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Medial Frontal Cortex GABA Concentrations in Psychosis Spectrum and Mood Disorders: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies

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ABSTRACT

BACKGROUND: Abnormalities of GABAergic (gamma-aminobutyric acidergic) systems may play a role in schizophrenia and mood disorders. Magnetic resonance spectroscopy allows for noninvasive in vivo quantification of GABA; however, studies of GABA in schizophrenia have yielded inconsistent findings. This may stem from grouping together disparate voxels from functionally heterogeneous regions.

METHODS: We searched PubMed for magnetic resonance spectroscopy studies of GABA in the medial frontal cortex (MFC) in patients with schizophrenia, bipolar disorder, and depression and in individuals meeting criteria for ultra-high risk for psychosis. Voxel placements were classified as rostral-, rostral-mid-, mid-, or posterior MFC, and meta-analyses were conducted for each group for each subregion.

RESULTS: Of 341 screened articles, 23 studies of schizophrenia, 6 studies of bipolar disorder, 20 studies of depression, and 7 studies of ultra-high risk met the inclusion criteria. Meta-analysis revealed lower mid- (standardized mean difference [SMD] = −0.28, 95% CI, −0.48 to −0.07, $p < .01$) and posterior (SMD = −0.29, 95% CI, −0.49 to −0.09, $p < .01$) MFC GABA in schizophrenia and increased rostral MFC GABA in bipolar disorder (SMD = 0.76, 95% CI, 0.25 to –1.25, $p < .01$). In depression, reduced rostral MFC GABA (SMD = −0.36, 95% CI, −0.64 to −0.08, $p = .01$) did not survive correction for multiple comparisons. We found no evidence for GABA differences in individuals at ultra-high risk for psychosis.

CONCLUSIONS: While limited by small numbers of published studies, these results substantiate the relevance of GABA in the pathophysiology of psychosis spectrum and mood disorders and underline the importance of voxel placement.

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Substantial evidence from several lines of research has suggested that disturbances in the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) play a role in the pathophysiology of both schizophrenia spectrum and mood disorders. Postmortem and preclinical studies in schizophrenia suggest abnormalities in fast-spiking, parvalbumin-positive GABAergic interneurons (1) as well as reductions in messenger RNA and protein levels of the 67-kDa isoform of glutamic acid decarboxylase (GAD67), the GABA-synthesizing enzyme (2–5). Although the bulk of the findings have been reported in schizophrenia/schizoaffective cohorts, similar results have also been found in patients with bipolar disorder (BD) (6–8). Decreased prefrontal GAD67 expression has been shown in depression (5,9) as well as reduced GABA concentrations in plasma (10,11) and cerebrospinal fluid (12–14), possibly linked to vulnerability of somatostatin-positive GABAergic interneurons (15). An important question is whether the postmortem findings reflect GABAergic alterations in vivo. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a powerful way to investigate in vivo GABA concentrations noninvasively. Measuring GABA poses specific challenges due to its relatively low concentration and high spectral overlap with more abundant metabolites; however, sequences such as MEGA-PRESS (16,17) take advantage of couplings within the GABA molecule, allowing GABA signals to be reliably separated from stronger signals.

While the postmortem evidence linking schizophrenia spectrum and mood disorders to GABAergic dysfunction is well replicated, ^{1}H-MRS studies have thus far yielded inconsistent findings. For example, in schizophrenia, ^{1}H-MRS studies have revealed increased (18,19), decreased (20,21), and normal (22) GABA concentrations when patients are compared with healthy control participants. Attempts to reach consensus by pooling study data via meta-analysis also seem contradictory, with evidence for reduced GABA concentrations found in some analyses (23–25), but not others (26,27). The picture for depression is a little clearer; however, there is evidence supporting both decreased (28–30) and normal (31–33) GABA concentrations.

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There are several possible explanations for these mixed findings. Individual studies may differ in the clinical characteristics of their samples, in terms of illness duration, symptom profile, or medication use. There may be large differences between studies in methodology, e.g., magnet strength or reference metabolite used. The location of the ^{1}H-MRS voxel may be especially critical. Because of the low concentration of GABA in comparison with other metabolites, large voxels, typically around $3 \times 3 \times 3$ cm^3, are collected to offset the low signal-to-noise ratio. The time to acquire these voxels is usually approximately 10 minutes per voxel, meaning that researchers generally only have enough time to collect 1 or 2 voxels per study. When meta-analyses combine data from these studies, often voxels from disparate brain regions are combined—across the whole brain, or entire frontal cortex—sometimes with minimal overlap. In healthy control participants, evidence indicates that GABA concentrations vary across the brain, with significant variance in GABA demonstrated between frontal cortex voxels, including those placed in the ventral midcingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex (34–36).

The medial frontal cortex (MFC) has been a frequent target of ^{1}H-MRS studies for psychiatric disorders because it has been strongly implicated in the etiologies of schizophrenia spectrum disorders and mood disorders. However, published studies have placed voxels across a large extent of the MFC, covering a functionally heterogeneous region. Meta-analysis of the MFC shows distinct functional profiles, with the rostral MFC being implicated in reward, decision making, social processing, and episodic memory; the middle MFC being implicated in cognitive control, negative affect, and pain; and the posterior MFC being implicated in motor function (37). These regions likely contribute to symptoms of psychosis spectrum and mood disorders in different ways; thus, combining GABA concentration findings across functionally heterogeneous regions may not be the best strategy to gain the benefit of pooled studies in a meta-analysis.

Given the importance of the various functions of the MFC for psychiatric disorders as well as the number of studies that have focused on the MFC, we performed meta-analyses of ^{1}H-MRS studies of medial frontal GABA concentrations in schizophrenia spectrum disorders, BD, and depression. Our primary focus was on schizophrenia, given the relative strength of the postmortem findings and the focus of our prior work (38). We also included mood disorders in the analysis, given both the evidence of altered GABA function in these disorders and the involvement of MFC regions in mood regulation, to compare and contrast with schizophrenia. We also included individuals with the ultra-high-risk (UHR) syndrome because this condition is thought to precede the development of schizophrenia. Voxels were classified as being in 1 of 4 medial frontal subregions (rostral, rostral-mid, mid, and posterior), and each of these subregions was examined separately. Our aim was to gain a more nuanced picture of the profile of medial frontal GABA dysfunction in psychiatric disorders.

METHODS AND MATERIALS

Search Strategy

Meta-analyses were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. ^{1}H-MRS studies that examined differences in GABA between healthy control participants and patients with schizophrenia, BD, depression, or UHR individuals were identified through a PubMed search using the term "(MRS OR Magnetic Resonance Spectroscopy) AND (GABA OR Gamma-aminobutyric Acid) AND (psychosis OR depression OR schizophrenia OR bipolar disorder)." Databases were searched for articles published before October 25, 2021. Titles and abstracts were examined to determine suitability for inclusion. Reference sections of the returned articles as well as review articles (38) and meta-analyses (23,25,27,39–42) were searched for additional articles that fulfilled inclusion criteria. We also searched the online preprint servers bioRxiv, medRxiv, and psyArXiv for studies that met our inclusion criteria.

Study Selection

Studies met inclusion criteria if they were an original research article; used ^{1}H-MRS to study in vivo GABA; compared groups with schizophrenia spectrum disorders, BD, depression, or UHR with healthy control participants; included ^{1}H-MRS voxels in the MFC; and were published in or translated into English. Articles were screened for overlapping samples, and when present, data from the article reporting the largest sample were included.

Data Extraction

From each study that met inclusion criteria, we extracted publication information (authors, year of publication), participant characteristics (diagnosis, sample size, age, gender, illness duration, medication status), methodological characteristics (field strength, acquisition sequence, reference metabolite, analysis software), voxel location, and GABA concentration (mean and standard deviation in each group). This information was extracted by one author (CJS) and independently verified by another (MS). When published articles did not include this information in the text, tables, or supplementary materials, the authors were contacted, or when possible, values were estimated using an online tool (https://automeris.io/WebPlotDigitizer/).

Voxel Classification

Using figures and text descriptions from the included publications, voxels were classified as rostral-, mid-, and posterior MFC. Several voxels formed a cluster which straddled the rostral- and mid MFC, and we classified these separately as rostral-mid MFC. A fully detailed examination of the classification process is provided in the Supplement.

Meta-analysis

Separate meta-analyses were conducted for each MFC subregion (rostral, rostral-mid, mid, and posterior) for each clinical population (schizophrenia, BD, depression, and UHR). Studies of schizophrenia frequently included schizoaffective and schizophreniform patients, which we refer to collectively as schizophrenia for simplicity and to be consistent with common practice in the literature. For comparison with our subregion analyses, we performed meta-analyses for each clinical population in which we included voxels from all MFC subregions. Results of these meta-analyses are described in the Supplement, including forest plot visualizations in Figures S1–S4. Data were analyzed using R version 4.1.1 using

the metafor package (43). Meta-analyses were conducted when at least 3 datasets met inclusion criteria for a subregion, for a clinical population. Results were summarized if this number was not met. Schizophrenia samples were classified as acute (average duration of illness $<$ 5 years) or chronic (average duration of illness $\geq$ 5 years), and depression samples were classified as depressed or remitted at the time of scanning. Analyses of these subgroups were conducted if at least 5 datasets met inclusion criteria for that subregion. Meta-regressions were performed to determine differences between the subgroups. Effect sizes were described using standardized mean differences (SMD; also known as Hedges' *g*) and 95% confidence intervals. The use of SMD allowed comparison of different units of GABA measurement (institutional units, ratios to reference metabolites). Random effects models were used to pool effect sizes because we assumed heterogeneity in both the clinical profile of patient samples and the methodology used in each study. Because examining GABA concentrations in schizophrenia was our primary interest, we corrected for multiple comparisons by applying a Bonferroni-corrected threshold of $p < .0125$ (.05/4) to determine statistical significance, as we performed 4 independent meta-analyses. For the meta-analyses of depression, BP, and UHR, we applied a Bonferroni-corrected threshold of $p < .0083$ (.05/6) for statistical significance because we performed a total of 6 meta-analyses investigating these samples.

Between-study heterogeneity was assessed with the I^2 index and the *Q*-statistic. Higher I^2 scores indicate higher variation between studies, with values of 25%, 50%, and 75% representing small, moderate, and high levels of heterogeneity, respectively. Significant *Q*-statistics suggest heterogeneity but do not indicate the extent of this heterogeneity (44). Publication bias was assessed by visually examining funnel plots for asymmetry and performing Egger's regression test for funnel plot asymmetry (45).

RESULTS

Study Characteristics

The literature review identified a total of 54 studies meeting inclusion criteria. The PRISMA flow diagram is presented in Figure 1. Of the 54 studies, 23 studies included participants with schizophrenia (18–20,22,46–63) (752 cases, 856 controls), 7 studies included individuals at UHR (51,63–68) (229 cases, 232 controls), 20 studies included individuals with depression (28,30,32,69–83) (463 cases, 499 controls), and 6 studies included participants with BD (84–89) (129 cases, 94 controls). Two studies included multiple clinical samples (51,63); therefore, these numbers sum to 56. Detailed study characteristics are presented in Table S1–S4. Voxels from each study were classified as rostral-, rostral-mid-, mid-, and posterior MFC, with classifications shown in Figure 2.

Medial Frontal GABA Concentrations in Psychosis Spectrum and Mood Disorders

Schizophrenia. Figure 3 shows results of the meta-analyses of individuals with schizophrenia in MFC subregions. GABA

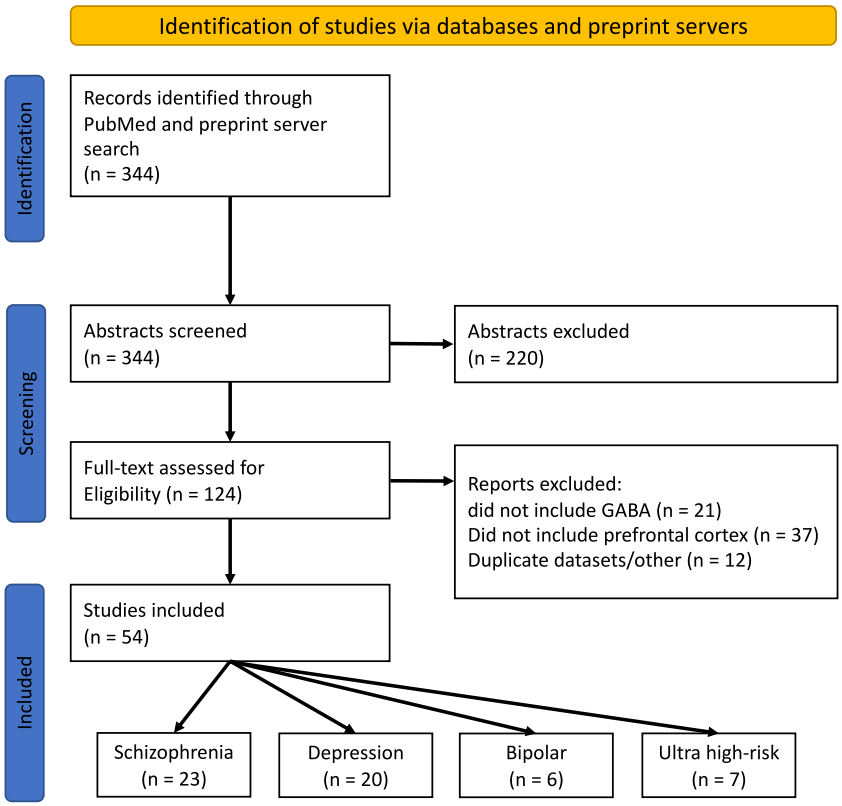

Figure 1. PRISMA flow diagram of search for meta-analyses. Note that 2 studies included both schizophrenia and ultra-high-risk samples, so the breakdown of included studies totals 56. GABA, gamma-aminobutyric acid; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

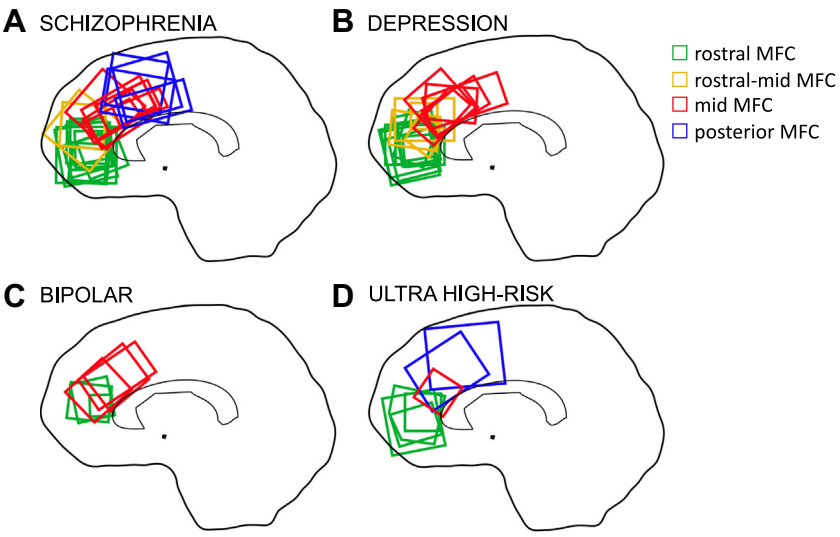

Figure 2. Voxel location in medial frontal cortex GABA ^{1}H-MRS studies. **(A)** ^{1}H-MRS studies of schizophrenia; **(B)** ^{1}H-MRS studies of depression; **(C)** ^{1}H-MRS studies of bipolar disorder; and **(D)** ^{1}H-MRS studies of individuals meeting ultra-high risk of developing psychosis criteria. GABA, gamma-aminobutyric acid; ^{1}H-MRS, proton magnetic resonance spectroscopy; MFC, medial frontal cortex.

concentrations were significantly reduced in both the mid- (SMD = −0.28, 95% CI, −0.48 to −0.07, p = .0087) and the posterior (SMD = −0.29, 95% CI, −0.49 to −0.09, p = .005) MFC in patients with schizophrenia compared with healthy control participants. I^2 values were 36.50% and 0.00%, respectively, suggesting small heterogeneity across studies. Subgroup analyses revealed that mid-MFC GABA concentrations were significantly reduced in acute patients (SMD = −0.38, 95% CI, −0.58 to −0.17, p = .0003), but not in chronic patients (SMD = −0.18, 95% CI, −0.58 to 0.23, p = .39); however, meta-regression did not indicate significant differences between the subgroups. GABA in the rostral MFC showed no difference compared with healthy control participants (SMD = 0.11, 95% CI, −0.27 to 0.48, p = .58), and likewise no significant effects were observed in the subgroup analyses of acute and chronic patients (acute: SMD = 0.19, 95% CI, −0.27 to –0.66, p = .42; chronic: SMD = −0.11, 95% CI, −0.27 to –0.48, p = .74). This region was notable for high heterogeneity in the combined group (I^2 = 74.83%) as well as in the acute (I^2 = 79.10%) and chronic (I^2 = 63.65%) subgroups. There were insufficient studies of posterior MFC GABA to perform subgroup analyses for this region. Reductions in GABA in the rostral-mid MFC in patients with schizophrenia did not survive corrections for multiple comparisons (SMD = −0.57, 95% CI, −1.10 to −0.03, p = .04).

Depression. Forest plots detailing the meta-analyses of regional MFC GABA concentrations in studies investigating depression are presented in Figure 4. While the meta-analysis of rostral MFC GABA in depression indicated a reduction compared with healthy control participants, the significance of this effect did not survive correction for multiple comparisons (SMD = −0.36, 95% CI, −0.64 to − 0.08, p = .01). Subgroup analyses of currently depressed patients revealed a similar effect size (SMD = −0.40, 95% CI, − 0.70 to − 0.11, p = .0073), but there were insufficient studies of remitted patients to perform an analysis of this group. Heterogeneity was moderate across the full sample (I^2 = 48.15%) and within the currently depressed subgroup (I^2 = 47.12%). We did not find any studies that reported posterior GABA in depression.

Bipolar Disorder. Figure 5A, B presents the meta-analyses of studies of BD. GABA concentrations in rostral MFC were higher in patients with BD compared with healthy control participants (SMD = 0.76, 95% CI, 0.26–1.25, p = .0026), and heterogeneity across studies was small (I^2 = 0.00%). We did not find any studies that published analyses of posterior GABA.

Ultra-high Risk. Plots summarizing the findings of GABA ^{1}H-MRS studies in UHR samples are presented in Figure 5C–E. Because of the limited number of studies published, we were only able to perform a meta-analysis of rostral MFC GABA, where we found no significant differences between individuals at UHR and healthy control participants (SMD = −0.78, 95% CI, −3.01 to –1.46, p = .50), and high between-study heterogeneity (I^2 = 97.19%). Only 2 published studies were found for each of the mid and posterior MFC subregions, and inspection of their findings did not reveal consistent GABA abnormalities.

Publication Bias

Visual inspection of funnel plots and results of Egger's test (provided in Figures S5–S7) did not suggest publication bias.

DISCUSSION

This study presents several meta-analyses in which regional MFC GABA concentrations were investigated, comparing individuals with schizophrenia spectrum disorders and mood disorders with healthy control participants. Our main findings were that 1) patients with schizophrenia have significantly decreased GABA concentrations in the mid- and posterior MFC, 2) patients with BD have increased GABA concentrations in the rostral MFC, and 3) reduced GABA concentrations in the rostral MFC in depression did not survive correction for multiple comparisons.

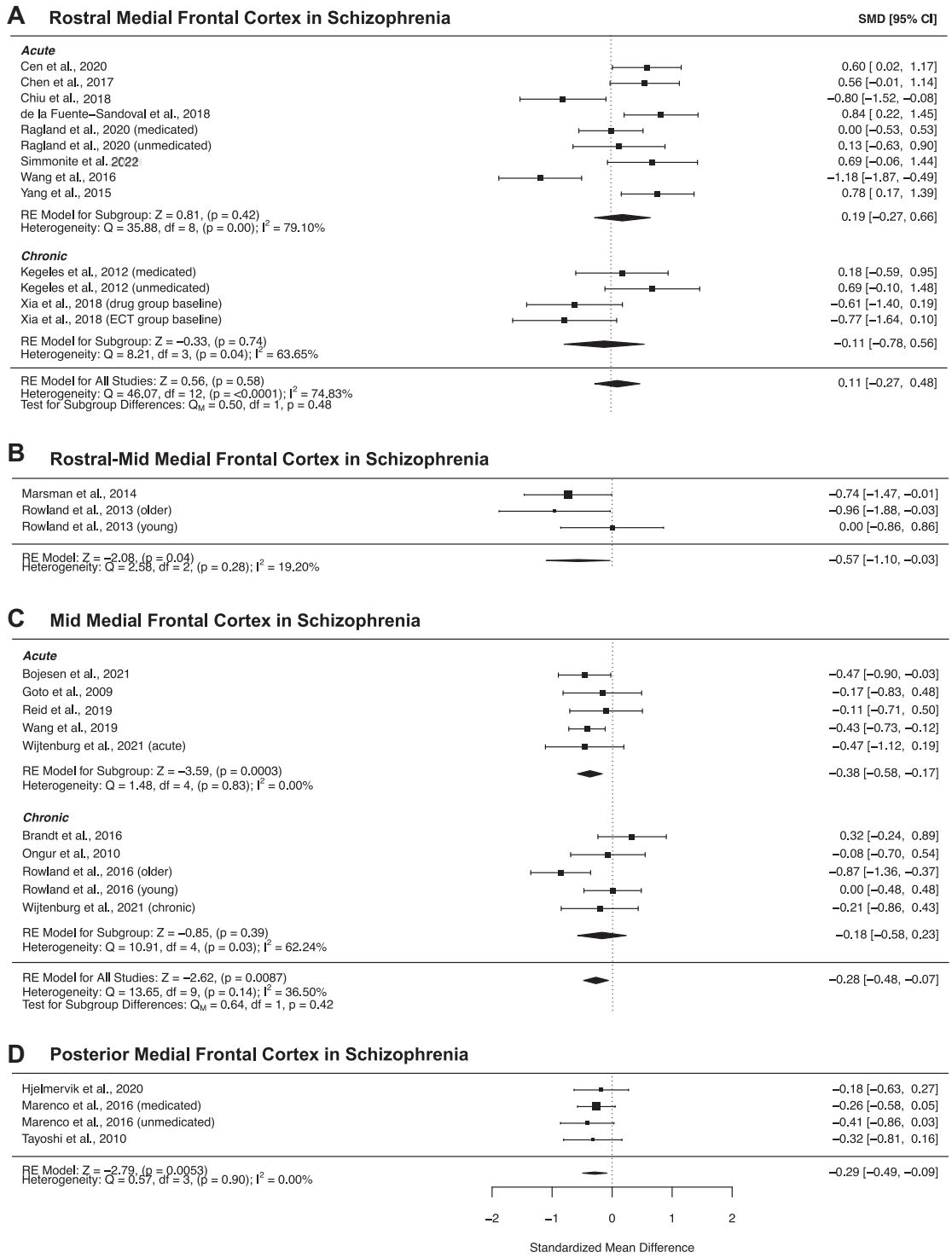

Figure 3. Forest plots showing summary effect sizes for group differences between individuals with schizophrenia and healthy control participants in the **(A)** rostral MFC, **(B)** rostral-mid MFC, **(C)** mid MFC, and **(D)** posterior MFC. Negative SMDs denote lower GABA concentrations in patients than healthy control participants; positive SMDs denote higher GABA concentrations in patients than healthy control participants. GABA, gamma-aminobutyric acid; MFC, medial frontal cortex; RE, random effects; SMD, standardized mean difference.

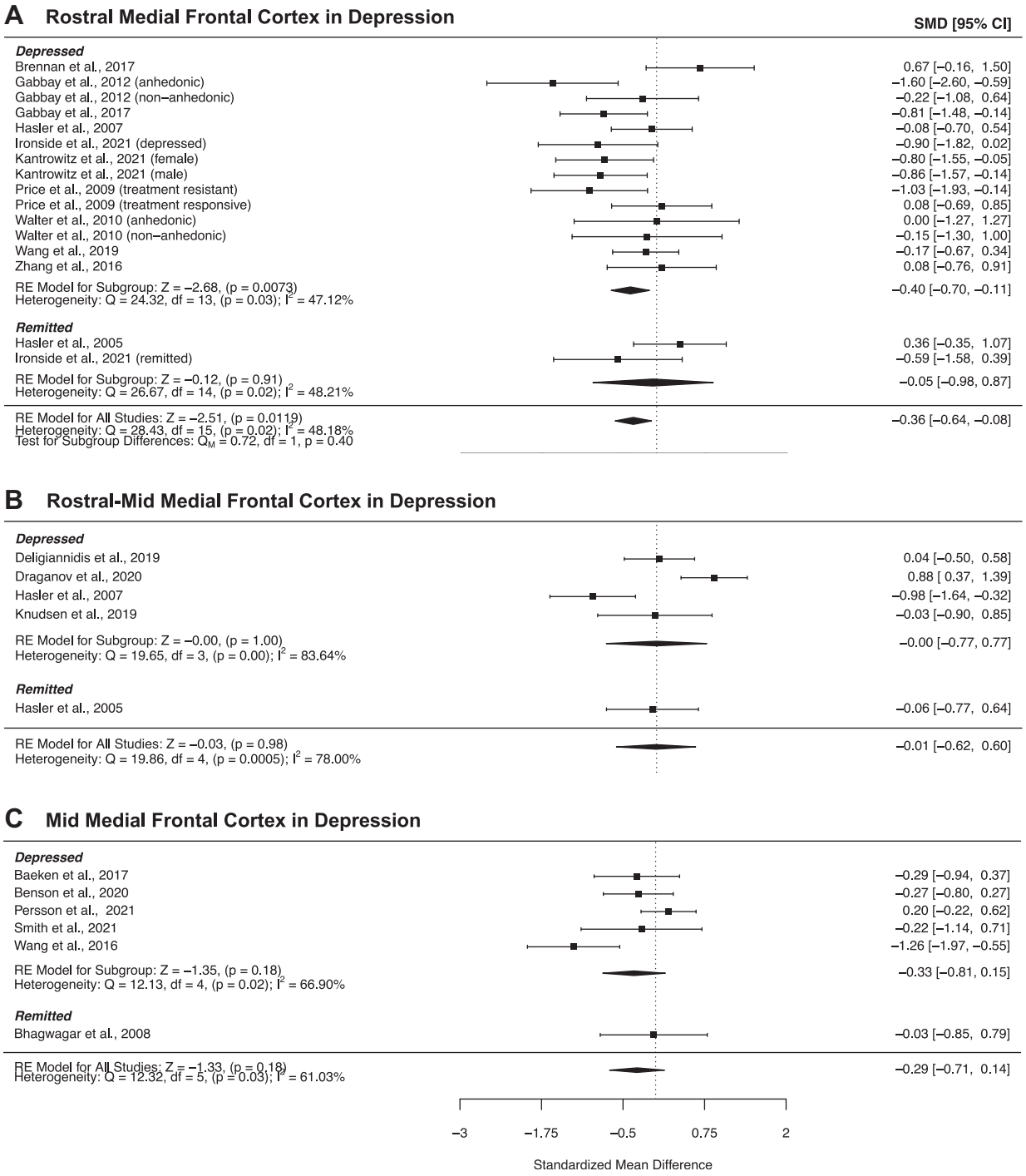

Figure 4. Forest plots showing summary effect sizes for group differences between individuals with depression and healthy control participants in the **(A)** rostral MFC, **(B)** rostral-mid MFC, and **(C)** mid MFC. Negative SMDs denote lower GABA concentrations in patients than healthy control participants; positive SMDs denote higher GABA concentrations in patients than healthy control participants. GABA, gamma-aminobutyric acid; MFC, medial frontal cortex; RE, random effects; SMD, standardized mean difference.

Decreased Mid and Posterior MFC GABA in Schizophrenia

In individuals with schizophrenia, our analysis indicated significantly decreased GABA concentrations in the mid and posterior regions of the MFC, while we found no significant differences in the rostral MFC. Decreases in the rostral-mid MFC did not meet criteria for statistical significance after correction for multiple comparisons. Subgroup analysis

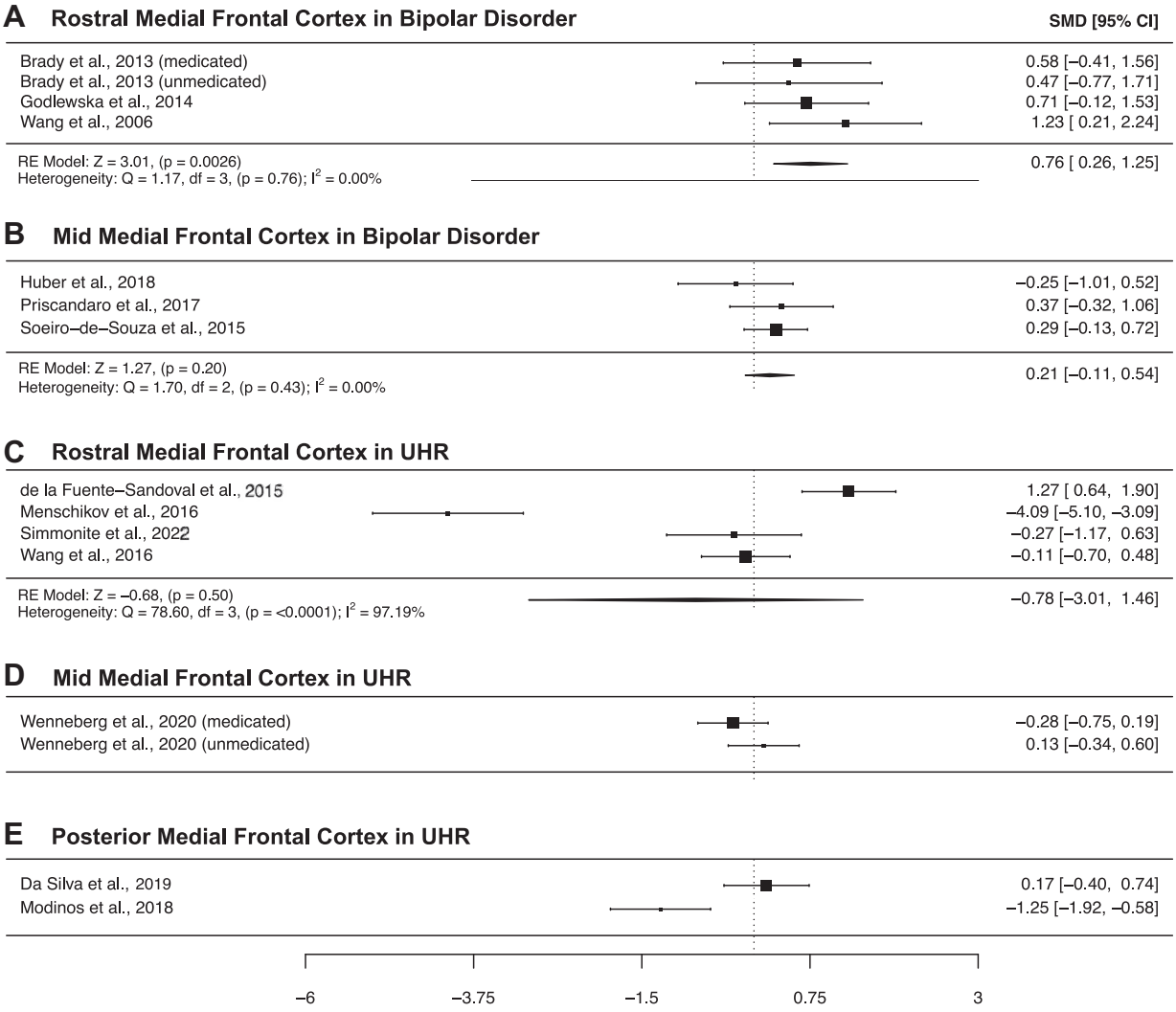

Figure 5. Forest plots showing summary effect sizes for group differences between individuals with bipolar disorder and healthy control participants in the **(A)** rostral MFC and **(B)** mid MFC, and individuals meeting UHR for psychosis criteria and healthy control participants in the **(C)** rostral MFC, **(D)** mid MFC, and **(E)** posterior MFC. Negative SMDs denote lower GABA concentrations in patients than healthy control participants; positive SMDs denote higher GABA concentrations in patients than healthy control participants. GABA, gamma-aminobutyric acid; MFC, medial frontal cortex; RE, random effects; SMD, standardized mean difference; UHR, ultra-high risk.

revealed that these declines were significant in acute patients, but not chronic patients (i.e., those with an illness duration of $>$ 5 years), suggesting that GABA abnormalities may be modulated by illness stage or mitigated by prolonged medication use. Our finding is similar to that of Nakahara *et al.* (24), who recently presented meta-analyses demonstrating reduced GABA concentrations in their midcingulate cortex (MCC) region (analogous to our mid- and posterior MFC subregions), but not in their anterior cingulate cortex (ACC) region (analogous to our rostral and rostral-mid MFC subregions) in first-episode psychosis and in a patient group comprising patients with first-episode psychosis and patients with schizophrenia as well as an unmedicated subgroup. The investigation of frontal GABA in schizophrenia by Kumar *et al.* (23) revealed reductions restricted to a subregion of the frontal cortex they termed ACC, at first appearance, suggesting that their findings were in contrast to ours and those of Nakahara *et al.* (24). While they did not provide a precise anatomical definition of the ACC region that they investigated, examination of the studies they included revealed voxels which spanned all 4 of our MFC subregions and both ACC and MCC regions in the study by Nakahara *et al.* (24). It is likely that differing terminologies for regions of the frontal cortex may result in differing classification schemes and explain apparent

discrepancies. In support of the conclusion that more anatomically focused investigations are more likely to reveal group differences in the MFC, when we combined all voxels in the MFC, we did not find significant group differences (see the Supplement).

Evidence from functional and structural studies have implicated the MFC as a key region in psychosis spectrum disorders (90). The MFC has been linked with several functions, including cognitive control (91), emotion regulation (92,93), and conflict monitoring (94,95), all of which are impaired in psychosis spectrum disorders. While there has been debate about the precise functional mapping of the MFC, meta-analysis has implicated rostral regions of the MFC in reward, episodic memory, and social processing and implicated more posterior regions in cognitive control (37). Our finding of decreased GABA concentrations in these regions is in line with postmortem studies of schizophrenia, which have consistently shown reductions in the messenger RNA and protein levels of GAD67 in the ACC (5,96), which is responsible for the majority of GABA synthesis, as well as findings of impaired cognitive control in functional measures (97,98). While it is important to note that ^{1}H-MRS studies do not distinguish between intracellular and extracellular GABA pools, making interpretation and reconciliation with postmortem findings difficult, the findings seem to be generally consistent.

While we found evidence of GABA reduction in the mid and posterior MFC in schizophrenia and in our subgroup of patients with acute schizophrenia, a search of the literature did not uncover enough investigations of GABA in these regions in UHR individuals for us to perform meta-analyses for that sample. Review of the available UHR publications did not indicate robust GABA reductions in either the mid- or posterior MFC, suggesting that the regional GABA reductions that we found in patients with schizophrenia were associated with the onset of symptoms rather than being a trait marker for vulnerability for schizophrenia.

Increased Rostral MFC GABA Concentrations in BD

Prior meta-analyses found no significant differences in GABA concentrations when including voxels from across the whole brain (25,39) or in the pregenual anterior cingulate/ventral midcingulate region of the frontal cortex (40). Our analysis focusing on the MFC found significantly increased GABA concentrations in the rostral MFC, a subregion that also included the pregenual anterior cingulate. Increased GABA was not significant in the mid MFC, and we were unable to perform an analysis of the posterior MFC because of a lack of studies investigating this region. To our knowledge, ours is the first meta-analysis of BD to investigate GABA concentrations in multiple subregions of the frontal cortex; however, our findings should be interpreted with caution owing to the small number of studies available for inclusion in our analysis.

Our finding of significantly increased GABA aligns with prior reports of elevated GABA levels in the plasma of patients with BD (99,100). Increased GABA could be the result of a primary pathological process, or it could be a compensatory response, e.g., to environmental stressors. In rodents, a chronic unpredictable stress model was observed to increase GABA levels in the ACC, as measured by MRS (101). Increased GABA could also be a secondary response to glutamatergic dysfunction. Ketamine infusion, which blocks excitatory NMDA receptors, has been shown to increase MFC GABA in humans (102).

As noted, the number of investigations of GABA concentrations in BD is limited, and therefore we were unable to perform subgroup analyses based on medication status. Furthermore, the samples reported often comprise both medicated and unmedicated participants, meaning that meta-analyses cannot untangle the effects of medication. One study included in our meta-analysis considered the use of GABA-modulating medications, such as benzodiazepines (which are used to treat anxiety or insomnia in psychosis spectrum and mood disorders), and found that such medications partially correct GABA concentrations to a healthy control level in their sample (84). This finding indicates that medication may obscure GABA concentration increases in BD.

Decreased GABA in the Rostral MFC in Depression Did Not Survive Correction for Multiple Comparisons

Previous meta-analyses have revealed reduced GABA concentrations in depression when considering voxels from across the whole brain (25,41). When focusing on the frontal cortex, Schur *et al.* (25) found no evidence of abnormal GABA concentrations in depression, while Romeo *et al.* (39) revealed significantly reduced GABA. Godfrey *et al.* (41) found significantly reduced GABA in an analysis of ACC GABA concentration comprising voxels in the ventromedial prefrontal cortex and the pregenual ACC (which were included in our rostral MFC subregion). While the studies included in Godfrey *et al.*'s (41) analysis of GABA were a subsection of those included in our investigation of the rostral MFC, our finding of reduced GABA in the rostral MFC was suggestive of a GABA deficit, although the failure to survive correction for multiple comparisons suggests caution around any definitive conclusions. Interestingly, when we conducted a meta-analysis that included voxels from across all MFC subregions, we found evidence to suggest reduced GABA concentrations in depression; however, the effect size was smaller than that for rostral MFC voxels alone, suggesting that there is indeed merit in considering these subregions separately.

Heterogeneity of Findings

We aimed to reduce heterogeneity by pooling effects from overlapping voxels placed in small, more functionally homogeneous regions and by performing subgroup analyses based on illness duration in schizophrenia and current symptom profile in depression. We succeeded in uncovering significant differences in GABA concentration across various psychiatric conditions, but we still found evidence for moderate to large amounts of between-study heterogeneity in some of the meta-analyses we conducted, although it appeared that heterogeneity in significant subregions tended to be slightly lower than when we included all subregions in the same analysis. This heterogeneity likely reflects several factors, including differences in patient sample characteristics, alongside differences in the methodological characteristics of data collection. While analyses of the mid- and posterior MFC in schizophrenia yielded low heterogeneity and significant group effects, other

voxels, such as the rostral MFC in schizophrenia, still exhibited high heterogeneity. MR spectra are affected by magnetic field inhomogeneities and susceptibility artifacts, and it is difficult to obtain good data in voxels that are close to bone or in air-filled sinuses, which may affect some regions, such as the rostral MFC, more than others, a fact that may have accounted for heterogeneous findings.

Another source of heterogeneity could be the difference in medication status across samples. While it is likely that the current medication status of an individual has an impact on GABA concentrations, we did not examine this directly in this study. For BD and UHR individuals, there were not enough eligible studies per region to perform any kind of subgroup analysis. Of the studies of depression that met our inclusion criteria, the vast majority (25 of 27 datasets) were composed of unmedicated participants or samples that were of mixed medication status, meaning that medication status could not be meaningfully probed. In patients with schizophrenia, we opted to perform subanalyses of acute and chronic schizophrenia. This subgrouping does not map directly onto a currently medicated versus unmedicated division, but investigating different illness stages does give some idea of the impact of prolonged medication use.

Limitations

Because of the limited number of studies available, particularly studies of BD and UHR individuals, we were unable to perform meta-analyses examining GABA concentrations in some regions of the MFC in some of our clinical populations of interest. Where we were able to perform meta-analyses, some contained only 3 or 4 datasets, and many studies that were included had small sample sizes. It is likely that some of these analyses were low powered or underpowered, which can lead to inflated effect sizes and reduce the likelihood that significant results are true effects (103). While we found no evidence of publication bias, i.e., the tendency for studies with positive findings to be more likely to be published, it is possible that the pooled effects from our meta-analyses are inflated. Caution should be exercised when evaluating the results of some analyses we present, which include studies with small samples. Care should be taken when comparing effects from these smaller analyses with those for which we were able to identify and include a greater number of samples.

A further limitation is that we were unable to investigate the impact of medication on GABA concentrations. Sample characteristics prevented us from exploring this important issue; however, previous evidence suggests that antipsychotic medications lead to changes in GABA concentrations, and typical and atypical antipsychotics may perhaps have differing effects (22).

Classification of voxels into the appropriate subregions was performed based on figures included in the articles and written descriptions when figures were not included. Classifications were reviewed and reclassified if necessary. Despite our best efforts, classifications were somewhat subjective, and accuracy depended on the example image or description provided.

Conclusions

This study used several ^{1}H-MRS meta-analyses to reveal medial frontal GABA alterations in psychosis spectrum disorders and suggests an avenue for clarifying inconsistencies in the literature. While more studies are required to fully explore the subregions of the MFC in individuals with BD and UHR, these results suggest abnormal GABAergic transmission in psychosis spectrum disorders and support the role of the GABA system in the pathophysiology of these disorders.

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