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Greater Choline-Containing Compounds and Myo-inositol in Treatment-Resistant Versus Responsive Schizophrenia: A ^{1}H-Magnetic Resonance Spectroscopy Meta-analysis

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Abstract

BACKGROUND: The neurobiology of treatment-resistant schizophrenia (TRS) is poorly understood, and meta-analytic consensus regarding magnetic resonance spectroscopic profiles of glutamate, choline-containing compounds, myo-inositol, and other metabolites in the condition is lacking.

METHODS: In this meta-analysis, we examined published findings for *N*-acetylaspartate, choline-containing compounds (phosphocholine+glycerophosphocholine), myo-inositol, creatine+phosphocreatine, glutamate, and glutamate+glutamine in the anterior cingulate cortex and dorsal striatum in people with TRS versus non-TRS as well as TRS versus healthy control participants (HCs) and TRS versus ultra TRS (i.e., TRS with clozapine resistance). A MEDLINE search revealed 9 articles including 239 people with pooled TRS and ultra TRS, 59 with ultra TRS, 175 with non-TRS, and 153 (HCs) that met meta-analytic criteria.

RESULTS: Significant effects included higher anterior cingulate cortex phosphocholine+glycerophosphocholine and myo-inositol in the pooled TRS and ultra TRS group than in both the non-TRS group and HCs as well as higher dorsal striatal phosphocholine+glycerophosphocholine in ultra TRS versus HCs, but no differences in other regional metabolites.

CONCLUSIONS: The observed metabolite profile in TRS (higher phosphocholine+glycerophosphocholine and myo-inositol signal) is consistent with the hypothesis that TRS has a neuroinflammatory component, although this meta-analysis is not a critical test of that hypothesis. A similar profile is seen in healthy aging, which is known to involve increased neuroinflammation and glial activation. Because the overall number of datasets was low, however, results should be considered preliminary and highlight the need for additional studies of brain metabolites in TRS and their possible association with inflammatory processes.

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Although antipsychotic medication is effective at reducing positive symptoms in most people with schizophrenia (SZ), a significant proportion (up to ~30%) do not respond to 2 adequate trials of first-line treatment (1–3). These individuals are then prescribed clozapine, for which a significant proportion (up to ~60%) still do not respond (4). Clozapine-resistant patients are then prescribed alternative forms of treatment, such as electroconvulsive therapy or combinations of anti-psychotics, for example, even when evidence is not strongly in favor of their efficacy (5–8). In many of these cases, therefore, symptoms persist indefinitely.

Because the primary mechanism of action for antipsychotic medications is the blockade of dopaminergic D2 receptors, it has been hypothesized that a reason that these medications fail in treatment-resistant SZ (TRS) is that, unlike non–treatment-resistant SZ (nTRS), the neurobiological basis of TRS is predominantly driven by nondopaminergic mechanisms [reviewed by (9)]. Hypothesized mechanisms include increased glutamatergic signaling (via NMDA receptor downregulation on GABAergic [gamma-aminobutyric acidergic] interneurons) (10) as well as neuroinflammatory processes (as evidenced by increased cytokine levels) (11,12). Electroconvulsive therapy (which induces seizures in the brain) may also be effective for TRS, although the mechanisms of action are unclear (13).

To gain further insight into the neurobiology of TRS, researchers have used neuroimaging techniques such as proton magnetic resonance spectroscopy (^{1}H-MRS), which allows for measurement of neurometabolite levels in the central nervous system. Commonly examined neurometabolite signals include glutamate, glutamate+glutamine (glx), *N*-acetyl-aspartate (NAA), creatine+phosphocreatine (Cr+PCr), phosphocholine+glycerophosphocholine (PCho+GPCho), myo-inositol, and GABA. As a ubiquitous cellular metabolite as well as the most widespread neurotransmitter in the mammalian brain (14), ^{1}H-MRS measures of glutamate are typically thought to convey information about the capacity for glutamatergic neurotransmission (15). NAA is synthesized almost exclusively in neuronal mitochondria. As such, it is thought to reflect the integrity of neuronal metabolism (16,17) and mitochondrial energy output (18). Cr+PCr together have major roles as carrier molecules for high-energy phosphate bonds in all brain cells. The ^{1}H-MRS Cr+PCr resonance is typically considered to be an indicator of general brain metabolic health (17). The combined signal from PCho and GPCho provides information about cell membranes because these 2 choline-containing compounds are part of the anabolic and catabolic pathways, respectively, of cell membrane phospholipid metabolism (19,20). An increase in membrane turnover or a higher density of cell membranes in the MRS voxel are among the factors that may be associated with an increase in the PCho+GPCho signal (17,21,22). Myo-inositol has a major role in cell volume regulation as a nonperturbing osmolyte (23). It also acts as a precursor to membrane lipids and second-messenger compounds (17) and serves as a precursor to phosphatidyl-inositol [which facilitates binding of neurotransmitters to their receptors (24)]. Notably, elevations in myo-inositol and/or PCho+GPCho have been consistently observed in some clinical conditions that are characterized by neuroinflammation, including neuroviral infections and traumatic brain injury (25–32) as well as in experimental models of glial activation (29,30). Importantly, however, elevated PCho+GPCho and myo-inositol have also been observed in noninflammatory states such as normal infancy and early childhood (33); thus, their elevation sometimes, but not necessarily, co-occurs with neuroinflammation.

Despite the potential of meta-analysis to advance understanding of the neurochemical basis of TRS, to our knowledge, only 1 meta-analysis has been conducted to date in this population. This meta-analysis compared glutamate and glx between TRS and nTRS and showed no significant differences between groups with an effect size of Hedges' g = 0.21 for glutamate and 0.09 for glx in the anterior cingulate cortex (ACC) (34). As noted by the authors, however, the sample size was limited because only 4 studies met the inclusion criteria for analysis. The previous meta-analysis also did not examine levels of other metabolites. Therefore, the goal of the current study was to conduct an updated meta-analysis of glutamate and glx in TRS, as well as to compare levels of NAA, Cr+PCr, PCho+GPCho, and myo-inositol between TRS and nTRS. Given current theories suggesting that glutamate and neuroinflammation are implicated in TRS, we hypothesized that our meta-analysis would demonstrate significantly higher glutamate, PCho+GPCho, and myo-inositol in TRS than in nTRS. We also compared metabolite levels for TRS versus healthy control (HC) participants well as TRS versus ultra TRS (people with TRS who also do not respond symptomatically to clozapine treatment).

METHODS AND MATERIALS

Study Selection

The MEDLINE database was searched on April 1, 2023 to identify journal articles using the following query: ([*treatment resistant schizophrenia* OR *treatment refractory schizophrenia* OR *clozapine resistant schizophrenia* OR *ultra resistant schizophrenia*] AND [*magnetic resonance spectroscopy* OR *^{1}H-MRS*]). This search yielded 27 records for screening, from which 9 articles were selected for eligibility [see Figure S1 for PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (35) and Table S1].

Meta-Analysis

Meta-analyses included comparisons between TRS and nTRS, TRS and HCs, and TRS and ultra TRS.[1] Because most of the datasets did not distinguish between TRS and ultra TRS, the ultra TRS and TRS datasets were pooled into a single group (TRS-All) for comparisons between TRS and nTRS.

For each brain region studied, author JS extracted and author RJM verified data. Extracted data included sample sizes, means, and standard deviations of metabolite values. Regional metabolites were only included if at least 3 datasets were available for analysis (i.e., $k \geq 3$). Studies were excluded if they lacked a comparison group (nTRS or HCs; 1 excluded). Studies were also excluded if they did not report metabolite standard deviation or a value that could be used to calculate standard deviation (1 excluded). For studies that reported partially overlapping samples, only data from the study with the largest sample size were included. When metabolite values normalized to both water and Cr+PCr were reported, the normalization method that produced the lowest coefficient of variation

[1]Notably, we did not compare the nontreatment-resistant schizophrenia group to the healthy control participant group in this meta-analytic study because it would not be an accurate representation of the data. This is because most proton magnetic resonance spectroscopy studies compare healthy control participants to participants with schizophrenia regardless of treatment status. To properly conduct this analysis would require segregating individuals with schizophrenia in these previous studies according to their treatment response profiles.

averaged across groups was used [because lower coefficients of variation values indicate higher ^{1}H-MRS data quality (36)]. Studies that did not examine glutamate, glx, NAA, Cr+PCr, PCho+GPCho, or myo-inositol were excluded because an insufficient number of datasets were available from other metabolites for analysis (2 excluded). One longitudinal study included a baseline scan of patients with SZ who were antipsychotic-naïve followed by a follow-up scan after 4 weeks of antipsychotic treatment; because all other studies included medicated patients, the 4-week data from this study was used for meta-analysis (37). Another longitudinal study scanned antipsychotic-medicated patients with SZ before and after treatment with riluzole; only baseline data from this study were included in analyses (38).

The effect size for each dataset was calculated as Hedges' g, which corrects for small sample sizes (39). The meta-analysis used an inverse variance-weighted, random-effects model to calculate the pooled effect size. For determining significance, tau^2 was calculated by the restricted maximum likelihood method. The analysis was conducted with JASP software, which uses the R-based metafor package as its computational engine (40). Heterogeneity across studies was quantified as I^2, and a χ^2 test of the Q statistic was used to test for significant departure from homogeneity. Small study bias was examined using Egger's test of asymmetry. Analyses with significant ($p < .05$) Egger's tests were re-analyzed with the most bias-causing dataset removed if k remained ≥3.

RESULTS

Of the 27 articles from MEDLINE that were assessed for eligibility, after applying inclusion and exclusion criteria (Table S1), data from 9 studies were extracted for inclusion in meta-analyses (37,38,41–47). Criteria for TRS and ultra TRS for these studies is provided in Table S2. All studies included TRS criteria over the course of at least 2 antipsychotic trials except for 1 study (37) that only included lack of clinical improvement for 1 trial as a criterion. MRS parameters (acquisition, normalization, voxel location, voxel size) for included datasets are provided in Table 1. Demographic and clinical information for all datasets is provided in Tables S3 and S4, respectively. Briefly, sample participants were ~40 years of age for most datasets, and there were more men than women. People with TRS and ultra TRS qualitatively presented with worse symptoms and were taking higher doses of antipsychotic medications than people with nTRS.

Detailed statistical results for all analyses are listed in Table 2.

TRS Versus nTRS

TRS and ultra TRS datasets were combined into the TRS-All group for TRS versus nTRS analyses.

Anterior Cingulate Cortex.—Across 6 datasets (173 TRS-All, 103 nTRS) in the ACC (41,42,44–47), we found significantly higher PCho+GPCho in TRS-All than in nTRS (Table 2; Figure 1). Across 4 datasets (103 TRS-All, 73 nTRS) (41,44–46), we also found significantly higher myo-inositol in TRS-All than in nTRS (Table 2; Figure 2).

No significant differences were observed between TRS-All and nTRS for ACC glutamate [5 datasets (126 TRS-All, 87 nTRS) (41, 42, 44–46); Table 2 and Figure S2], glx [7 datasets (205 TRS-All, 131 nTRS) (41–47); Table 2 and Figure S3], Cr+PCr [4 datasets (131 TRS-All, 71 nTRS) (41,44,46,47); Table 2 and Figure S4], or NAA [6 datasets (173 TRS-All, 103 nTRS) (41,42,44–47); Table 2 and Figure S5]. After removing a small study outlier (41), the NAA effect size became smaller (Table 2).

Dorsal Striatum.—No significant differences were observed between TRS-All and nTRS for dorsal striatal glutamate [4 datasets (108 TRS-All, 87 nTRS) (37,42,44,46); Table 2 and Figure S6], glutamate+glutamine (glx) [4 datasets (108 TRS-All, 87 nTRS) (37,42,44,46); Table 2 and Figure S7], Cr + PCr [3 datasets (91 TRS-All, 75 nTRS) (37,44,46); Table 2 and Figure S8], NAA [4 datasets (108 TRS-All, 87 nTRS) (37,42,44,46); Table 2 and Figure S9], PCho+GPCho [4 datasets (108 TRS-All, 87 nTRS) (37,42,44,46); Table 2 and Figure S10], or myo-inositol [3 datasets (91 TRS-All, 75 nTRS) (37,44,46); Table 2 and Figure S11]. Excluding the 1 study that did not include at least 2 failed antipsychotic trials as a TRS criterion (37) did not appreciably alter these results.

TRS Versus HCs

TRS and ultra TRS datasets were combined into the TRS-All group for TRS versus HC analyses.

Anterior Cingulate Cortex.—Across 5 datasets (154 TRS-All, 112 HCs) in the ACC (41,42,44,46,47), we found significantly higher PCho+GPCho in the TRS group than the HC group (Table 2; Figure 3). Across 3 datasets (84 TRS-All, 64 HC) (41,44,46), we also found significantly higher myo-inositol in the TRS-All group than in the HC group (Table 2; Figure 4).

No significant differences were observed between TRS-All and HCs for ACC glutamate [5 datasets (126 TRS-All, 95 HC) (38,41,42,44,46); Table 2 and Figure S12], glx [7 datasets (205 TRS-All, 145 HC) (38,41–44,46,47); Table 2 and Figure S13], Cr+PCr [4 datasets (131 TRS-All, 99 HC) (41,44,46,47); Table 2 and Figure S14], or NAA [6 datasets (173 TRS-All, 130 HC) (38,41,42,44,46,47); Table 2 and Figure S15]. After removing a small study outlier (41), the difference between TRS-All and HC glutamate became larger but remained nonsignificant (Table 2).

Dorsal Striatum.—Across 3 datasets (90 TRS-All, 62 HCs) (42,44,46), significantly greater PCho+GPCho was observed in TRS-All than in HCs (Table 2; Figure S16). No significant differences were observed for glutamate [3 datasets (90 TRS-All, 62 HC) (42,44,46); Table 2 and Figure S17], glx [3 datasets (90 TRS-All, 62 HC) (42,44,46); Table 2 and Figure S18], or NAA [3 datasets (90 TRS-All, 62 HC) (42,44,46); Table 2 and Figure S19]. An insufficient number of datasets were available to analyze Cr+PCr or myo-inositol.

Ultra TRS Versus TRS

Anterior Cingulate Cortex.—No significant differences were observed between ultra TRS and TRS for ACC glx [3 datasets (57 ultra TRS, 66 TRS) (42,44,47); Table 2 and

Figure S20], NAA [3 datasets (57 ultra TRS, 66 TRS) (42,44,47); Table 2 and Figure S21], or PCho+GPCho [3 datasets (57 ultra TRS, 66 TRS) (42,44,47); Table 2 and Figure S22]. An insufficient number of datasets were available to analyze glutamate, Cr+PCr, or myo-inositol.

DISCUSSION

In this first-ever, to our knowledge, ^{1}H-MRS meta-analysis of choline-containing compounds (PCho+GPCho) and myo-inositol in TRS, we observed 1) significantly higher PCho+GPCho in the ACC in TRS than in nTRS, 2) significantly higher myo-inositol in the ACC in TRS than in nTRS, 3) significantly higher PCho+GPCho in the ACC and dorsal striatum in TRS than in HCs, and 4) significantly higher myo-inositol in the ACC in TRS than in HCs. Glutamate, glx, Cr+PCr, and NAA were also examined, but no significant group differences were found. Effect sizes for ACC differences in PCho+GPCho and myo-inositol between TRS and nTRS were between small and moderate (g = 0.36 and 0.46, respectively). Effect sizes were larger for these regional metabolites between TRS and HCs (g = 0.63 and 0.99, respectively). No significant differences were observed between TRS and ultra TRS, although the number of datasets was low (k = 3 for all metabolite comparisons). Related to this point, the overall number of datasets available for analysis was low (maximum k = 7), suggesting that these results should be considered preliminary and highlighting the need for additional research in this area. Nonetheless, the finding that qualitatively greater PCho+GPCho and myo-inositol were observed in TRS (vs. nTRS) in every study that reported these metabolites as well as the lack of evidence suggesting small sample size bias in these analyses suggests that these differences constitute a reliable effect and thus may have important implications for the neurobiology of TRS.

Greater PCho+GPCho and myo-inositol in TRS suggests the possible involvement of a neuroinflammatory process. Elevated PCho+GPCho signal has been observed in conditions that are characterized by inflammation and glial activation, such as chronic hepatitis C (25,48), HIV infection (26), and rheumatoid autoimmune diseases (49). A recent meta-analysis showed elevated PCho+GPCho in moderate to severe traumatic brain injury, but only after the acute phase of the injury (31). The time course of the increase in PCho+GPCho signal may reflect the time course of inflammation and regeneration (including membrane remodeling) following acute brain injury (31,50). Myo-inositol serves as a nonreactive osmolyte that is abundantly expressed in glial cells. One of its important functions involves the regulation of cell volume during morphological changes such as those that occur during glial activation (27). Elevated levels of myo-inositol have been observed in HIV infection (26,51), multiple sclerosis (52), and experimental models associated with histopathological or diffusion imaging evidence of glial activation (30,53). Finally, it is interesting to note that both greater PCho+GPCho and greater myo-inositol are associated with human aging [reviewed in (54); also see (55,56)]. A general increase in chronic inflammation is a hallmark of aging (57). Transcriptomic data have shown that aging is associated with increased markers for astrocytes and microglia (58) and specifically with increased markers of reactive astrocytes in the prefrontal cortex (59). These glial changes may be the mechanism that is responsible for the similar neurometabolic profiles observed in aging and TRS.

The current neurometabolic findings in TRS are similar in some ways but differ in others from recent meta-analytic findings across all individuals with SZ (regardless of treatment response; hereafter abbreviated as SZ-All). As in MRS studies of TRS, the ACC is the brain region that has been examined most frequently in studies of SZ-All. The most consistent finding in SZ-All has been reduced NAA in the ACC and other regions (60–62). The current findings suggest that the pathological process associated with reduced NAA in SZ-All is not more pronounced in TRS. However, a contrasting pattern of results was observed for PCho+GPCho in a recent meta-analysis in SZ-All that showed that choline-containing compounds are elevated in the ACC, other frontal regions, and the striatum (62). Therefore, the current results suggest that the neurometabolic processes that are associated with elevated PCho+GPCho in SZ-All are even more pronounced in TRS. Interestingly, for myo-inositol, the current results are in the opposite direction from that seen in SZ-All. Specifically, we found higher myo-inositol in TRS than nTRS and in TRS than in HCs, whereas a recent meta-analysis showed significantly reduced ACC myo-inositol across SZ-All (vs. HCs) (63). Although the number of TRS studies contributing to the current result is small, the finding of elevated myo-inositol suggests that a distinctive neurometabolic process characterizes TRS. Furthermore, it is possible that this process may be related to activation of astrocytes because a recent study found that blood inflammatory markers decreased in treatment responders but not in nonresponders (64). Because reduced NAA most likely reflects a neuronal process while elevated PCho+GPCho and myo-inositol generally reflect glial processes, the current results suggest that the overall neurometabolic differences between nTRS and TRS that are observable at a meta-analytic level primarily reflect glial dysfunction in TRS.

If TRS is associated with an inflammatory process, then 1) anti-inflammatory agents may have clinical benefit in TRS, and 2) MRS measurements of PCho+GPCho and myo-inositol may have utility as biomarker indices of the effects of these interventions. The only Food and Drug Administration-approved drug for TRS, clozapine, has been shown to have anti-inflammatory effects in vitro (65–68). Anti-inflammatory interventions such as exercise (69) and cannabidiol (70) may also hold promise for TRS, although evidence is highly preliminary and inconclusive. A 2019 meta-analysis of the effects of anti-inflammatory agents in SZ also found an overall (across all studies) decrease in Positive and Negative Syndrome Scale total scores, positive symptoms, and negative symptoms (71). Interventions that significantly reduced symptoms included aspirin, estrogens, estrogen receptor modulators, pregnenolone, minocycline, and *N*-acetyl-cysteine (71). However, the efficacy of these agents in TRS is still unclear.

Surprisingly, no differences were observed in glutamate or glx between TRS and nTRS. Although this result should be considered preliminary due to the low number of datasets that were available for analysis, taken together with the findings for PCho+GPCho and myo-inositol, it suggests that factors that affect glutamate levels are unlikely to be the sole or primary pathogenic process that increases risk for TRS. Nonetheless, a glutamatergic contribution to TRS should not be ruled out for several reasons. First, although nonsignificant, ACC glutamate was still qualitatively higher in TRS than nTRS, with an effect size of 0.24. Therefore, it is possible that our analysis was insufficiently powered and that this difference would become statistically significant over a larger number

of datasets. These preliminary glutamate results contrast with the significantly reduced ACC glutamate seen meta-analytically across SZ-All ($g = -0.19$) (36), suggesting that the future availability of additional studies may provide meta-analytic evidence that TRS is characterized by a distinctive neurometabolic process related to abnormal glutamatergic neurotransmission. It has previously been shown that glutamate effect sizes across SZ-All are larger in studies with better MRS data quality (indexed by metrics such as coefficients of variation and Cramér–Rao lower bound) as well as in studies using MRS echo times ≤ 20 ms (36). None of the studies included in the current meta-analysis used echo times < 30 ms. Adoption of stricter spectral data quality inclusion criteria and shorter echo times in future studies may increase their sensitivity for demonstrating abnormal glutamate levels in TRS.

Although differences in PCho+GPCho and myo-inositol between TRS and nTRS were remarkably consistent across datasets, due to small sample sizes, these results should be considered preliminary and will thus require re-analysis as new studies are published. A second limitation of these findings is that almost all studies (and 100% of ACC studies) examined people with chronic SZ, with an average age >40 years (with 1 exception with a mean age of 34 years). Therefore, we are unable to determine the extent to which long periods of antipsychotic use may have contributed to the observed results. Future studies with first-episode (i.e., antipsychotic-naïve) or recent-onset samples would help to disentangle these effects. Indeed, to our knowledge, only 1 such study has been conducted to date; this study found trend-level higher glutamate in the striatum in TRS than in responders (37). Finally, it is worth noting that all 6 ACC metabolite values in these meta-analyses were numerically higher in the TRS group than the nTRS group, and 5 of the 6 were higher in the TRS group than the HC group. This overall pattern of results could reflect a lower level of signal for the reference molecule in the ACC of the TRS group than the other 2 groups. Because 67% of the ACC metabolite datasets in these contrasts used water as the reference molecule, we cannot exclude the possibility that low water content, abnormal water relaxation, or miscorrection of the water reference signal in the TRS group could change the interpretation of our primary findings.

Conclusions

The results of these analyses provide preliminary evidence that PCho+GPCho and myo-inositol are greater in TRS than in responders. This pattern suggests that TRS may be associated with a neuroinflammatory process, with potentially intriguing implications for future work involving anti-inflammatory interventions for TRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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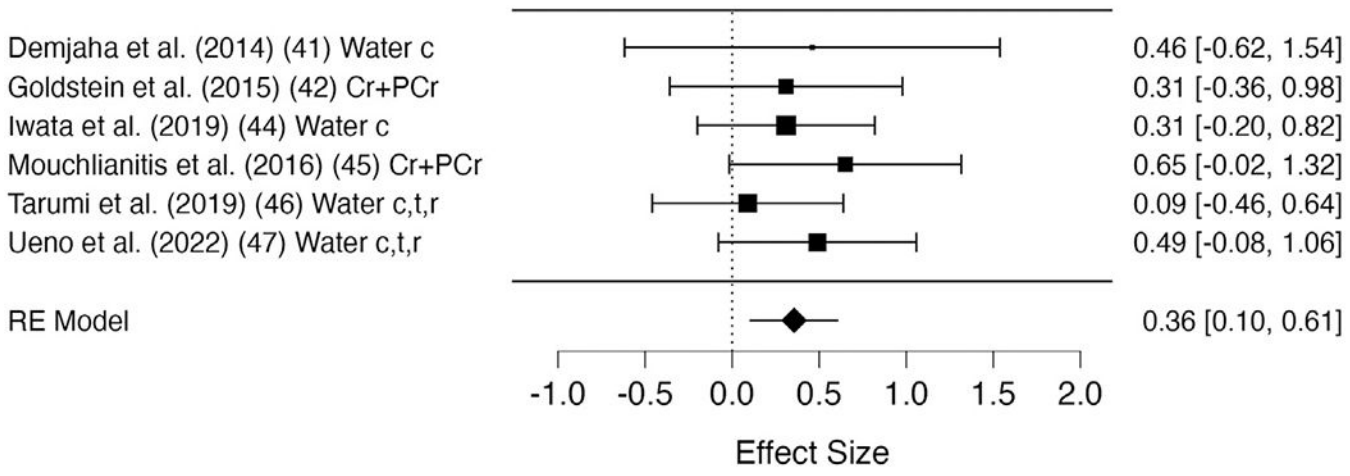

Figure 1.

Meta-analysis forest plot for 6 datasets reporting anterior cingulate cortex choline-containing compounds in treatment-resistant schizophrenia vs. non–treatment-resistant schizophrenia. Author, year, reference number, and normalization method are at left. Hedges' *g* and 95% CIs are at center and right. Effect sizes greater than zero indicate higher levels in the treatment-resistant schizophrenia group. All studies used 3T scanners with point resolved spectroscopy localization and an echo time of 30 or 35 ms except Ueno *et al.* (47) (echo time = 68 ms). c, corrected for water content of cerebrospinal fluid in voxel; Cr+PCr, creatine+phosphocreatine; r, corrected for water relaxation in cerebrospinal fluid, gray matter, and white matter; RE, random effects; t, corrected for water content of tissue (gray matter and white matter) in voxel.

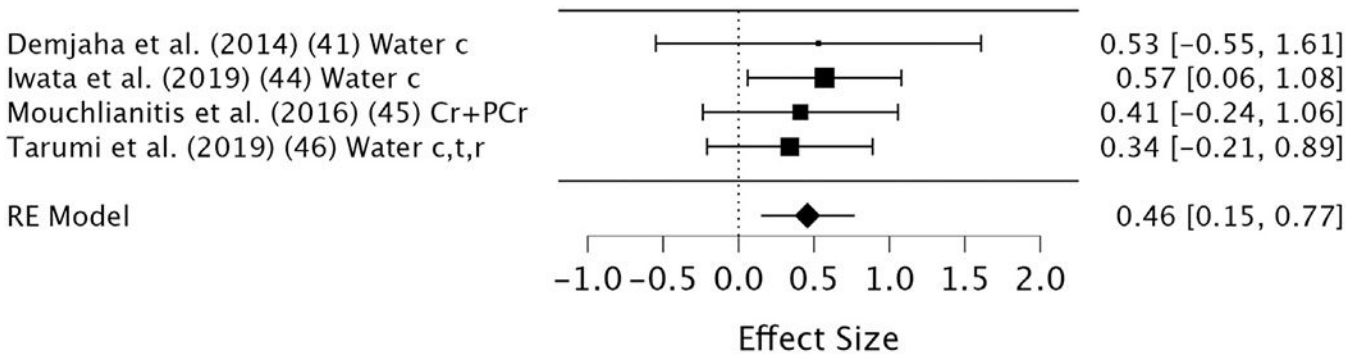

Figure 2.

Meta-analysis forest plot for 4 datasets reporting anterior cingulate cortex myo-inositol in treatment-resistant schizophrenia vs. non–treatment-resistant schizophrenia. Author, year, reference number, and normalization method are at left. Hedges' *g* and 95% CIs are at center and right. Effect sizes greater than zero indicate higher levels in the treatment-resistant schizophrenia group. All studies used 3T scanners with point resolved spectroscopy localization and an echo time of 30 or 35 ms. c, corrected for water content of cerebrospinal fluid in voxel; Cr+PCr, creatine+phosphocreatine; r, corrected for water relaxation in cerebrospinal fluid, gray matter and white matter; RE, random effects; t, corrected for water content of tissue (gray matter and white matter) in voxel.

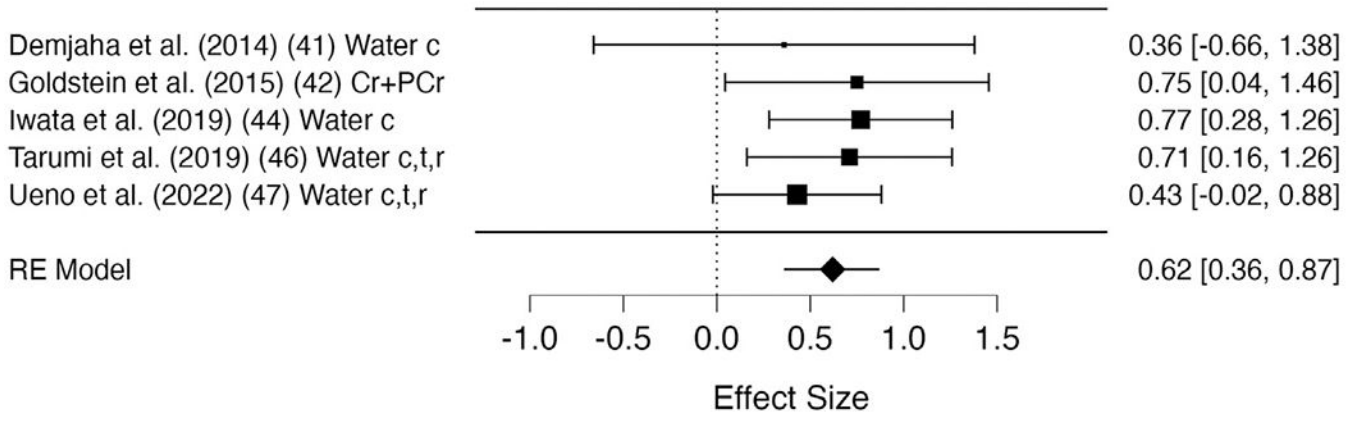

Figure 3.

Meta-analysis forest plot for 5 datasets reporting anterior cingulate cortex choline-containing compounds in treatment-resistant schizophrenia vs. healthy control participants. Author, year, reference number, and normalization method are at left. Hedges' *g* and 95% CIs are at center and right. Effect sizes greater than zero indicate higher levels in the treatment-resistant schizophrenia group. All studies used 3T scanners with point resolved spectroscopy localization and an echo time of 30 or 35 ms except Ueno *et al.* (47) (echo time = 68 ms). c, corrected for water content of cerebrospinal fluid in voxel; Cr+PCr, creatine+phosphocreatine; r, corrected for water relaxation in cerebrospinal fluid, gray matter, and white matter; RE, random effects; t, corrected for water content of tissue (gray matter and white matter) in voxel.

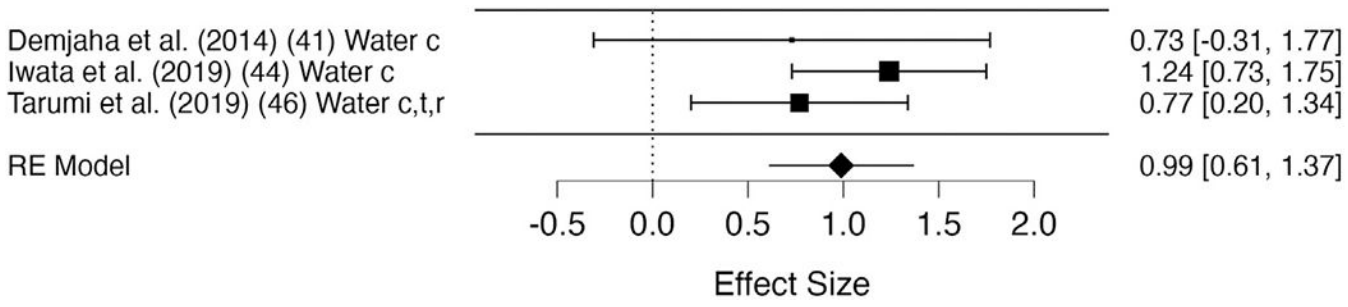

Figure 4.

Meta-analysis forest plot for 3 datasets reporting anterior cingulate cortex myo-inositol in treatment-resistant schizophrenia vs. healthy control participants. Author, year, reference number, and normalization method are at left. Hedges' *g* and 95% CIs are at center and right. Effect sizes greater than zero indicate higher levels in the treatment-resistant schizophrenia group. All studies used 3T scanners with point resolved spectroscopy localization and an echo time of 30 or 35 ms. c, corrected for water content of cerebrospinal fluid in voxel; r, corrected for water relaxation in cerebrospinal fluid, gray matter, and white matter; RE, random effects; t, corrected for water content of tissue (gray matter and white matter) in voxel.

Table 1.

Magnetic Resonance Spectroscopy Methods for Studies Included in Analyses

Study	Metabolite	Normalization	Voxel Location	Voxel Size, mm^3
ACC				
Demjaha *et al.* (41)	All 6	Water c	Unknown ACC	20 × 20 × 20
Huang *et al.* (43)	Glx	NAA	Rostrodorsal ACC	21.5 × 21.5 × 21.5
Iwata *et al.* (44)	All 6	Water c	Rostrodorsal ACC	30 × 20 × 15
Goldstein *et al.* (42)	All except myo-inositol, Cr+PCr	Cr+PCr	Pregenual ACC	12.6 × 12.6 × 12.6
Mouchlianitis *et al.* (45)	All except Cr+PCr	Cr+PCr	Rostrodorsal ACC	20 × 20 × 20
Pillinger *et al.* (38)	Glx, glutamate, NAA	Cr+PCr[a] and water c, t	Pregenual ACC	20 × 20 × 20
Tarumi *et al.* (46)	All 6	Water c, t, r	Rostrodorsal ACC	30 × 20 × 15
Ueno *et al.* (47)	Glx, NAA, PCho/GPCho, Cr+PCr	Water c, t, r	Rostrodorsal ACC	20 × 40 × 30
Dorsal Striatum				
Iwata *et al.* (44)	All 6	Water c	Left dorsal caudate	25 × 15 × 20
Goldstein *et al.* (42)	All except myo-inositol, Cr+PCr	Cr+PCr	Left putamen	15 × 15 × 35
Reyes-Madrigal *et al.* (37)	All except myo-inositol	Water c	Right dorsal caudate	20 × 20 × 20
Tarumi *et al.* (46)	All 6	Water c, t, r	Right dorsal caudate	25 × 15 × 20

All voxels were localized with point resolved spectroscopy. All anterior cingulate cortex (ACC) voxel locations were bilateral.

All 6, glutamate, glutamate+glutamine, NAA; c, corrected for water content of cerebrospinal fluid in voxel; Cr+PCr, creatine+phosphocreatine; Glx, glutamate+glutamine; NAA, *N*-acetylaspartate; PCho+GPCho, phosphocholine+glycerophosphocholine; r, corrected for water relaxation in cerebrospinal fluid, gray matter, and white matter; t, corrected for water content of tissue (gray matter and white matter) in voxel.

[a]Only creatine-normalized data for this study were used for meta-analyses because this normalization resulted in the smallest coefficients of variation.

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Table 2.

Results Summary

Comparison/Region/Metabolite	*k*	*g*	95% CI	Z	*p*	Heterogeneity			Egger's Test	
						Q	I^2	*p*	Z	*p*
TRS vs. nTRS										
ACC										
Myo-inositol[a]	4	0.46	0.15 to 0.77	2.89	.004	0.40	0	.94	0.02	.98
PCho+GPCho[a]	6	0.36	0.10 to 0.61	2.76	.006	1.95	0	.86	0.49	.62
Cr+PCr	4	0.27	−0.19 to 0.73	1.14	.26	6.53	54	.088	0.92	.36
Glutamate	5	0.24	−0.09 to 0.56	1.44	.15	5.31	21	.26	0.81	.42
NAA	6	0.24	−0.09 to 0.57	1.43	.15	11.01	37	.051	2.49	.013
NAA [w/o Ref. (41) (Outlier)]	5	0.14	−0.12 to 0.40	1.03	.30	3.59	0	.46	0.05	.96
Glx	7	0.12	−0.10 to 0.35	1.07	.28	4.35	0	.63	−0.29	.77
Dorsal Striatum										
Myo-inositol	3	0.24	−0.08 to 0.55	1.46	.14	1.37	0	.50	0	.99
Glutamate	4	0.18	−0.26 to 0.61	0.80	.42	6.47	54	.091	0.38	.70
PCho+GPCho	4	0.16	−0.14 to 0.45	1.05	.30	0.51	0	.92	−0.10	.92
Glx	4	0.15	−0.22 to 0.51	0.78	.43	4.30	34	.23	1.07	.29
Cr+PCr	3	0.09	−0.52 to 0.70	0.29	.77	6.87	72	.032	2.44	.015
NAA	4	0.03	−0.26 to 0.32	0.19	.85	1.53	0	.68	0.73	.47
TRS vs. HC										
ACC										
Myo-inositol[a]	3	0.99	0.61 to −1.37	5.07	<.001	1.74	10	.42	−0.67	.50
PCho+GPCho[a]	5	0.62	0.37 to 0.88	4.77	<.001	1.53	0	.82	−0.08	.94
Cr+PCr	4	0.34	−0.10 to 0.78	1.51	.13	7.57	59	.056	0.19	.85
Glx	7	0.23	−0.11 to 0.57	1.32	.19	14.06	56	.029	0.26	.80
NAA	6	0.12	−0.29 to 0.53	0.59	.56	14.06	64	.015	−0.26	.80
Glutamate	5	−0.06	−0.71 to 0.59	−0.19	.85	16.25	80	.003	3.23	.001
Glutamate [w/o Ref. (41) (Outlier)]	5	−0.32	−0.79 to 0.14	−1.36	.17	7.56	61	.056	1.32	.19

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						Heterogeneity			Egger's Test	
Comparison/Region/Metabolite	***k***	***g***	**95% CI**	**Z**	***p***	**Q**	I^2	***p***	**Z**	***p***
Dorsal Striatum										
PCho+GPCho[a]	3	0.39	0.06 to 0.72	2.34	.019	0.64	0	.72	0.09	.93
Glx	3	0.25	−0.07 to 0.58	1.52	.13	0.19	0	.91	0.37	.71
NAA	3	0.00	−0.32 to 0.33	0.02	.99	0.39	0	.82	−0.36	.72
Glutamate	3	−0.21	−0.54 to 0.12	−1.23	.22	2.04	2	.36	0.09	.93
Ultra TRS vs. TRS										
ACC										
Glx	3	0.28	−0.07 to 0.64	1.55	.12	0.04	0	.98	0.04	.96
NAA	3	0.07	−0.28 to 0.42	0.40	.69	0.96	0	.62	−0.93	.35
PCho+GPCho	3	0.01	−0.35 to 0.36	0.04	.97	0.80	0	.67	−0.55	.58

Results are listed in order of descending effect size.

ACC, anterior cingulate cortex; Cr+PCR, creatine+phosphocreatine; *g*, Hedges' *g*; Glx, glutamate+glutamine; HC, healthy control participant; I^2, heterogeneity; k, number of datasets in analysis; NAA, *N*-acetyl-aspartate; nTRS, non–treatment-resistant schizophrenia; PCho+GPCho, phosphocholine+glycerolphosphocholine; Q, χ^2 statistic for departure from homogeneity; TRS, treatment-resistant schizophrenia; ultra TRS, ultra treatment-resistant schizophrenia.

[a]Metabolites that showed significant group differences.