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Neurometabolite Alterations Associated With Cannabis Use: A Proton Magnetic Resonance Spectroscopy Meta-Analysis

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Received: 6 January 2025 | **Revised:** 17 April 2025 | **Accepted:** 9 May 2025

Funding: This work was supported by National Institute on Drug Abuse, T32DA007288; National Institute on Alcohol Abuse and Alcoholism, K01AA031745, K24AA031052.

Keywords: cannabis use disorder | meta-analysis | neurometabolites | proton magnetic resonance spectroscopy | substance use disorders

ABSTRACT

Little is known about the neurometabolic effects of cannabis use. Using meta-analytic modeling of proton magnetic resonance spectroscopy (1H-MRS) studies, this study aimed to assess the differences in brain metabolite levels associated with cannabis use (PROSPERO: CRD42020209890) to inform treatment development for cannabis use disorder (CUD). Hedge's *g* with random-effects modeling was used, and heterogeneity and publication bias indices were assessed. A complete literature search was conducted, and 15 studies met the inclusion criteria (e.g., 1H-MRS, cannabis group compared to a control group, brain region-specific results, necessary data to complete modeling). There were 29 models across gray matter regions in the brain. All models had between 2 and 5 studies (*k*), indicating that results should be interpreted with caution due to the limited number of available studies. Compared to the control groups, the cannabis-using groups showed lower levels of GABA and N-acetylaspartate in the anterior cingulate cortex ($k = 3$); lower glutamate in the basal ganglia/striatum ($k = 2$); and lower glutamine and *myo*-inositol in the thalamus ($k = 2$; although the two effect sizes came from the same sample). This is the first meta-analysis to consolidate the extant 1H-MRS studies focused on the neurometabolic effects of cannabis. Despite the few studies available, the evidence suggests cannabis use may impact important neural processes, including glutamatergic and GABAergic functioning (glutamate, glutamine, and GABA), neural health (N-acetylaspartate), and glial functioning (*myo*-inositol). The findings should be interpreted with caution considering the small sample size; the inability to test the impact of demographic, substance use, and methodological factors; and the heterogeneity of studies. Understanding the neurobiological effects of cannabis may inspire novel pharmacotherapy and/or psychosocial interventions for CUD.

1 | Introduction

The *Cannabis sativa* plant, generically referred to as cannabis, is one of the most widely used psychoactive substances globally, with about 4% of the world population using cannabis annually (Ransing et al. 2022; UNODC and UNOoD 2022). Within the United States, rates of cannabis use are increasing with rapidly changing legalization of cannabis products (Cerdá et al. 2020). The prevalence of viewing cannabis use as low risk has doubled from 2002 to 2018 (47%) (Levy et al. 2021). Further, over half of adults in the United States who already use cannabis see daily cannabis use as having no risk and even endorsed benefits of frequent cannabis use across various life domains, including school and work (Kohlwes et al. 2023). While most people who use cannabis do not develop problematic use, approximately 9.7% of people (12 years or older) will develop cannabis use disorder (CUD) (Center for

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Summary

- Little is known about the neurometabolic effects of cannabis use, which can be measured with proton magnetic resonance spectroscopy.
- Using meta-analytic modeling across gray matter regions of the brain, we found associations between cannabis use and lower levels of GABA and N-acetylaspartate in the anterior cingulate cortex; lower glutamate in the basal ganglia/striatum; and lower glutamine and *myo*-inositol in the thalamus.
- Despite the few studies available, the evidence suggests cannabis use may impact important neural processes.

Behavioral Health Statistics and Quality 2023), which is a maladaptive pattern of cannabis use that can result in poorer long-term outcomes. Changes in legalization and a lower perception of risk have resulted in increased rates of cannabis use and CUD, primarily within adolescents and young adults (Cerdá et al. 2020; Center for Behavioral Health Statistics and Quality 2023, 2022). As such, it is important that effective treatments are available for those who need them; however, CUD treatments are currently limited in number and efficacy (Sherman and McRae-Clark 2016).

Having a comprehensive understanding of the neural effects of cannabis use will help to promote novel psychosocial interventions and pharmacotherapy treatments, as well as potentially providing markers for treatment effects for CUD. While it can be difficult to measure in vivo effects of cannabis use in humans, certain neuroimaging techniques can provide critical insights. Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive neuroimaging technique that allows for the quantification of certain abundant neurometabolites within the human brain, providing a unique window into potential cannabis-related neurobiological alterations (Hellem et al. 2015). 1H-MRS methods commonly allow for the quantification of glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA), N-acetylaspartate (NAA), choline-containing metabolites (Cho), creatine-containing metabolites (Cr), and *myo*-inositol (mI).

1H-MRS neurometabolite alterations have been synthesized using meta-analysis for other substances, specifically alcohol (Kirkland et al. 2022) and stimulants (i.e., cocaine and methamphetamine) (Smucny and Maddock 2023). Alcohol use disorder (AUD) and misuse were associated with widespread and diverse neurometabolite alterations across 43 studies, with differences noted in levels of NAA, Cho, Cr, and GABA across gray and white matter. For stimulant use disorder, 28 studies were identified, and substance-related differences were noted in NAA, Cr, and mI (Smucny and Maddock 2023). These recent meta-analyses indicate that 1H-MRS can be a useful tool for identifying and synthesizing specific and broad effects that different substances may have on neurometabolite levels.

With the steady rise of cannabis use and consequences, it is important to synthesize the existing 1H-MRS literature using meta-analysis to have an initial understanding of the effects of cannabis on neurometabolites above and beyond the existing individual studies. This will allow for comparison to previously reported meta-analyses on alcohol and stimulants, in addition to informing future research into CUD treatments. Broad inclusion criteria were used to capture all existing work and relevant populations, rather than focusing only on CUD. Due to the number of studies available within each metabolite and brain region, we were not able to complete sub-group analyses or meta-regressions (Borenstein and Higgins 2013; Richardson et al. 2019). Capturing the effects of cannabis on neurometabolite levels may lead to novel pharmacotherapy or psychosocial interventions, in addition to contributing to the general neural implications of cannabis use.

2 | Methods

2.1 | Search Strategy and Study Eligibility

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Page et al. 2021). The protocol was pre-registered with PROSPERO (Protocol Number: CRD42020209890).

Relevant extant literature assessing the differences in brain metabolite levels between cannabis-using groups relative to controls was identified by systematically searching PubMed, PsychINFO, Scopus, Google Scholar, CINHAL, and TRIP using the terms such as "magnetic resonance spectroscopy" or "MRS" and "cannabis," "cannabis use disorder," "marijuana," "weed" (see Supplementary Materials: Data S1 for full search terms). Inclusion criteria were as follows: (1) use of in vivo 1H-MRS; (2) cannabis-using group defined by The Diagnostic and Statistical Manual of Mental Disorders, International Classification of Diseases, or other study-specific criteria; (3) healthy control group defined by study-specific criteria; (4) direct comparison between the cannabis-using group and control group; (5) appropriate data to complete meta-analysis (e.g., summary data for each metabolite or other usable data, such as a *p*-value); and (6) published in English. Exclusion criteria were: (1) carbon or phosphorus MRS, preclinical imaging; (2) other human neuroimaging technique (e.g., fMRI); (3) metabolite measures from body fluids (e.g., blood); and (4) comorbid psychiatric disorder or other illness (e.g., HIV, bipolar disorder) as the main population of interest. Studies were not excluded based on year published, age of participants, or metabolite quantification method (i.e., absolute metabolite concentration and metabolite resonance intensity relative to water or Cr). Systematic searches were conducted by one author (BDB) on October 12, 2023. All identified studies were then reviewed for potential inclusion by four reviewers, with at least two reviewers per study (AEK, BDB, RG, or SA) using Covidence Systematic Software (Veritas Health Innovation, Melbourne, Australia. Available at: www.covidence.org). Inter-rater reliability was high for title/abstracts (98% agreement, Cohen's kappa $k = 0.85$) and full-text screening (89% agreement, $k = 0.68$). Reasons for exclusion at the full-text review stage are provided in the Supplementary Materials: Data S1 and include the following: study designs (e.g., cannabis administration), patient populations (e.g., individuals with early psychosis), or study outcomes (e.g., resting-state connectivity) that did not align with the objectives of this meta-analysis; manuscripts that were not peer-reviewed (e.g., dissertations); and duplicate records identified during full-text review.

2.2 | Data Extraction

Study reviewers (AEK, BDB, RG, or SA) independently extracted data from all eligible studies using Covidence. A comprehensive list of extracted data variable names is included in the Supplementary Materials: Data S1, which includes general paper information (first author name, year, journal), inclusion/exclusion criteria for the cannabis and control groups, participant characteristics (number of participants, age, sex breakdown, demographics), MRS acquisition parameters (scanner manufacture, magnet strength, sequence type and details, voxel of interest, data quality outcomes), and MRS-derived data (group level descriptive statistics of reported neurometabolites, directionality of results, statistical data). Conflicting data entries were resolved via consultation between reviewers (LMS as tiebreaker); however, all entries were resolved via consultation between reviewers. If data critical for the meta-analytic models were missing, corresponding authors were contacted at least 2 times to request the required data. Of the four authors contacted, only one provided data and their study was included in the models (Watts et al. 2020). To determine the methodological quality of the studies, reviewers independently completed the Appraisal Tool for Cross-sectional Studies (AXIS) (Downes et al. 2016) modified for 1H-MRS studies (Peek et al. 2020) within Covidence (Table S1).

2.3 | Meta-Analysis Statistical Analyses

Comprehensive Meta-Analysis Version 4.0 (Borenstein et al. 2013) was used for all analyses. Significance was set at $p \leq 0.05$. The main models required at least 2 studies within a brain region per metabolite. For longitudinal studies, only baseline data were included to maintain independence of data (Peek et al. 2020). If a study had more than 1 measurement within the same brain region, the data were treated as independent (Peek et al. 2020), but noted as being from the same sample in the results. In models with 3 or more studies available, a remove-one analysis was performed as a sensitivity analysis to assess the impact of each study individually on the overall estimate. Hedges' g (unbiased standardized mean difference estimate) was used as the measure of effect size (Hedges and Olkin 1985) with random-effects modeling (Borenstein and Higgins 2013). Heterogeneity within studies was assessed through the Cochran's Q, I^2, tau, and tau^2 statistics (see Supplementary Materials: Data S1 for more details). Publication bias was assessed in models with >2 studies by: (1) funnel plots, (2) Duval and Tweedie trim and fill method (Duval and Tweedie 2000); and (3) Egger's regression (Egger et al. 1997).

3 | Results

3.1 | Study Selection

Fifteen studies were included in the meta-analysis (Figure 1) (Watts et al. 2020; Bitter et al. 2014; Blest-Hopley et al. 2020; Chang et al. 2006; Fenzl et al. 2023; Hermann et al. 2007; Mashhoon et al. 2013; Muetzel et al. 2013; Newman et al. 2022; Prescot et al. 2011, 2013; Subramaniam et al. 2022; van de Giessen et al. 2017; Zuo, Davis, Kuppe, et al. 2022; Zuo, Davis, and Lukas 2022). All study characteristics and 1H-MRS methods are detailed in Table S2. The average sample size (cannabis and control groups combined) for each study was 42 (SD = 19). Two studies included only male participants (13.3%), with most studies having more male participants than female participants (males in cannabis group $n = 218$, males in control group $n = 172$, females in cannabis group $n = 90$, females in control group $n = 147$; total percent male = 60.8%). The average age of participants included in each study was 23.5 (SD = 6.3; min average age = 16.0, max average age = 42.2). Race/ethnicity was rarely reported; thus, it was not able to be reported in the table. Other substance use was reported in 12 studies (80.0%); however, the type of substance and the level of detail reported were inconsistent. For 1H-MRS, scanner types included Siemens ($n = 9$; 60.0%), GE ($n = 2$; 13.3%), Philips ($n = 1$; 6.7%), and Varian Unity ($n = 3$; 2.0%). The magnetic field strengths were 1.5 T ($n = 1$; 6.7%), 3 T ($n = 11$; 73.3%), and 4 T ($n = 3$; 20.0%%). Two studies (13.3%) used magnetic resonance spectroscopic imaging (MRSI) to cover multiple brain volume-of-interest (VOIs), and 13 studies (86.7%) used single-voxel spectroscopy. Acquisition sequences were PRESS ($n = 11$), MEGA PRESS ($n = 3$), J2D JD-PRESS ($n = 1$), and HERMES ($n = 1$); of note, some studies used more than one 1H-MRS sequence. Software used for analysis consisted of LC Model ($n = 12$), automated spectral fitting program ($n = 1$), Gannet ($n = 1$), or jMRUI ($n = 1$). For metabolite quantification, 9 studies (60.0%) used absolute concentration methods, 4 studies (26.7%) used ratio-to-Cr methods, and 2 studies (13.3%) used ratio-to-water.

3.2 | Overall Model Results

Data were organized by metabolite and VOI (Table S3 for number of studies per metabolite and VOI). Model specifics for each brain region with ≥ 2 studies (Table 1) and the corresponding heterogeneity indices (Table 2) are presented below. Six VOIs were identified for meta-analytic modeling. Of these, the anterior cingulate cortex (ACC), basal ganglia/striatum, and thalamus showed a significant difference between cannabis-using groups and control groups. The strongest findings were in the ACC (Figure 2), where GABA ($k = 3$, $g = -0.61$, $p = 0.003$; $Q = 1.88$, $p = 0.39$; $I^2 = 0.00\%$) and NAA ($k = 3$, $g = -0.65$, $p = 0.003$; $Q = 0.93$, $p = 0.63$; $I^2 = 0.00\%$) levels were found to be significantly lower in the cannabis-using groups compared to controls. Within the basal ganglia/striatum (Figure 3), Glu levels were also lower in the cannabis-using group compared to controls ($k = 2$, $g = -0.45$, $p = 0.05$; $Q = 0.95$, $p = 0.33$; $I^2 = 0.00\%$). Within the thalamus (Figure 4), the cannabis group showed lower levels of Gln ($k = 2$, $g = -0.61$, $p = 0.04$; $Q = 0.01$, $p = 0.91$; $I^2 = 0.00\%$) and mI ($k = 2$, $g = -1.14$, $p = 0.001$; $Q = 1.25$, $p = 0.26$; $I^2 = 19.97\%$). It is important to note that the thalamus studies included right and left hemisphere measurements from the male-only sample within the same study (Mashhoon et al. 2013), limiting the inferences that can be made about this finding. Forest plots for VOIs with no significant findings are presented in Figure S1.

In terms of heterogeneity, 17.2% of models showed high heterogeneity in the included studies as indicated by Q ($p < 0.05$) and I^2 ($> 75\%$) statistics (Table 2). Models with the highest heterogeneity included Frontal Gray Matter NAA ($Q = 10.56$; $p = 0.001$; $I^2 = 90.53\%$); ACC Glu ($Q = 22.61$; $p < 0.001$; $I^2 = 82.31\%$); ACC Cr ($Q = 16.34$; $p < 0.001$; $I^2 = 87.76\%$); ACC mI ($Q = 8.58$; $p = 0.01$; $I^2 = 76.70\%$); and basal ganglia/striatum Cho ($Q = 8.23$; $p = 0.02$; $I^2 = 75.71\%$). None of the significant

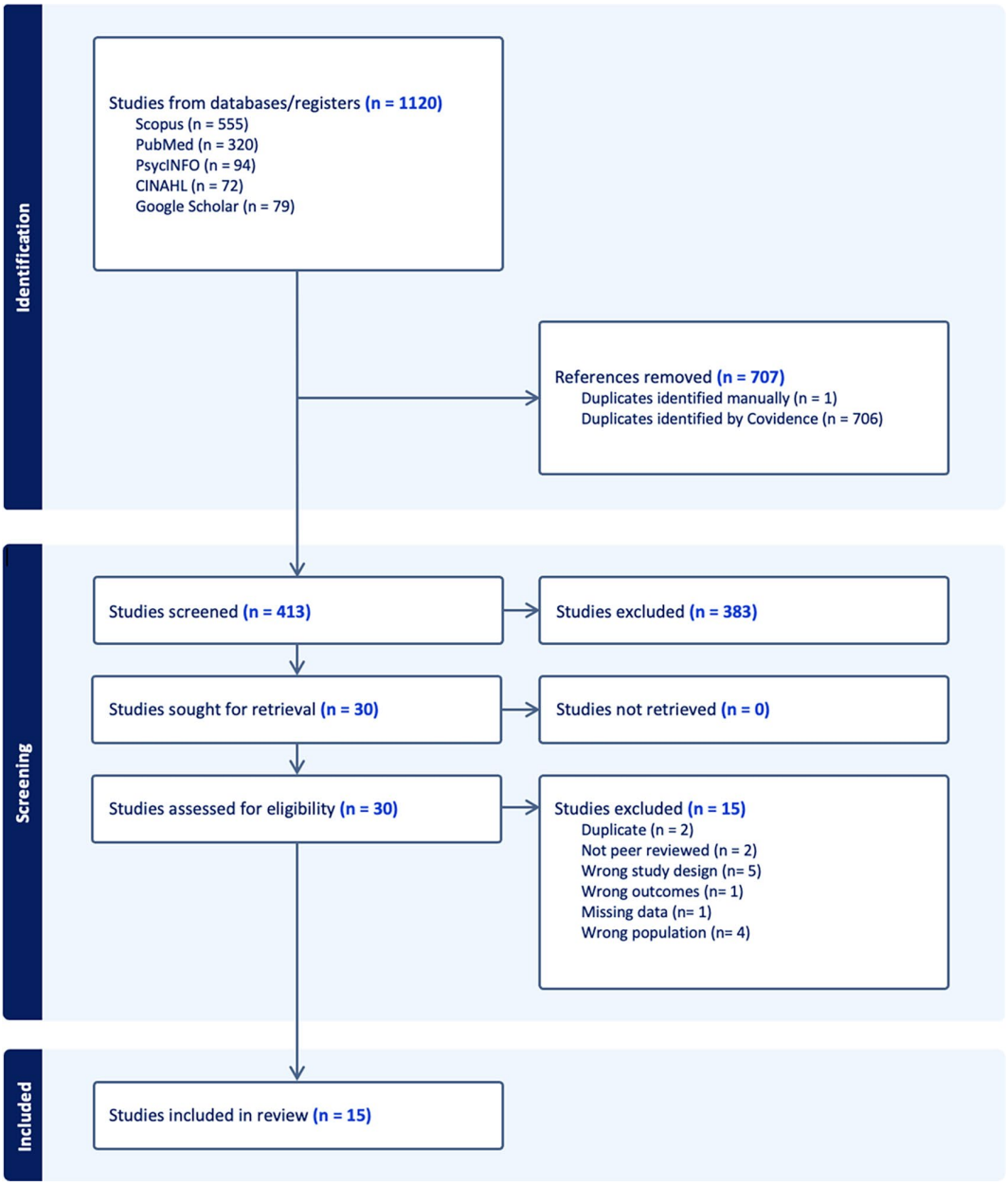

FIGURE 1 | PRISMA flow-chart of included studies.

models detailed above showed signs of high heterogeneity, which could either be due to consistent study methods and populations or the limited number of studies included in each model.

There had to be > 2 studies within a metabolite and VOI to conduct publication bias analyses (Table S4). Of these, Egger's regression indicated significant publication bias for Glu ($p = 0.01$) and mI ($p = 0.02$) models within the ACC. The Duval and Tweedie trim and fill method also indicated publication bias for Glx within the basal ganglia/striatum and Cho within temporal gray matter. The result for Glx in the basal ganglia/striatum suggests that correcting for publication bias may lead to significantly lower levels of Glx in cannabis users compared to controls ($g = -0.55$, 95% CI: −0.99, 0.00). This indicates that as more studies within this field are published, more significant differences in neurometabolite levels may be found in association with cannabis use.

4 | Discussion

This work represents the initial synthesis of neurometabolic alterations associated with cannabis use. Fifteen studies were identified as meeting the inclusion criteria. In comparison to the control groups, cannabis-using groups showed significantly lower levels of GABA and NAA within the ACC; Glu within the basal ganglia/striatum; and Gln and mI within the thalamus. The evidence suggests cannabis use may alter important neural processes, including glutamatergic and GABAergic functioning (glutamate, Gln, and GABA), neural health (NAA), and glial functioning (mI). Due to the limited

TABLE 1 | Meta-analytic model results for all brain regions and metabolites.

	k	Hedge's *g*	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*p*
Anterior cingulate cortex								
Glu	5	−0.50	0.35	0.12	−1.18	0.17	−1.46	0.15
Gln	0	—	—	—	—	—	—	—
Glx	2	−0.17	0.35	0.12	−0.85	0.52	−0.48	0.63
GABA	**3**	**−0.61**	**0.21**	**0.04**	**−1.01**	**−0.20**	**−2.93**	**0.003**
NAA	**3**	**−0.65**	**0.22**	**0.05**	**−1.07**	**−0.22**	**−2.97**	**0.003**
Cho	2	−0.05	0.38	0.14	−0.79	0.69	−0.13	0.90
Cr	3	−0.55	0.54	0.29	−1.60	0.51	−1.01	0.31
mI	3	−0.50	0.39	0.15	−1.25	0.26	−1.29	0.20
Basal ganglia/striatum								
Glu	**2**	**−0.45**	**0.23**	**0.05**	**−0.91**	**0**	**−1.97**	**0.05**
Gln	1	—	—	—	—	—	—	—
Glx	3	−0.18	0.23	0.05	−0.63	0.26	−0.80	0.42
GABA	1	—	—	—	—	—	—	—
NAA	2	0.18	0.24	0.06	−0.29	0.64	0.75	0.46
Cho	3	−0.16	0.38	0.14	−0.90	0.58	−0.42	0.68
Cr	2	−0.27	0.34	0.12	−0.94	0.40	−0.80	0.42
mI	2	−0.36	0.39	0.15	−1.12	0.39	−0.94	0.35
Frontal gray matter								
Glu	0	—	—	—	—	—	—	—
Gln	0	—	—	—	—	—	—	—
Glx	0	—	—	—	—	—	—	—
GABA	0	—	—	—	—	—	—	—
NAA	2	−1.01	0.89	0.8	−2.76	0.74	−1.13	0.26
Cho	2	0.12	0.19	0.04	−0.25	0.49	0.64	0.52
Cr	1	—	—	—	—	—	—	—
mI	0	—	—	—	—	—	—	—
Hippocampus								
Glu	2	−0.16	0.24	0.06	−0.63	0.32	−0.66	0.51
Gln	0	—	—	—	—	—	—	—
Glx	1	—	—	—	—	—	—	—
GABA	0	—	—	—	—	—	—	—
NAA	2	0.22	0.42	0.18	−0.60	1.04	0.52	0.61
Cho	2	−0.04	0.31	0.1	−0.65	0.57	−0.12	0.90
Cr	2	−0.23	0.25	0.06	−0.71	0.25	−0.94	0.35
mI	1	—	—	—	—	—	—	—
Thalamus								
Glu*	2	−0.36	0.29	0.08	−0.92	0.21	−1.23	0.22

(Continues)

TABLE 1 | (Continued)

	k	Hedge's *g*	Standard error	Variance	Lower limit	Upper limit	*Z*-value	*p*
Gln*	**2**	**−0.61**	**0.29**	**0.09**	**−1.19**	**−0.04**	**−2.08**	**0.04**
Glx	0	—	—	—	—	—	—	—
GABA	0	—	—	—	—	—	—	—
NAA*	4	−0.24	0.16	0.03	−0.55	0.08	−1.49	0.14
Cho*	4	−0.06	0.27	0.07	−0.58	0.46	−0.24	0.81
Cr	1	—	—	—	—	—	—	—
mI*	**2**	**−1.14**	**0.35**	**0.12**	**−1.83**	**−0.46**	**−3.26**	**0.001**
Temporal gray matter								
Glu*	2	−0.06	0.29	0.08	−0.63	0.50	−0.22	0.83
Gln*	2	0.03	0.29	0.08	−0.54	0.59	0.09	0.93
Glx	0	—	—	—	—	—	—	—
GABA	0	—	—	—	—	—	—	—
NAA*	3	0.20	0.35	0.13	−0.49	0.89	0.56	0.58
Cho*	3	−0.06	0.17	0.03	−0.4	0.28	−0.37	0.71
Cr	1	—	—	—	—	—	—	—
mI*	2	−0.28	0.37	0.14	−1.01	0.44	−0.78	0.44

Note: Bold = significant $p \leq 0.05$.
*2 VOIs (right and left hemisphere) from Mashhoon et al. (2013) (Hermann et al. 2007).

number of studies available, all results should be interpreted with caution. This is especially pertinent for the basal ganglia/striatum and thalamic findings for two main reasons. First, Glu and Gln metabolite levels are dynamic and present methodological complexities that can prohibit accurate assessment of these metabolites (e.g., TE, magnet strength) (Ramadan et al. 2013). Second, the thalamic models included bi-hemispheric measurements from an all male sample, creating a lack of independence within the data. Nonetheless, these findings provide initial and novel insights into how cannabis may impact the brain.

While three brain regions were found to have altered neurometabolic levels related to cannabis use, the ACC alterations indicating lower levels of GABA and NAA are the strongest findings in terms of number and quality (e.g., low heterogeneity) of studies available. Logistically, the ACC is often a brain region of interest when acquiring 1H-MRS neurometabolic data due to the large presence of gray matter in this region and the ability to get lower shimming values (higher data quality) compared to deeper brain regions. The ACC is also highly implicated in substance use behaviors, including cognitive control, reward monitoring, craving, and incentive salience (Zhao et al. 2021; Kalivas and Volkow 2005). Neurochemical changes in the ACC may be related to substance-related cognitive deficits and clinical symptomology, such as increased craving or decreases in behavioral performance (Zhao et al. 2021). The alterations in GABA, specifically, may be due to the delta-9-tetrahydrocannabinol (THC) component of cannabis, as THC is an agonist of cannabinoid receptors (CB1) that are expressed on GABAergic neurons (Watts et al. 2020). THC is therefore able to inhibit the release of GABA throughout the brain due to the nature of the endocannabinoid system (Laaris et al. 2010; Wilson and Nicoll 2002; Heng et al. 2011). While cannabis-related changes in GABA levels and GABAergic neurotransmission can affect everyone, it may be especially detrimental for adolescents who are experiencing intense neurodevelopment (Heng et al. 2011). Since NAA is thought to be a marker of neuronal viability and integrity, the lower levels noted here may be an indicator of the neurotoxic effects of cannabis. The neurotoxicity of cannabis is debated (Rocchetti et al. 2013; Abdel-Salam 2022), but there are some preclinical and clinical studies that support a toxic effect of THC-rich cannabis on neuronal integrity (Abdel-Salam 2022). This is particularly concerning given the rising rates of THC in modern cannabis products (Freeman et al. 2021).

In terms of clinical applications, limited work has investigated the connection between neurometabolite alterations related to cannabis use and cognitive or behavioral features. Of the 15 papers included in this meta-analysis, only 3 (20%) investigated the relationship between cognitive or behavioral outcomes and neurometabolite levels (Subramaniam et al. 2022; Zuo, Davis, Kuppe, et al. 2022; Zuo, Davis, and Lukas 2022). Subramaniam et al. (2022) found no significant relationships between impulsivity measures and GABA or Glx levels within the ACC of adolescents who used cannabis; however, there were also no differences in impulsivity outcomes when compared to controls, which may explain this null finding. Zuo, Davis, and Lukas (2022) found that higher Glu levels in ACC over 21 days of abstinence were related to less cannabis craving and withdrawal symptoms, and higher ACC GABA levels were related to poorer sleep quality. Within the striatum, higher baseline

TABLE 2 | Heterogeneity results for brain regions and metabolites ($k > 2$).

	Tau	Tau^2	*Q*	*p*	I^2
Anterior cingulate cortex					
Glu	**0.70**	**0.49**	**22.61**	**0.00**	**82.31**
Glx	0.41	0.17	3.05	0.08	67.18
GABA	0.00	0.00	1.88	0.39	0.00
NAA	0.00	0.00	0.93	0.63	0.00
Cho	0.38	0.15	2.01	0.17	50.27
Cr	**0.87**	**0.76**	**16.34**	**0.00**	**87.76**
mI	**0.58**	**0.34**	**8.58**	**0.01**	**76.70**
Striatum					
Glu	0.00	0.00	0.95	0.33	0.00
Glx	0.17	0.03	2.47	0.29	18.92
NAA	0.00	0.00	0.77	0.38	0.00
Cho	**0.57**	**0.32**	**8.23**	**0.02**	**75.71**
Cr	0.33	0.11	1.82	0.18	44.98
mI	**0.47**	**0.22**	**3.74**	**0.05**	73.23
Frontal gray matter					
NAA	**1.20**	**1.45**	**10.56**	**0.001**	**90.53**
Cho	0.00	0.00	9.74	0.32	0.00
Hippocampus					
Glu	0.00	0.00	0.00	0.96	0.00
NAA	0.47	0.22	2.67	0.10	62.6
Cho	0.27	0.07	1.55	0.21	35.3
Cr	0.00	0.00	0.54	0.46	0.00
Thalamus					
Glu	0.00	0.00	0.23	0.63	0.00
Gln	0.00	0.00	0.01	0.91	0.00
NAA	0.00	0.00	1.84	0.61	0.00
Cho	0.39	0.15	6.67	0.08	55.03
mI	0.22	0.05	1.25	0.26	19.97
Temporal gray matter					
Glu	0.00	0.00	0.11	0.74	0.00
Gln	0.00	0.00	0.79	0.37	0.00
NAA	**0.50**	**0.25**	**6.26**	**0.04**	68.06
Cho	0.00	0.00	0.26	0.88	0.00
mI	0.32	0.10	1.6	0.21	37.42

Note: Bold = high heterogeneity marked by significant *Q* statistic at $p < 0.05$ and/or $I^2 > 75\%$.

levels of GABA were associated with fewer cannabis withdrawal symptoms at day 7 and day 21 of abstinence (Zuo, Davis, Kuppe, et al. 2022). While none of these studies investigated cognitive and behavioral outcomes in relation to NAA, work in other populations has noted complex associations with cognitive factors (Yang et al. 2021; Bakhshinezhad et al. 2022; Huber et al. 2018). Additional research is needed to understand the clinical implications of neurometabolic alterations related to cannabis use.

The use of 1H-MRS to measure neurometabolic effects of cannabis has gradually increased over the last two decades; however, it is still far behind 1H-MRS work in alcohol and stimulants (Kirkland et al. 2022; Smucny and Maddock 2023). There are overlapping and distinct neurometabolic findings across each substance (Figure 5). Interestingly, the lower levels of GABA and NAA within the ACC related to cannabis use are consistent with findings from alcohol-specific studies. While the alcohol studies included older participants on average (mid-40s) compared to the cannabis samples (mid-20s), the ACC-specific findings in the alcohol meta-analysis were driven by younger, non-treatment-seeking samples. This may indicate that the ACC is a particularly vulnerable brain region for alcohol and cannabis use, the most commonly used substances in adolescence and early adulthood. There were no overlapping findings between cannabis and stimulant use disorders, but alcohol and stimulant use studies both noted lower levels of NAA in frontal gray and white matter regions. Across all three meta-analyses, NAA seems to be the metabolite most affected by substance use. Future substance use disorder treatments may be able to directly (pharmacotherapy) or indirectly (psychosocial interventions) target NAA levels.

There are several limitations to the current work. Importantly, most of the models only had 2–5 estimates per brain region, leading to reduced statistical power, generalizability, and the inability to dig deeper into potential factors impacting neurometabolic changes related to cannabis use. While technically meta-analytic models can be completed with only 2 studies (Borenstein et al. 2009; Valentine et al. 2010), as done in this paper, the results of such models must be considered preliminary due to the reduced statistical power. This is compounded in models that included bi-hemispheric regions of interest, such as the thalamic results, which confound the independence of data within the models. Further, the studies included had varying levels of heterogeneity indices, which can heighten spurious significant effects in models with few studies. The use of random-effects, which assumes the models are affected by random sampling error, identifiable covariates, and unidentified confounders, accounts for some of this heterogeneity (Valentine et al. 2010); however, it does not make up for the limited number of studies available. The presented effect sizes, indices of heterogeneity, and study sample sizes can provide a priori estimates for future meta-analyses on this topic.

Further, due to the limited number of available studies within each brain region and metabolite, we were not able to conduct sub-group or meta-regressions (Borenstein and Higgins 2013; Richardson et al. 2019), which can provide critical contextual information. We were not able to assess the effects of CUD diagnosis compared to non-CUD studies; substance use treatment-seeking status; or other demographic factors, such as age, sex, education, or race/ethnicity. These factors will be crucial in future meta-analyses. Some of these factors have previously impacted alcohol-specific meta-analyses (i.e., treatment seeking status, abstinence duration, age, and sex distribution) (Kirkland et al. 2022) as well as clinical profiles (Tomko

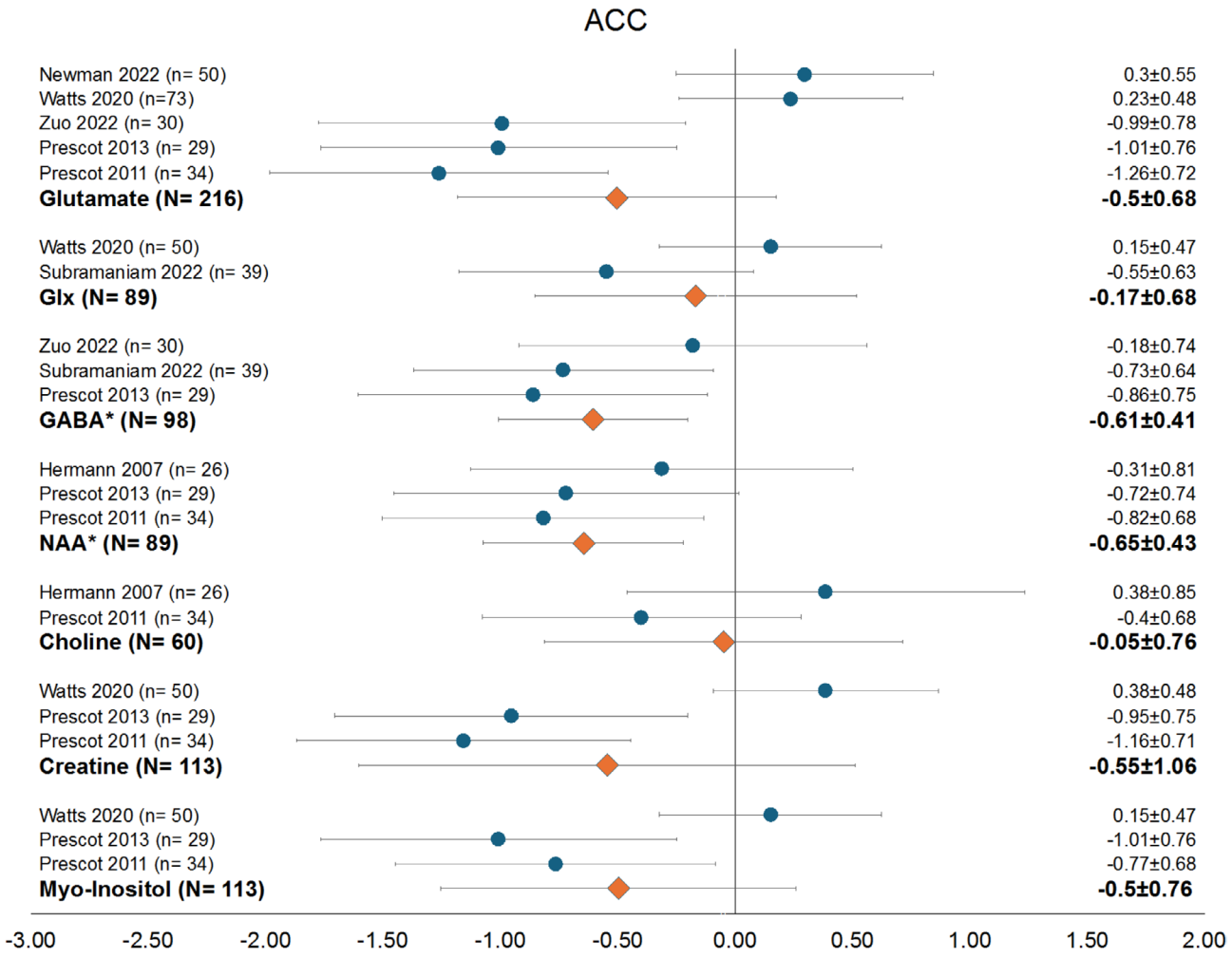

FIGURE 2 | Significant neurometabolite differences in the ACC between cannabis-using groups and control groups. Levels of NAA and GABA within the anterior cingulate cortex (ACC) were noted as being lower in the cannabis-using groups. The diamond markers indicate overall model effect sizes for each metabolite, while the circles indicate individual study effect sizes. Glutamate (Glu), glutamine (Gln), glutamate + glutamine (Glx), gamma-aminobutyric acid (GABA), N-acetylaspartate (NAA), choline-containing metabolites (Cho), creatine-containing metabolites (Cr), and *myo*-inositol (mI).

et al. 2023), while demographic variables did not impact models assessing the effects of stimulant use on neurometabolic levels (Smucny and Maddock 2023). The average age of participants in the cannabis use studies skewed younger (mid-20s) than the alcohol (mid-40s) or stimulant (30s) use meta-analyses, suggesting that capturing neurometabolic impacts of cannabis earlier in life may support intervention effects. There may also be sex effects. Fourteen of the fifteen studies included a majority of male participants, with two studies including only male participants (Hermann et al. 2007; Mashhoon et al. 2013). Given that the thalamic models finding lower levels of Gln and mI were driven by the Mashhoon et al. study (Mashhoon et al. 2013), this finding only considers the neurometabolic impact of cannabis within the thalamus of *males*. Also of note, we were not able to account for cannabis use characteristics, such as frequency, quantity, duration, or cannabinoid content, which could impact the detection and extent of neurometabolite alterations (Laaris et al. 2010). Beyond the limited number of studies to complete sub-group and meta-analytic models, there was inconsistent reporting of demographic variables (e.g., race), cannabis use variables, and substance use behaviors outside of cannabis use. Several studies were not able to be included in the final models due to insufficient data (e.g., no reported average and variation indices). Future studies should make a unified effort to collect and report standardized demographic, clinical, and substance use information to support a more comprehensive understanding of how cannabis may differentially impact neurometabolite levels (Öz et al. 2021; Choi et al. 2021; Wilson et al. 2019).

Similarly to demographic and cannabis use characteristic limitations, we were not able to assess the impact of methodological parameters or data quality. Given the wide variety of parameters reported, this will be an essential piece in future work. The appropriateness of the sequence parameters, their resulting data quality, and the quantification methods for neurometabolites underpin the ability to interpret outcomes in individual studies, which is compounded in a meta-analysis. For example, the alcohol meta-analysis found important differences in absolute compared to relative concentrations (i.e., ratio-to-Cr) in several neurometabolites and brain regions, while meta-regressions showed significant effects for echo time (TE) (Kirkland et al. 2022). For stimulant use disorder, follow-up analyses found

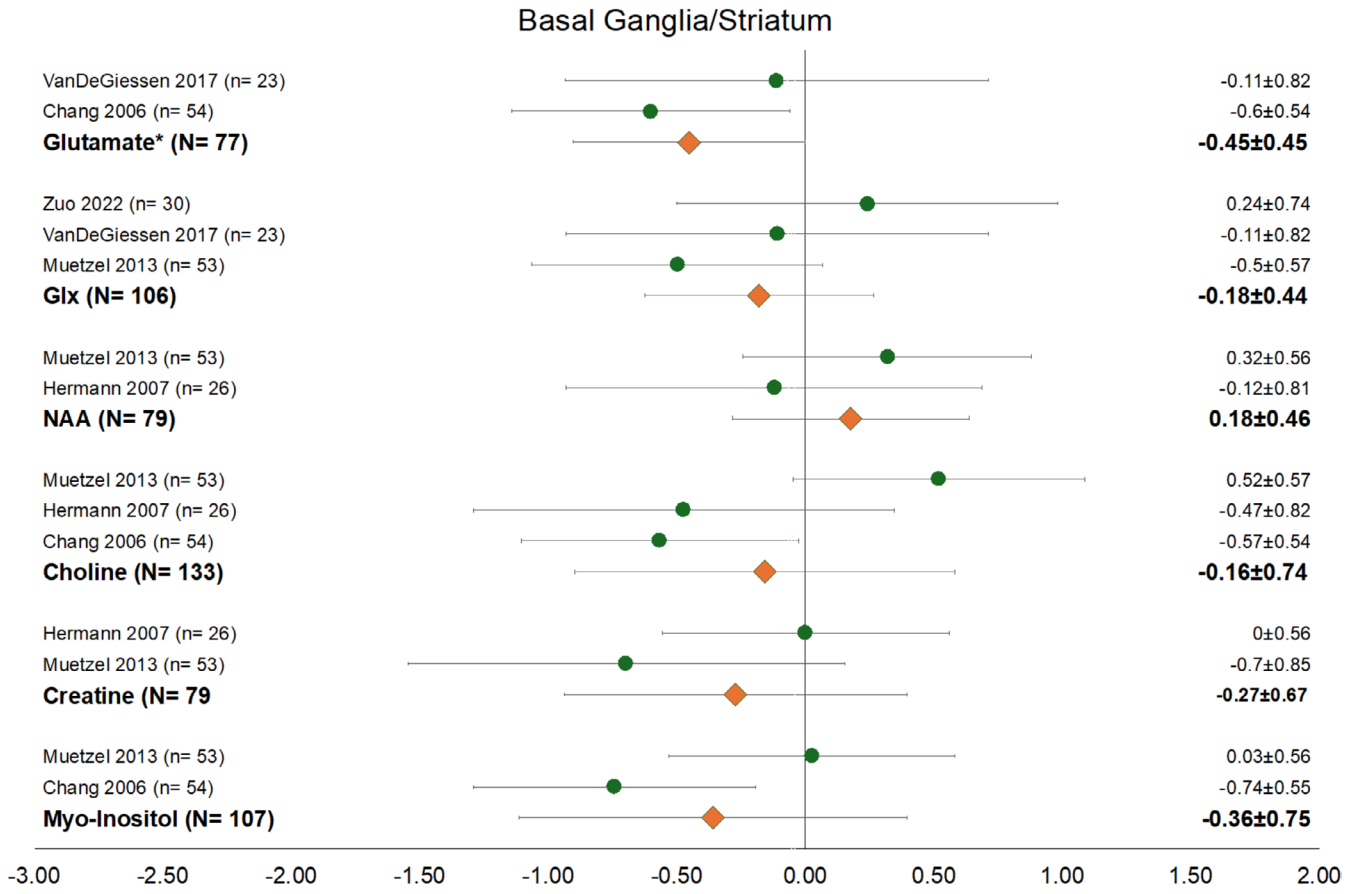

FIGURE 3 | Significant neurometabolite differences in the basal ganglia/striatum between cannabis-using groups and control groups. Levels of Glu within the basal ganglia/striatum was noted as being lower in the cannabis-using groups. The diamond markers indicate overall model effect sizes for each metabolite, while the circles indicate individual study effect sizes. Glutamate (Glu), glutamine (Gln), glutamate + glutamine (Glx), gamma-aminobutyric acid (GABA), N-acetylaspartate (NAA), choline-containing metabolites (Cho), creatine-containing metabolites (Cr), and *myo*-inositol (mI).

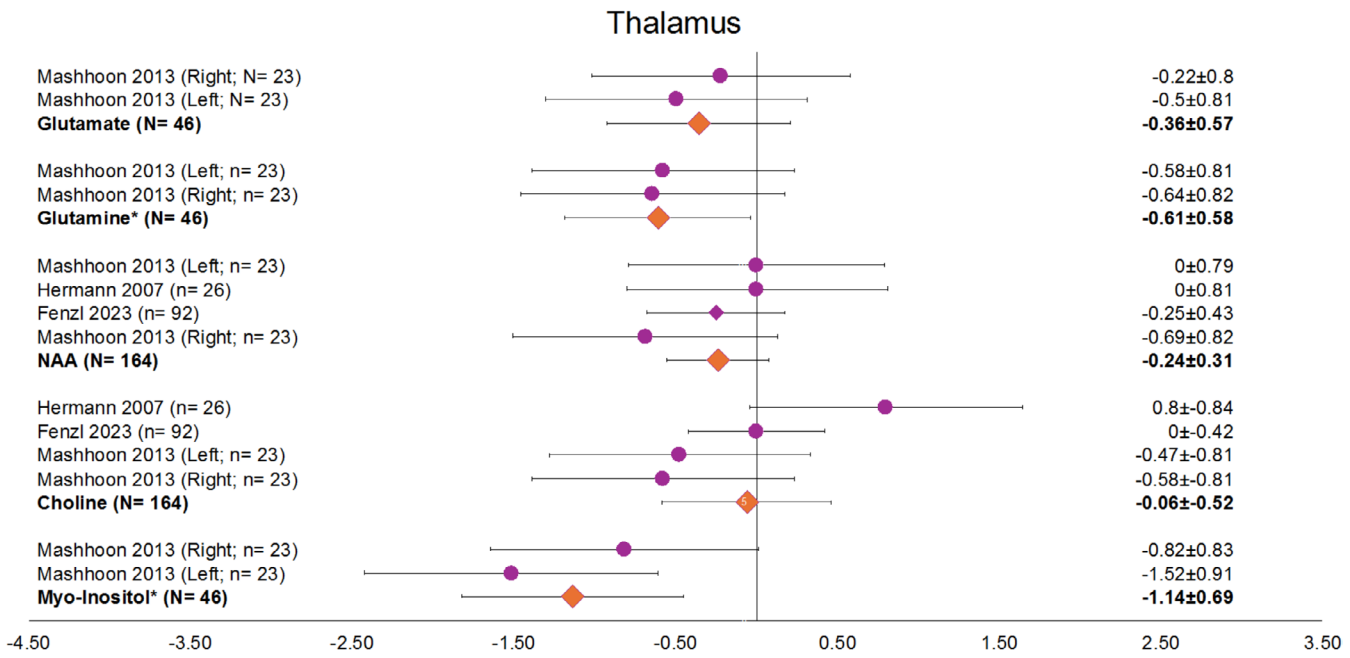

FIGURE 4 | Significant neurometabolite differences in the thalamus between cannabis-using groups and control groups. Levels of Gln and mI in the thalamus were noted as being lower in the cannabis-using groups. The diamond markers indicate overall model effect sizes for each metabolite, while the circles indicate individual study effect sizes. Glutamate (Glu), glutamine (Gln), glutamate + glutamine (Glx), gamma-aminobutyric acid (GABA), N-acetylaspartate (NAA), choline-containing metabolites (Cho), creatine-containing metabolites (Cr), and *myo*-inositol (mI).

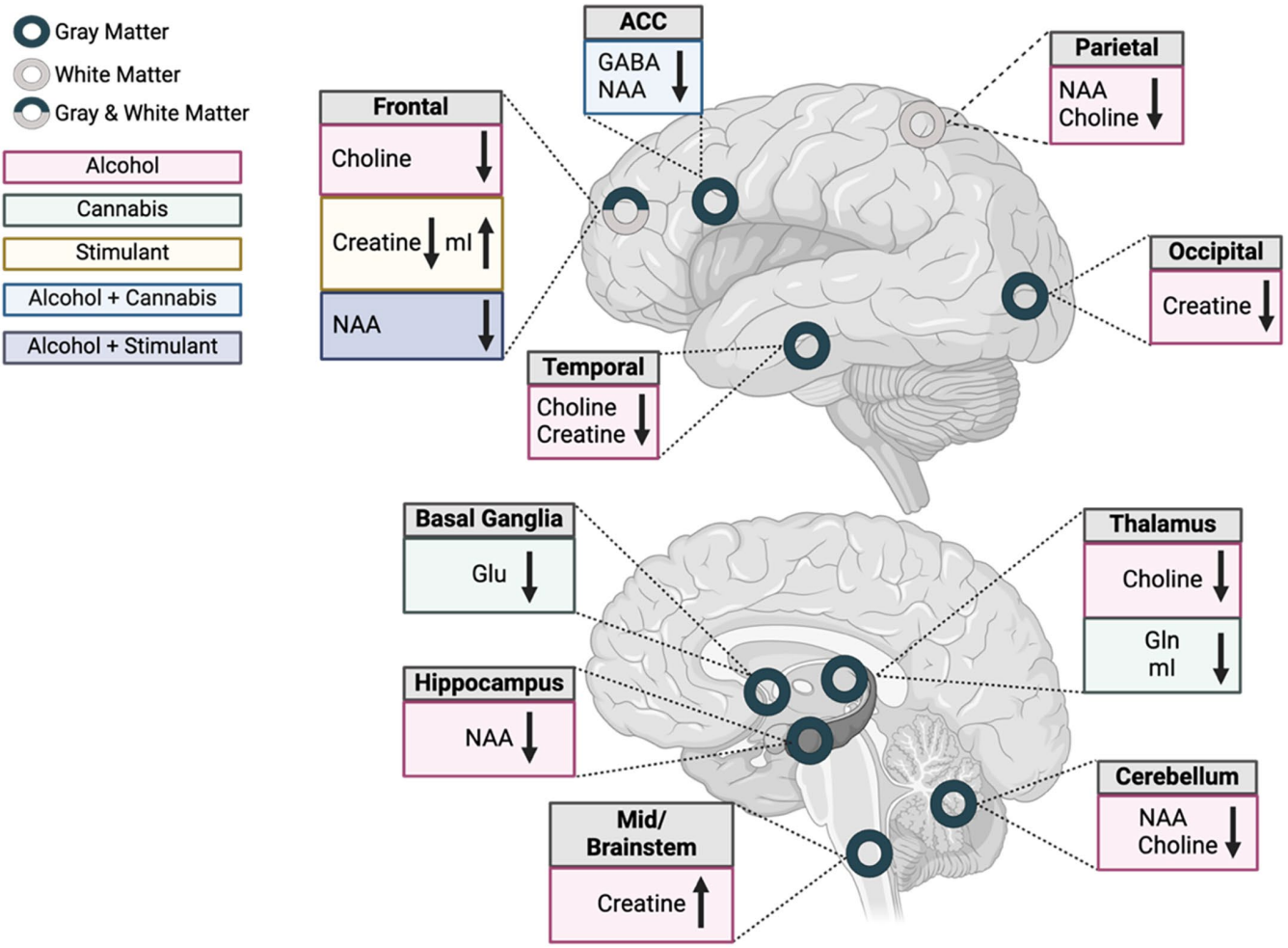

FIGURE 5 | Overview of neurometabolic alterations associated with alcohol, stimulant, and cannabis use. The cannabis specific findings are from the current work. The alcohol-specific findings are from Kirkland et al. (2022). The stimulant specific findings are from Smucny and Maddock (2023). Anterior Cingulate Cortex (ACC), glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA), N-acetylaspartate (NAA), choline-containing metabolites (Cho), creatine-containing metabolites (Cr), and *myo*-inositol (mI).

significant effects of TE and coefficient of variation (Smucny and Maddock 2023). It is important to note the potential impact of absolute compared to relative concentrations, where the latter assumes an internal stability of the reference metabolite, particularly when using a ratio-to-Cr method (Barantin et al. 1997; Li et al. 2003). While this study did not find any differences in Cr related to cannabis use, Cr has been shown to be impacted by alcohol (Kirkland et al. 2022), age, and pathology (Öz et al. 2021; Wilson et al. 2019). It is reasonable to think that these parameters will also impact the assessment of cannabis-related changes in neurometabolic levels. As more studies using 1H-MRS within cannabis are published, we will be able to capture potentially important methodological considerations (Öz et al. 2021; Choi et al. 2021; Wilson et al. 2019; Barantin et al. 1997; Li et al. 2003).

Finally, there was indication of publication bias and some methodological quality concerns. The publication of scientific articles is associated with the statistical significance of results, where papers reporting significant results are more likely to be published than null papers, which can introduce bias in meta-analyses (Lin and Chu 2018). Here, we report indication of publication bias for Glu and mI in the ACC using Egger's regression (Egger et al. 1997). Both the Glu and mI models in the ACC also had high levels of heterogeneity which can influence the Egger's regression significance. Glx in the basal ganglia/striatum and Cho in the temporal gray matter models also showed publication bias using Dual and Tweed Trim and Fill method (Duval and Tweedie 2000). The Dual and Tweed Trim and Fill method suggested a significant *corrected* effect for Glx in the basal ganglia/striatum model, which would mirror the significant Glu effect in this region; however, this is with 2 of the 3 available studies "trimmed" essentially relying on the significant results from only a singular study. This finding highlights how the low number of studies included in these assessments may influence the presence and magnitude of publication bias. Of note, none of the models with potential publication bias were significant. In terms of methodological quality, a consistent finding was a lack of justified sample size via an a priori power analysis for every study. This could introduce underpowered results into the models. As previously mentioned, there were also several important variables that were not adequately described across almost half of the studies, ranging from demographic information to substance use to 1H-MRS data quality indices. Missing or under-reported data was not restricted to older studies, suggesting that the guidelines for minimum reporting standards are not being consistently followed. It is also important that researchers

continue to maintain up-to-date 1H-MRS acquisition, processing, and quantification procedures.

5 | Conclusion

In conclusion, 1H-MRS can identify brain metabolite levels altered by cannabis use. The most robust findings were lower levels of GABA and NAA within the ACC, which align with recent alcohol-specific findings. The current work was limited by the available extant literature, which prevented investigation into important factors via meta-regressions or sub-group analyses, and inconsistent reporting of neurometabolite outcomes. This meta-analysis serves as an indicator for where the 1H-MRS literature stands regarding cannabis and other substance use, and as a reminder that moving toward a more complete understanding of the neurobiological consequences of substance use can inform future interventions, including medication development.

Author Contributions

Conceptualization: A.E.K., B.D.B., and L.M.S. Methodology: A.E.K., B.D.B., and L.M.S. Software: A.E.K., B.D.B., S.O.A., and R.G. Formal analysis: A.E.K. Data curation: A.E.K., B.D.B., S.O.A., and R.G. Writing – original draft: A.E.K. Writing – review and editing: All authors. Visualization: A.E.K. Supervision: L.M.S.

Acknowledgements

We would like to acknowledge Teri Lynn Herbert (MUSC) for her invaluable help with setting up the literature searches for this meta-analysis. A.E.K. is funded through the NIAAA K01 (K01AA031745), B.D.B. is funded through the NIDA T32 (DA007288), and L.M.S. is funded through an NIAAA K24 (AA031052).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.