frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 21 September 2018
doi: 10.3389/fpsyt.2018.00438

Putative Astroglial Dysfunction in Schizophrenia: A Meta-Analysis of ^{1}H-MRS Studies of Medial Prefrontal Myo-Inositol

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Background: Several lines of evidence support a role for astroglial pathology in schizophrenia. Myo-inositol is particularly abundant in astroglia. Many small sized studies have reported on myo-inositol concentration in schizophrenia, but to date these have not been pooled to estimate a collective effect size.

Methods: We reviewed all proton magnetic resonance spectroscopy (1H-MRS) studies reporting myo-inositol values for patients satisfying DSM or ICD based criteria for schizophrenia in comparison to a healthy controls group in the medial prefrontal cortex published until February 2018. A random-effects model was used to calculate the pooled effect size using *metafor* package. A meta-regression analysis of moderator variables was also undertaken.

Results: The literature search identified 19 studies published with a total sample size of 585 controls, 561 patients with schizophrenia. Patients with schizophrenia had significantly reduced medial prefrontal myo-inositol compared to controls (RFX standardized mean difference = 0.19, 95% CI [0.05–0.32], $z = 2.72$, $p = 0.0067$; heterogeneity $p = 0.09$). Studies with more female patients reported more notable schizophrenia-related reduction in myo-inositol ($z = 2.53$, $p = 0.011$).

Discussion: We report a small, but significant reduction in myo-inositol concentration in the medial prefrontal cortex in schizophrenia. The size of the reported effect indicates that the biological pathways affecting the astroglia are likely to operate only in a subset of patients with schizophrenia. MRS myo-inositol could be a useful tool to stratify and investigate such patients.

Keywords: myo-inositol, astroglia, schizophrenia, inflammation, spectroscopy

OPEN ACCESS

Edited by:
Stefan Borgwardt, Universität Basel, Switzerland

Reviewed by:
Tiago Reis Marques, Imperial College London, United Kingdom
Dragos Inta, Zentralinstitut für Seelische Gesundheit (ZI), Germany

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Specialty section:
This article was submitted to Molecular Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *28 April 2018*
Accepted: *24 August 2018*
Published: *21 September 2018*

Citation:
Das TK, Dey A, Sabesan P, Javadzadeh A, Théberge J, Radua J and Palaniyappan L (2018) Putative Astroglial Dysfunction in Schizophrenia: A Meta-Analysis of ^{1}H-MRS Studies of Medial Prefrontal Myo-Inositol. Front. Psychiatry 9:438. doi: 10.3389/fpsyt.2018.00438

INTRODUCTION

A role for astroglial pathology has been long suspected in schizophrenia (1–3). Astrocytes are critical for reducing oxidative stress and restoring redox balance in the brain, thus preventing neurotoxicity (4, 5). Astrocytes enable the crucial glutamate-glutamine cycle that helps clear extracellular glutamate from synaptic space as well as reduce the deleterious cellular ammonia

content (6, 7). In addition, two crucial indicators of neuronal connectivity—synaptic maintenance and myelination—appear to rely on astrocytic guidance (8–10). Thus, abnormalities in astrocytic function can produce neuronal dysconnectivity as well as glutamatergic abnormalities that are known to occur in schizophrenia (11). Indeed, converging genetic and molecular evidence now supports the case for a primary role of astroglial dysfunction in schizophrenia (10, 12).

In vivo imaging of astrocytic integrity holds promise in clarifying the nature of its dysfunction in schizophrenia. ^{1}H-MRS does not specifically differentiate between brain cell types; nevertheless, given that myo-inositol is particularly abundant in astroglia rather than the neurons and other cells, it can be considered an astroglial marker (13, 14). The MRS measure of myo-inositol predominantly reflects astrocytic intracellular compartment, where it has osmotic functions (15, 16). An increase in MRS myo-inositol resonance relates to markers of astroglial activation (17, 18), associated with gliosis (19, 20), and occurs in response to brain injury (21, 22), thus reflecting an inflammatory response. On the other hand, myo-inositol also has an important role as an intracellular second messenger in calcium mediated glutamatergic signaling (23). Reduced myo-inositol resonance may relate to astroglial dysfunction and consequently, aberrant extracellular glutamate clearance from synaptic space. Thus, low levels of myo-inositol may in turn facilitate excitotoxic damage and local inflammatory processes that are currently subjects of investigation in the pathophysiology of schizophrenia (1).

Many small sized studies have reported on myo-inositol concentration in schizophrenia, but to date these have not been pooled to estimate a collective effect size (24). Examining the state of myo-inositol abnormalities will aid in our understanding of the role of astroglial cells in schizophrenia. We reviewed MRS studies reporting myo-inositol resonance in schizophrenia and conducted a meta-analysis to synthesize the nature of myo-inositol abnormalities in the medial prefrontal cortex of patients with schizophrenia. We focussed on the medial prefrontal cortex as most MRS studies in schizophrenia have placed voxels in this brain region (24).

METHODS

Search Process

We followed the guidelines set out by the consensus statement from PRISMA group (25). Our literature search started with the MEDLINE electronic database to identify journal articles published until 28 February 2018. We used the following Medical Subject Headings and freeform search terms: (schizophrenia OR schizo* OR psychos* OR psychot*) AND ("1H-MRS" OR "1H NMRS" OR "1HMRS" OR "MRS" OR "Magnetic resonance spectroscopy" OR "Spectroscopy" OR "proton magnetic resonance spectroscopy") AND ("myo-inositol" OR "inositol" OR "myo-inositol"). We noted that in many reports, myo-inositol was reported as a secondary measure, and not included in keywords or abstracts. As a result, we used the terms ("glutathione" OR "NAA" OR "n-acetyl aspartate" OR "glutamine" OR "GSH" OR "neurometabolic" OR "Glutamate" OR "Glu" OR "GABA" OR "Lactate" OR "creatinine") instead of the 3 terms denoting myo-inositol in order to identify all eligible studies. We attempted to contact authors whenever the individual studies indicated that myo-inositol resonance of adequate quality was measured in the brain region of interest (see below) but when the data was not published. We also undertook a manual search of reference lists of review articles and eligible full text articles. Third, we repeated the search with Google Scholar to identify journal articles that were not indexed on MEDLINE. Finally, we also searched the citation records of Google Scholar for all identified full text articles in order to locate in press articles that are not yet indexed. Two authors (AD and PS) undertook independent searches using the inclusion and exclusion criteria without any exchange of notes.

Inclusion/Exclusion Criteria

Peer-reviewed articles in English language reporting myo-inositol concentrations in the brain in patients with schizophrenia or schizoaffective disorder in comparison with a healthy control group were included. We did not include studies that only report on patients with bipolar disorder or depression related psychosis. We selected studies where the largest proportion of MRS voxel was placed on the medial prefrontal cortex, anterior to the posterior commissure, as per the cingulate boundaries defined by Vogt et al. (26). This ensured that both caudal and rostral ACC placements were included, but posterior cingulate voxels were excluded. In line with Egerton et al. (27), we will use the term medial frontal cortex (mFC) to describe this region of distributed voxel placement.

We excluded 1H-MRS studies that reported within-subject changes in myo-inositol without the required group comparison contrast and studies that excluded adult samples of age >16. If a single study was reported as 2 samples, the largest sample was included. In case of partial overlap, both studies were included with weighting based only on the non-overlapping sample for the smaller study (28, 29). We also excluded studies where no information was available on voxel placement (30) or when study-specific Cramer-Rao Lower Bound (a measure of MRS signal quality and reliability) was exceeded for myo-inositol signal (31).

We extracted the study-specific mean and standard deviation of 1H-MRS myo-inositol concentration for the control and patient groups. As the meta-analysis was based on effect size from group differences, we included absolute as well as ratio measures of myo-inositol concentrations, as long as both patients and controls in a dataset had identical metrics reported. When a study reported on more than 1 demographically stratified patient group, all contrasts were included in the meta-analysis (29); when groups were stratified according to clinical characteristics (e.g., treatment response) but compared against a single control group, the contrasts were combined to form a single dataset (weighted mean and pooled SD for a single patient group) (32). When voxels were split into 2 hemispheres, average values were computed (mean value from the 2 hemispheres and

pooled SD). We contacted authors when these values were not reported or if moderator variables for meta-regression were not available.

Meta-analysis was conducted using the *metafor* package of R CRAN (33). We used a random-effects model to calculate the pooled effect size, with 95% confidence limits. This approach enables more robust inferences when there is a notable heterogeneity among individual studies. We assessed heterogeneity using I^2 statistics for quantification and Cochran's Q for statistical significance test. Potential publication bias was quantified using Egger's test. Sensitivity testing was carried out using a jack-knife approach. During each of the iterations of this leave-one-out jack-knife testing, one study was left out and the meta-analytical estimate for (n-1) studies was recalculated. Meta-regression analyses were undertaken to investigate the effect of (1) age (based on mean age of patients) (2) gender (based on % female patients) (3) medication status (based on % unmedicated patients) (4) scanner strength (in Tesla) and (5) duration of illness (based on mean years of illness).

RESULTS

Search Results

The literature search identified 19 studies (one with 2 eligible contrasts (29)), published between 2002 and 2018, with a total of 561 patients and 585 controls (PRISMA flow diagram presented **Figure 1**) (29, 32, 34–49). The sample sizes ranged from 10 to 75 for controls and 9–72 for patients (**Table 1**). Mean illness duration varied between 0.49 and 27.4 years.

The voxel placement of individual studies is shown in **Figure 2**. MRS parameters for individual studies are shown in **Table 2**.

Meta-Analysis Results

The estimate of heterogeneity had a trend level statistical significance ($I^2 = 14.61\%$; Cochran's $Q = 27.64$, $p = 0.09$) among the 20 datasets eligible for analysis. Random effects analysis revealed reduced myo-inositol content in patients

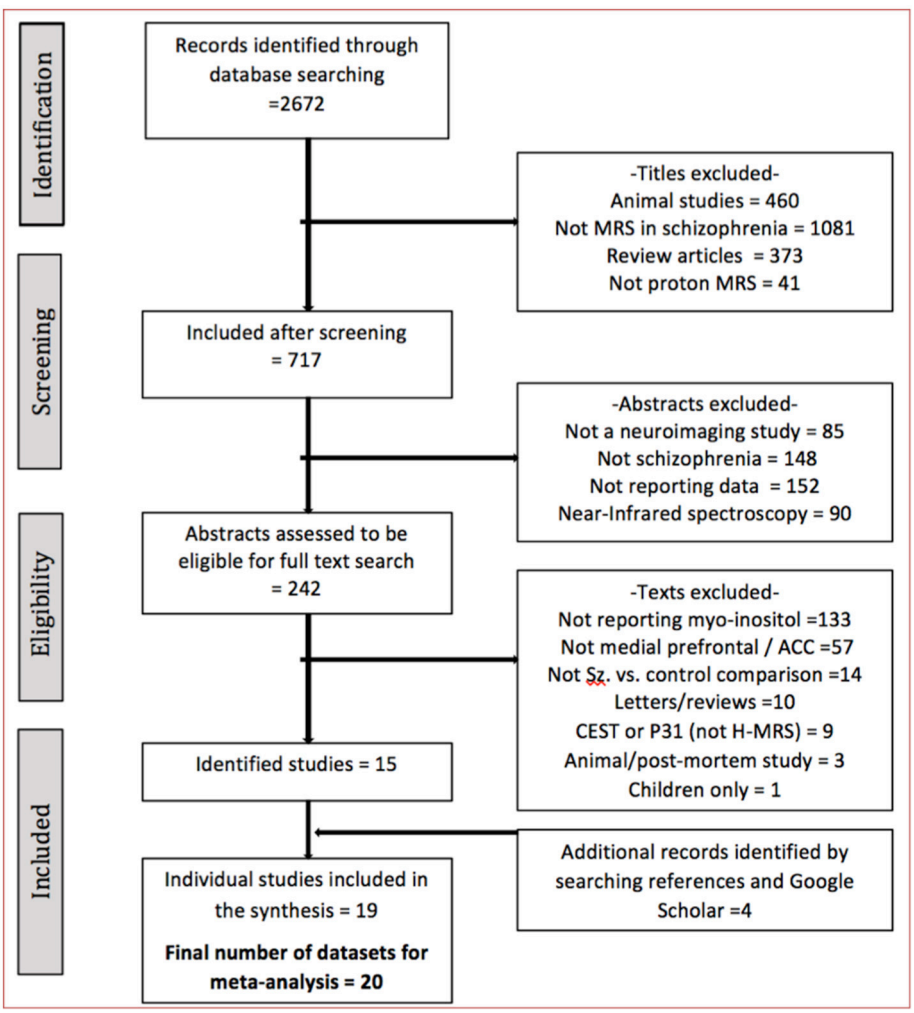

FIGURE 1 | The literature search process.

TABLE 1 | Clinical and demographic features of studies included in the meta-analysis.

Study	Year	Number of patients/controls	Patients mean ml (SD)	Controls Mean ml (SD)	% Female patients	Age patient Mean (SD) in years	Age controls Mean (SD) in years	Unmedicated patients in %	Illness duration Mean (SD) in years
Theberge	2002	20/20	8.82 (3.92)	8.72 (2.71)	35.00	25.40 (7.20)	25.52 (7.29)	100	1.75 (2.00)
Delamillieure	2002	17/14	0.63(0.19)	0.66(0.13)	17.65	31.25(6.09)	30.14(6.39)	29.41	8.42(5.45)
Theberge	2003	21/21	9.73 (3.1)	8.74 (3.38)	4.76	37.10 (10.60)	33.30 (11.73)	0	15.6 (8.92)
Yasukawa	2005	15/20	0.98 (0.28)	1.29 (0.24)	46.67	32 (4.9)	36.1 (6.8)	13.33	1.7 (2.10)
Ongur	2008	17/21	0.92(0.33)	1.09(0.32)	41.18	41.8 (9.8)	34.3(10)	0	NA
Tayoshi	2009	30/25	6.73 (2.2)	8.22 (2.35)	53.33	33.8 (9.5)	34.9 (10.7)	0	10.3 (8.7)
Ongur	2010	21/19	0.25 (0.03)	0.27 (0.04)	33.33	39 (10.8)	36.3 (9.8)	13.33	21.1 (7.3)
Shirayama	2010	19/18	5.7 (0.68)	5.55 (0.72)	36.84	30.5 (5.6)	31.4 (8.4)	5.26	7.3 (5.2)
Lutkenhoff	2010	9/21	7.90(1.73)	8.26(2.65)	44.44	48.8(11.5)	55.7(3.8)	0	27.4(11.1)
Bustillo	2014	72/75	10.97 (5.47)	11.03 (4.96)	15.28	36.43 (14.25)	35.04 (12.17)	3.7	15.9 (5.5)
Demjaha	2014	14/10	6.88 (1.66)	6.39 (1.07)	54.17	44.8 (10.9)	44.2 (8.9)	0	16.2(9.4)
Chiappelli	2015	59/69	6.84 (0.84)	6.94 (0.60)	30.51	37.1 (10.6)	33.3 (11.73)	5.08	NA
Brandt	2016	24/24	6.36 (1.34)	6.69 (0.88)	20.83	37.5 (16.7)	36.6 (14.6)	0.00	NA
Rowland	2016a	45/53	6.8 (0.9)	6.90 (0.60)	35.56	37.7 (12.8)	37.1 (13.1)	8.9	14.7 (12.1)
Rowland	2016b	27/29	5.8 (0.64)	5.80 (0.42)	37.04	34.4 (13.1)	29.7 (9.4)	18.52	13.1 (12.1)
Chiu	2017	19/14	5.13 (2.65)	7.71 (1.63)	42.11	29.11 (6.68)	27.71 (5.88)	0	1.47 (1.23)
Taylor	2017	16/18	8.4 (1.3)	8.00 (0.80)	18.75	22.7 (2.9)	23.9 (4.6)	6.06	2.46 (1.31)
Wijtenburg (young)	2017	48/54	6.6 (0.7)	6.72 (0.50)	29.17	25.2 (4.5)	25.2 (4.8)	8.33	6.1 (5.8)
Wijtenburg (older)	2017	47/39	6.82 (0.9)	7.00 (0.80)	44.68	49.5 (5.4)	51.2 (5.7)	4.26	25.4 (9.3)
Reid	2018	21/21	4.88 (0.47)	5.03 (0.50)	23.81	23.2 (4.4)	23.5 (4.5)	4.76	0.49 (0.86)

ml, myo-inositol (absolute or ratio measure of concentration).

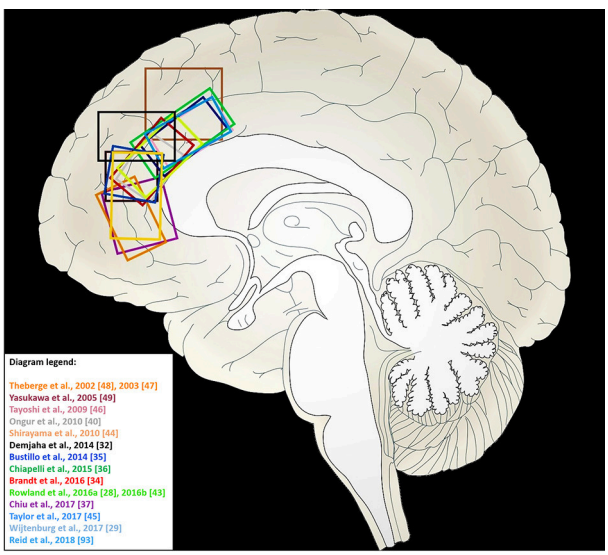

FIGURE 2 | Voxel locations in medial frontal cortex for 1H-MRS studies of myo-inositol included in this meta-analysis. Studies from which a sagittal view of the MRS voxel could not be obtained are not included in this illustration.

with schizophrenia compared to healthy controls (effect estimate = 0.19, 95% CI [0.05–0.32], $z = 2.72$, $p = 0.0067$). These results are displayed in the forest plot **Figure 3**.

Sensitivity/Bias Analysis

All the 16 iterations of the leave-one out analyses were statistically significant, indicating that the meta-analytical estimates were reliable and not influenced by any single study. Egger's test for funnel plot asymmetry (**Figure 4**) was not statistically significant ($t = 0.77$, $p = 0.45$), indicating low probability of publication bias.

Meta-Regression Analysis

There was a statistically significant moderator effect of the percentage of female patients included in the samples in the effect size for myo-inositol ($z = 2.53$, $p = 0.011$). With this moderator, heterogeneity significantly decreased (Cochran's Q = 21.2, $p = 0.27$). Specifically, studies with more female patients were more likely to report reduced myo-inositol concentrations in patients compared to controls (**Figure 5**). We did not find any statistically significant moderator effect of the proportion of unmedicated patients ($z = -0.60$, $p = 0.55$), scanner strength ($z = -1.21$, $p = 0.22$), echo time ($z = 1.59$, $p = 0.11$), repetition time ($z = 0.13$, $p = 0.9$), age of patients ($z = -0.05$, $p = 0.95$), and duration of illness ($z = -0.94$, $p = 0.34$).

DISCUSSION

The main finding from this meta-analysis is the observation of a small, but statistically significant reduction in myo-inositol concentration in the medial frontal cortex in schizophrenia. There is a notable heterogeneity across MRS studies; a substantial

TABLE 2 | MRS parameters of individual studies.

Study	Year	Field strength (T)	MRS fitting model	Voxel size/volume (cm × cm × cm) or cc	MRS sequences	TE/TR (ms)
Theberge	2002	4	fitMAN	1.0 × 1.5 × 1.0	STEAM	20/2,000
Delamillieure	2002	1.5	In-house analysis	3 × 1.5 × 2.5	STEAM	30/1,500
Theberge	2003	4	fitMAN	1.0 × 1.5 × 1.0	STEAM	20/2,000
Yasukawa	2005	1.5	In-house analysis	1.8 cc	PRESS	30/1,500
Ongur	2008	4	LCModel	2.0 × 2.0 × 2.0	PRESS	48/2,000
Tayoshi	2009	3	LCModel	1.7 × 1.7 × 1.5	STEAM	18/5,000
Ongur	2010	4	LCModel	2.3 × 2.2 × 2.3	MEGA-PRESS	30/5,000
Shirayama	2010	3	LCModel	2.8 × 3.0 × 2.2	PRESS	68/2,000
Lutkenhoff	2010	3	LCModel	2.0 × 2.0 × 2.0	PRESS	30/3,000
Bustillo	2014	3	LCModel	2.0 × 2.0 × 3.0	PRESS	40/1,500
Demjaha	2014	3	LCModel	2.0 × 2.0 × 2.0	PRESS	30/3,000
Chiappelli	2015	3	LCModel	4.0 × 3.0 × 2.0	PR-STEAM	6.5/2,000
Brandt	2016	7	LCModel	3.0 × 2.0 × 1.2	STEAM	28/3,000
Rowland	2016a	3	LCModel, GannetFit	4.0 × 3.0 × 2.0	PR-STEAM	14/3,000
Rowland	2016b	7	LCModel	3.0 × 2.0 × 2.0	STEAM	6.5/2,000
Chiu	2017	3	GannetFit	3.0 × 3.0 × 3.0	MEGA-PRESS	68/2,000
Taylor	2017	7	fitMAN	2.0 × 2.0 × 2.0	STEAM	10/3,000
Wijtenburg (young)	2017	3	In house analysis	3.0 × 4.0 × 2.0	PR-STEAM	6.5/2,000
Wijtenburg (older)	2017	3	In house analysis	3.0 × 4.0 × 2.0	PR-STEAM	6.5/2,000
Reid	2018	7	LCModel	2.7 × 2.0 × 1.0	STEAM	5/10,000

LCModel, Linear Combination Model; STEAM, STimulated Echo Acquisition Mode; PRESS, Point REsolved Spectroscopic Sequence; MEGA-PRESS, MEshcher-GArwood Point RESolved Spectroscopy; PR-STEAM, Phase Rotation STimulated Echo Acquisition Mode; TE/TR, Echo Time/Repetition Time.

proportion of this heterogeneity is explained by the sex distribution in individual studies. In studies with higher number of female patients, the myo-inositol reduction is much more pronounced. We found no evidence of publication bias, and the meta-analytic estimates were sensitive to removal of any of the individual studies. These results indicate that myo-inositol reduction in medial frontal cortex occurs in some patients with schizophrenia, especially in a subset that is more likely to include female patients.

To our knowledge, this is the first meta-analysis of MRS myo-inositol studies in schizophrenia. Post-mortem studies in schizophrenia indicate a reduction in frontal myo-inositol (50) as well as reduced glial cell count (51), of 32–35% in layer 5 (52, 53) and 20% in layer 6 of the prefrontal cortex (54), though contradicting results indicating normal (55, 56) or increased glial cell counts also exist (57, 58). In this context, reduced myo-inositol resonance reported in our meta-analysis, when taken together with reduced glutamate levels reported in established cases of schizophrenia (59), may reflect deficits in astrocyte activation and recruitment [as proposed in (21)], rather than an actual reduction in the cell count.

Our meta-regression analysis indicates that studies with female subjects are more likely to report lower myo-inositol resonance among patients. An association between sex and myo-inositol has not been reported so far in schizophrenia (36, 46). Interestingly, Chiappeli et al. reported that depressive symptoms, rather than sex, are associated with lower myo-inositol in schizophrenia (36). Both reductions in myo-inositol (60) and glial loss (61) in the medial prefrontal cortex are reported in depressive disorder. Given that one-third of patients with schizophrenia require antidepressant treatments (62), it is possible that myoinositol reduction is prominent in a subgroup of patients prone to depression. We were not able to test this notion, as except for Chiappeli et al. other MRS studies have not reported on the distribution of affective symptom severity among patients with schizophrenia. Nevertheless, it is worth noting that depression is much more common among women, than men with schizophrenia (63). Sex-specific epigenetic differences have been noted in the enzymes that regulate myo-inositol turnover in rat tissues (64). Importantly, astrocytes exhibit sexual dimorphism during development (65) and in their response to inflammation in later life (66, 67). Further investigations in larger samples of female human subjects, and in patients with and without affective symptoms are warranted.

Meta-analyses of medial prefrontal MRS studies suggest that glutamate (68), N-acetyl aspartate levels (69) are reduced in schizophrenia indicating possible dendritic reduction (70), while no consistent changes are noted in GABA concentration (27) or pH levels (71). Glutamate levels are higher during early stages of schizophrenia, but appear reduced in older cohorts with more established illness (68). We did not observe any age- or illness duration related effects on myo-inositol reduction, suggesting that astroglial dysfunction could be an invariant feature of schizophrenia, possibly contributing to the observed course of glutamatergic abnormalities. Preclinical studies suggest that at excitotoxic levels of glutamatergic signaling, inositol

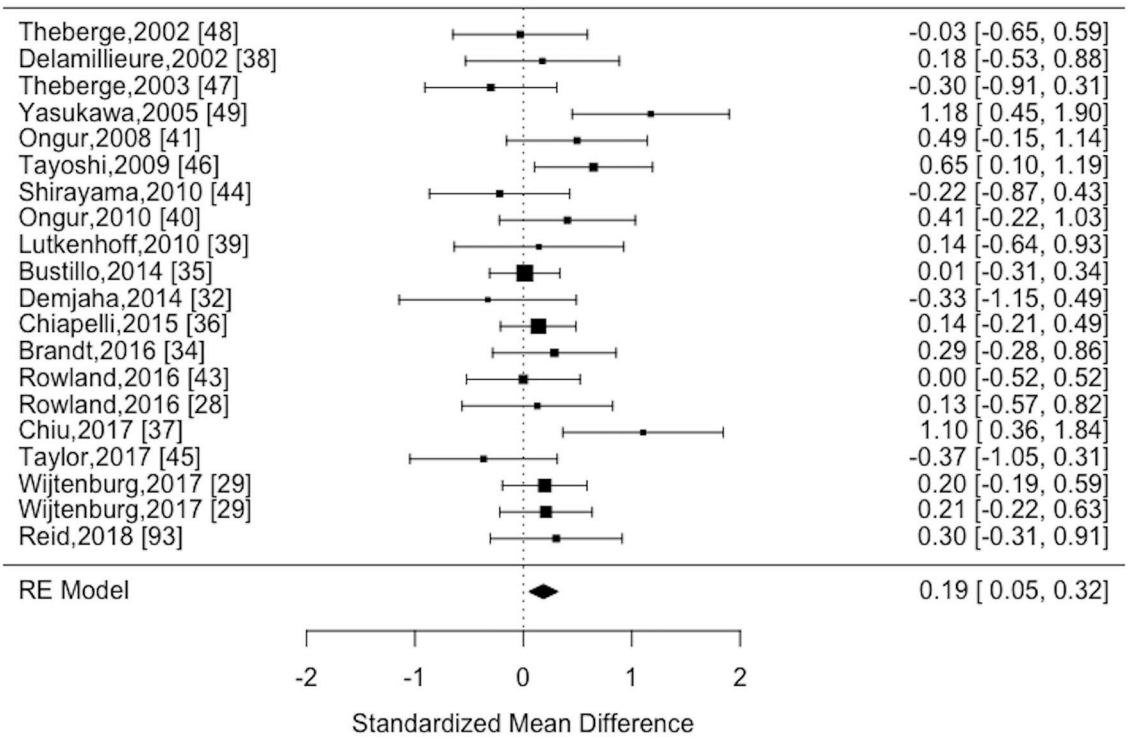

FIGURE 3 | Forest plot of MRS myo-inositol studies comparing schizophrenia vs. healthy controls.

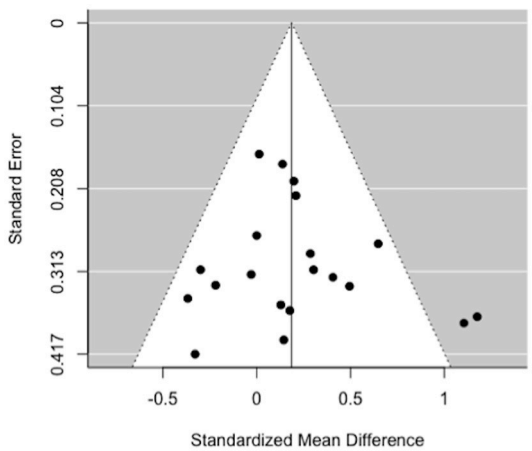

FIGURE 4 | Funnel plot of MRS myo-inositol studies comparing schizophrenia vs. healthy controls.

turnover could be notably reduced. In this context, the putative dysfunction of synaptic transmission in schizophrenia could share a common origin, simultaneously affecting the neuron-astroglia network. Similar to NAA, myo-inositol also reflects cellular membrane integrity. Thus a combined NAA and myo-inositol changes could reflect the status of dendritic spine development or loss, as shown in preclinical studies (72). While the existing MRS literature cannot be taken as conclusive due to several technical limitations (as highlighted in the meta-analyses cited above), the observations to date make a compelling case to consider astrocytic dysfunction in further detail in schizophrenia.

There are several caveats that need to be considered when interpreting the results reported here. We limited our analysis to medial prefrontal cortex, as the number of studies examining other brain regions is limited and voxel placements are more diverse. As a result, the observed myo-inositol reduction may not be generalizable to other brain regions. In fact, an increase in MRS myo-inositol signal has been reported in regions such as basal ganglia (73) and parietal lobe (74) in patients with schizophrenia, while a reduction occurs in medial temporal white matter (75). Secondly, mood stabilizers acutely deplete inositol levels (76). None of the included studies reported on the use of mood stabilizer drugs in the patient samples. The effect of antipsychotics on myo-inositol concentration is hitherto unknown. Antipsychotics can reduce astrocyte count, and thus contribute to reduced myo-inositol concentration (77), though regional differences can be expected from existing data (78). We did not find any systematic association between either unmedicated patient numbers or duration of illness (which often relates also to cumulative antipsychotic exposure in clinical settings) to the reported effect sizes. Furthermore, both schizophrenia and antipsychotics can affect metabolite relaxation rates (mostly T1, but likely also T2) (79–81). Therefore, the choice of acquisition technique, at a given field strength, could affect the ability to detect a difference between patients and controls. Nevertheless, we did not observe any linear relationship

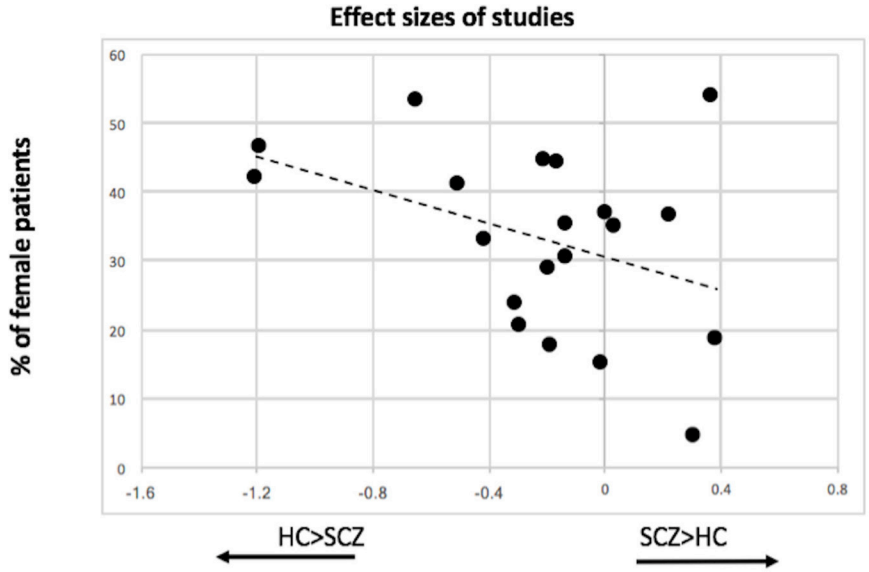

FIGURE 5 | Association between proportion of female patients included in individual MRS studies and the effect size of myo-inositol resonance.

between echo time, scanner strength, repetition time and effect sizes reported in individual studies. We noted several studies where MRS sequences were suitable to extract myo-inositol concentrations alongside other metabolites, but myo-inositol levels were not measured or reported. Though our estimate of publication bias was low, it is likely that MRS myo-inositol concentration is largely underreported in the literature. Finally, we did not include analysis that primarily contrasted bipolar disorder or depression with psychosis with healthy controls or patients with schizophrenia. Thus, the observed changes in myo-inositol cannot be taken to be specific for schizophrenia.

Prenatal exposure to maternal immune activation (MIA) reduces cingulate cortex myo-inositol in mice, which in turn relates to physiological markers of schizophrenia phenotype such as deficits in pre-pulse inhibition and reduced glutamic acid decarboxylase (GAD_{67}) levels (82). These changes were reversed when the offspring were exposed to a *n-3 polyunsaturated fatty acid* (PUFA) enriched post-weaning diet (82). Consistent with this observation, healthy human subjects who have reduced omega-3 fatty acid profile (measured from erythrocytes), show reduced medial prefrontal myo-inositol and exhibit slower reaction times in a continuous performance task (83). We speculate that these observations, considered alongside the reported reduction in myo-inositol levels in schizophrenia, may indicate a specific developmental perturbation. It is worth noting that dietary replacements may not have the same intended effect across disorders; for example, in major depressive disorder where myo-inositol level is reduced, inositol supplementation appears to be beneficial (84, 85), though similar effects have not been observed in schizophrenia (86, 87). Studies that investigate the effect of dietary interventions on brain myo-inositol levels in specific diagnostic subgroups are warranted to further understand the translational potential of such approaches.

It is important to note that both increased (21, 22) and reduced (88–91) brain myo-inositol levels have been noted in various inflammatory states. Thus, the reduced myo-inositol level noted in schizophrenia does not contradict the role of neuroinflammation in this illness. In fact, this observation adds an important clarification that the inflammatory changes observed to date may be secondary to a permissive astrocytic environment, whereby reduced myo-inositol levels in astrocytes facilitate osmotic damage, as well as glutamatergic excess. Without longitudinal data that tracks pre-psychotic and post-psychotic changes in same individuals, this notion of primary astrocytic dysfunction should be considered to be merely speculative.

In summary, in patients with schizophrenia, a small but statistically significant reduction in medial prefrontal myo-inositol resonance is observable. The size of the reported effect indicates that the biological pathways affecting the myo-inositol system are likely to operate only in a subset of patients with schizophrenia. In this regard, MRS myo-inositol could be a useful tool to parse heterogeneity as well as to explore treatment stratification in schizophrenia. Furthermore, combining MRS myo-inositol measurement with *in-vivo* probes of astroglial function (e.g., PET ligands selective for the astrocytic imidazoline binding sites (92)) could take this investigation further in the near future.

AUTHOR CONTRIBUTIONS

LP conceived, designed, supervised the analysis, and wrote the draft manuscript. TD undertook the statistical analysis, prepared figures and tables, and contributed to writing the manuscript. JR undertook the statistical analysis and contributed to writing the manuscript. AD and AJ undertook literature search, prepared figures/tables, and contributed to writing the

manuscript. PS undertook literature search, verified extracted data, and contributed to writing the manuscript. JT contributed to the conception of the review and contributed to writing the manuscript.

FUNDING

This work was funded by the Canadian Institute of Health Research (Foundation Grant 375104 to LP), Bucke Family Fund (LP and PS), and the Academic Medical Organization of South Western Ontario (LP). This work was also supported by Miguel Servet contract from the Carlos III Health Institute (Spain) to JR (CP14/00041).

ACKNOWLEDGMENTS

We acknowledge the authors who provided data on request: Dr. Juan Bustillo.

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Conflict of Interest Statement: LP reports personal speaker/advisory fees from Otsuka Canada, Janssen Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Otsuka Canada outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.