication in glutamate, glutamine, and glutamate/glutamine ratio concentrations;
- The sample characteristics (e.g. proportion of represented psychiatric diagnoses) within which significant relationships were identified.

Risk of bias in individual studies

During data collection a quality assessment will be conducted for each eligible record. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (Wells, et al., 2019) will be implemented to evaluate factors such as the selection, definition and representativeness of the sample; the comparability of the cohorts; and the assessment of the exposure condition. Additional pre-determined checklist items will be developed by the authors to assess the quality (i.e. validity, standardisation, replication) of the measures and/or methods used. For example, the means by which the presence and nature of schizophrenia is evaluated as well as the methods used to measure glutamate neurometabolite concentration will be assessed. The recruitment methods employed and the population from which the participant samples are drawn will also be examined. Records will be given a rating from one to five stars to indicate their level of quality with regards to each of these factors. A copy of the full NOS and additional checklist items will be provided in the appendix of the final systematic review. The risk of bias assessment will be discussed with SPC, SLR and BD to ensure agreement and completeness.

DATA SYNTHESIS

Criteria for quantitative synthesis

The suitability to undertake a meta-analysis will be decided after an initial scan of the number of appropriate studies.

Additional analyses

Any sub-group analysis will be decided post-hoc, depending on the suitability of the extracted data.

Qualitative synthesis

A narrative synthesis of the data will be provided within the discussion of the systematic review to summarise the nature of the relationship between brain glutamate, glutamine, and, where possible, the glutamate/glutamine ratio and the different phenotypic stages of schizophrenia – i.e. in FEP, chronic schizophrenia (i.e. non-clozapine antipsychotic pharmacotherapy), and schizophrenic patients undertaking clozapine pharmacotherapy. A summary will also be provided of the sample characteristics from which the data were extracted, as well as the statistical techniques employed to yield the identified results. Results will be tabulated where appropriate.

Meta-bias(es)

Where appropriate meta-biases, such as publication bias, will be assessed via relevant methods (e.g. funnel plots and correlations of effect sizes to sample sizes).

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