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Authors

Smucny, Jason

Maddock, Richard J

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Spectroscopic meta-analyses reveal novel metabolite profiles across methamphetamine and cocaine substance use disorder

Jason Smucny[*], **Richard J. Maddock**

Department of Psychiatry and Behavioral Sciences, University of California, Davis, USA

Abstract

Background: Although proton magnetic resonance spectroscopy (MRS) has been used to study metabolite alterations in stimulant (methamphetamine and cocaine) substance use disorders (SUDs) for over 25 years, data-driven consensus regarding the nature and magnitude of these alterations is lacking.

Method: In this meta-analysis, we examined associations between SUD and regional metabolites (N-acetyl aspartate (NAA), choline, myo-inositol, creatine, glutamate, and glutamate+glutamine (glx)) in the medial prefrontal cortex (mPFC), frontal white matter (FWM), occipital cortex, and basal ganglia as measured by 1 H-MRS. We also examined moderating effects of MRS acquisition parameters (echo time (TE), field strength), data quality (coefficient of variation (COV)), and demographic/clinical variables.

Results: A MEDLINE search revealed 28 articles that met meta-analytic criteria. Significant effects included lower mPFC NAA, higher mPFC myo-inositol, and lower mPFC creatine in SUD relative to people without SUD. mPFC NAA effects were moderated by TE, with larger effects at longer TEs. For choline, although no group effects were observed, effect sizes in the mPFC were related to MRS technical indicators (field strength, COV). No effects of age, sex, primary drug of use (methamphetamine vs. cocaine), duration of use, or duration of abstinence were observed. Evidence for moderating effects of TE and COV may have implications for future MRS studies in SUDs.

Conclusions: The observed metabolite profile in methamphetamine and cocaine SUD (lower NAA and creatine with higher myo-inositol) parallels that observed in Alzheimer's disease and mild cognitive impairment, suggesting these drugs are associated with neurometabolic differences similar to those characterizing these neurodegenerative conditions.

[*]Correspondence to:Imaging Research Center, University of California Davis Medical Center, Sacramento, CA95817, USA. jsmucny@ucdavis.edu (J. Smucny).

CRediT authorship contribution statement

Author J.S. performed the literature search, extracted the data, analyzed the data, and wrote the paper. Author R.J.M. verified data, analyzed the data, and wrote the paper.

Declaration of Competing Interest

No conflicts declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.109900.

Keywords

Choline; Myo-inositol; MRS; NAA; N-acetyl-aspartate; Spectroscopy

1. Introduction

The growing prevalence of deleterious and often fatal stimulant use disorders (SUDs) (such as methamphetamine and cocaine) represents a critical and worsening health crisis. According to a 2021 study, between 2015 and 2019 the number of USA overdose deaths from psychostimulants (other than cocaine) tripled, with the number of people using methamphetamine and cocaine increasing by 60% and the number with methamphetamine use disorder increasing by 62% (Han et al., 2021). Frequent methamphetamine use (>100 days in the past year) also increased by 66% (Han et al., 2021). For cocaine itself, although use has decreased in the USA in recent decades, 5.2 million Americans 12+ years old reported using the drug in the last year, 1.3 million had a use disorder in the last year, and 19,447 died from an overdose (https://www.samhsa.gov/data/release/2020-national-survey--drug-use-and-health-nsduh-release). Given the highly addictive nature of these drugs and their known deleterious consequences on physical and mental health (Barr et al., 2006; Degenhardt et al., 2017), it is critical to thoroughly understand the neurobiological effects associated with SUDs.

Proton (1 H)-magnetic resonance spectroscopy (MRS) is a noninvasive, readily administered method of analyzing the levels of neurotransmitters and metabolites in the human brain. MRS has been used to study SUDs since the late 1990 s. The most common metabolites examined in SUDs are N-acetyl-aspartate (NAA), choline, myo-inositol, total creatine (creatine+phosphocreatine), glutamate, glutamate+glutamine (glx), and gamma-aminobutyric acid (GABA). To our knowledge, however, no meta-analysis has yet been conducted across these studies to discern the nature and magnitude of differences in their levels in people with methamphetamine and/or cocaine SUD. A brief introduction to the neuronal processes associated with these metabolites is provided below.

1.1. N-acetyl-aspartate (NAA)

One of the most abundant metabolites in the brain, NAA is thought to be an indicator of neuronal integrity and viability (Maddock and Buonocore, 2012; Moffett et al., 2007) as well as mitochondrial energy output (Clark, 1998), and also acts as an acetate source during myelin production (Chakraborty et al., 2001). Lower NAA is associated with inflammatory, traumatic, and degenerative processes in disorders such as multiple sclerosis (Chang et al., 2013; Rigotti et al., 2007), traumatic brain injury (Joyce et al., 2022), and Alzheimer's disease (Song et al., 2021). In 1 H-MRS, NAA signal is often measured as the combination of NAA and N-acetyl-aspartyl-glutamate (NAAG), which is a peptide neurotransmitter co-released with glutamate and which activates the type 3 metabotropic glutamate receptor. Indeed, studies often do not specify if the reported NAA signal is segregated from NAAG. The combined NAA+NAAG signal is mostly comprised of the NAA fraction.

1.2. Choline

The main choline-containing compounds measured by MRS are phosphocholine and glycerophosphocholine. These compounds are essential in phospholipid metabolism and consequently may index cell membrane turnover (Klein, 2000; Saito et al., 2022) as well as the density of cell membranes in MRS voxels (Maddock and Buonocore, 2012). Higher choline is also associated with neuroinflammation and glial activation (Chang et al., 2013).

1.3. Myo-inositol

Myo-inositol, by far the most abundant stereoisomer of inositol in the mammalian brain (about 90% of inositol forms are myo-) (Fisher et al., 2002), has numerous roles in normal brain function, including acting as a precursor to membrane lipids and second messenger compounds (Maddock and Buonocore, 2012), participating in osmotic regulation (Fisher et al., 2002), and serving as a precursor to phosphatidyl-inositol (which facilitates binding of neurotransmitters to their receptors (Hammond and Balla, 2015)). Elevated myo-inositol levels have been associated with neurodegenerative disorders, inflammation, glial activation, and gliosis (Bitsch et al., 1999; Kim et al., 2005).

1.4. Creatine

The MRS total creatine signal is combination of creatine and phosphocreatine. The primary functions of the creatine/phosphocreatine system in the brain are to act as a buffer and mediator for high-energy phosphate bonds from subcellular regions of energy production to regions of energy consumption (Maddock and Buonocore, 2012). Creatine also helps prevent apoptosis by stabilizing mitochondrial membranes (Dolder et al., 2003). Accordingly, creatine MRS signal is generally considered to be measure of brain metabolic health.

As the creatine signal is thought to be relatively stable over time and similar throughout the brain, it is often used an internal “reference” signal to normalize signals from other metabolites (e.g., expressing NAA levels as a ratio of NAA/creatine) (Buonocore and Maddock, 2015; Maddock and Buonocore, 2012). Notably, however, recent evidence suggests creatine levels may increase with age (Lind et al., 2020) as well as be affected by certain pathological states (e.g., alcohol misuse (in occipital cortex/brainstem) (Kirkland et al., 2022) and Alzheimer’s disease/mild cognitive impairment (Song et al., 2021)). Thus, creatine may not be an appropriate reference signal in all participant populations.

1.5. Glutamate and glutamine

Glutamate is the primary excitatory transmitter in the mammalian brain. It is also one of the brain’s most abundant molecules, as a significant fraction of brain glucose metabolism is directed towards its astrocytic synthesis (Hertz, 2006). In addition to its role in excitatory neurotransmission, glutamate metabolism has a key role in the energy-producing tricarboxylic acid (TCA) cycle (Nissen et al., 2015).

In addition to glutamate, the combined signal from both glutamate and glutamine is often estimated in 1 H-MRS studies. These compounds together participate in the glutamate/glutamine cycle). This glutamate+glutamine signal, usually referred to as *glx*, acts as a

reasonable surrogate of the total pool of glutamate and glutamate available for use as an excitatory transmitter and for metabolic functions (Maddock and Buonocore, 2012).

1.6. Gamma-aminobutyric acid (GABA)

GABA is the most abundant inhibitory neurotransmitter. It is synthesized from glutamate by glutamic acid decarboxylase, and also can be recycled to glutamate during the TCA cycle (Petroff, 2002). Reliable detection of GABA typically requires specialized MR acquisitions, such as the MEGA-PRESS editing sequence (Mescher et al., 1998).

1.7. Study rationale

Based on their associated neuronal processes, one may hypothesize that several of these metabolites may be altered in SUDs. Nonetheless, with the possible exception of lower NAA (reviewed by Hellem et al. 2015), evidence for alterations in any other metabolite associated with methamphetamine and/or cocaine SUD remains inconclusive. As MRS studies are typically conducted using small sample sizes, it is possible that the increase in statistical power offered by meta-analysis will reveal significant differences in these metabolites even in the presence of small effect sizes (as well as determine the effect size of the NAA difference if it in fact exists). Furthermore, in a meta-analysis of MRS studies in schizophrenia, we have recently found that glutamate is lower in the illness with effect sizes that increase as a function of MRS measurement quality (ascertained by coefficient of variation (COV, linewidth, and Cramer-Rao lower bound (CRLB)) and echo time (Smucny et al., 2021). We therefore examined (when possible; see Methods) the moderating effects of these factors in the present meta-analyses. We also compared effect sizes between datasets that used creatine as a reference indicator vs. those that used unsuppressed water. Finally, as exploratory measures, we examined the moderating effects of demographic (age, sex) and clinical (primary drug used (cocaine or methamphetamine), duration of drug use, duration of abstinence) variables.

2. Material and methods

2.1. Study selection

The MEDLINE database was searched on July 8, 2022 to identify journal articles using the following query: ((*methamphetamine* OR *cocaine* OR *amphetamine*) AND (*magnetic resonance spectroscopy* OR *MRS*)). This search yielded 462 records for screening, of which 53 articles were further selected for eligibility (Fig. S1 and Table S1 in Supplement).

2.2. Meta-analysis

For each brain region studied, authors J.S. extracted and R.M. verified data. Extracted data included sample sizes, means, and standard deviations (SDs) of metabolite values. Studies were excluded if they lacked a comparison (control) group and or only examined acute (single dose) drug effects. Additional information regarding exclusion criteria as well as data pooling (e.g., for longitudinal studies) is provided in the Supplement.

Effect size for each dataset was calculated as Hedge's *g*, which corrects for small sample sizes (Hedges and Olkin, 1985). 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 meta for package as its computational engine (JASP Team, 2020). Heterogeneity across studies was quantified as I^2, and a chi-square test of the Q statistic tested for significant departure from homogeneity. Consistent with our prior MRS meta-analysis in schizophrenia (Smucny et al., 2021), meta-analytic hypothesis testing was performed only in brain regions for which ≥ 7 datasets were available.

Echo time (log TE) and field strength were examined as potential moderators using meta-regression, while normalization method (water vs. creatine) was examined using subgroup analysis. Studies estimating metabolites from multiple TEs were not included when analyzing TE effects. Demographic and clinical variables were also examined via meta-regression (pooled mean age, pooled %male, duration of use, and duration of abstinence) or subgroup analysis (abstinent versus non-abstinent status). When moderator analyses were significant, subgroups of studies were analyzed separately for descriptive purposes. In determining whether these factors account for heterogeneity across datasets, moderator analysis was limited to brain regions for which $k \geq 10$ datasets were available (as recommended by the Cochrane Handbook (Higgins et al., 2020)). Small study bias was tested using the Egger's test; datasets inducing bias were identified from Egger funnel plots. Dataset outliers were defined as having a 95% CI outside of the range of the 95% CI of all datasets for that analysis. If a primary analysis had a significant Egger's test and/or outliers, data were re-analyzed without the most biased dataset and/or outliers. If the Egger's test was still significant after this initial screen, the dataset with the next-highest degree of bias was removed and the process continued until the Egger's test became non-significant. Results with and without the removed datasets were both reported. For moderator analyses, if moderator data was missing for a study, that study was excluded from analysis of that particular moderator.

2.2.1. Effect of quality metrics—Based on results from our prior MRS meta-analysis (Smucny et al., 2021), moderators related to data quality (COV, linewidth, signal to noise ratio (SNR), and Cramer-Rao lower bound (CRLB)) were also extracted (if reported) for potential analysis. For COV values, we calculated the average COV (as SD/mean) of the SUD and control (non-SUD) groups.

We hypothesized any true difference in metabolite values between groups would be most evident in studies with relatively better-quality measurements (i.e., lower COVs). We reasoned that the relationship between measurement quality and effect size would be logistic (sigmoid), rather than linear. That is, we expected there would be a quality threshold beyond which pooled effect sizes would become larger and more consistent. Formally, we hypothesized there was a quality threshold T, for which the meta-analytic result would be significantly stronger in studies surpassing T than for those falling short of T. Additional details on this analysis are provided in the Supplement.

3. Results

Of the 53 articles assessed for eligibility from MEDLINE, after applying inclusion and exclusion criteria (Table S1 in Supplement), data from 36 studies were extracted for potential inclusion in meta-analyses. From these studies, only voxel locations for which results were available from at least 7 datasets for a given metabolite were analyzed. Eight studies were thereby subsequently excluded (Table S1). A listing of voxel locations with <7 datasets is provided in Table S2. Overall, datasets from 28 studies were included in meta-analyses (Abe et al., 2013; Burger et al., 2018; Chang et al., 2005, 1999, 1997; Cloak et al., 2011; Crocker et al., 2014, 2017; Ernst and Chang, 2008; Ernst et al., 2000; Howells et al., 2014; Hulka et al., 2016; Ke et al., 2004; Kim et al., 2018; Li et al., 1999; Lin et al., 2015; Martinez et al., 2014; Nordahl et al., 2002; Sailasuta et al., 2010; Salo et al., 2011, 2007; Schmaal et al., 2012; Sekine et al., 2002; Sung et al., 2013, 2007; Taylor et al., 2007; Wu et al., 2018; Yang et al., 2009). Summary information across all datasets is provided in Table S3. Briefly, sample participants were ~30 years of age and primarily (~2/3) male. The primary drug of choice by people with SUD in most datasets was methamphetamine (as opposed to cocaine). All datasets recruited participants who were currently using or had been using cocaine or methamphetamine for at least 2 years. If a dataset included abstinent individuals with SUD, mean length of abstinence ranged from 10 days to 2 years for all regional metabolites with the exception of occipital cortex NAA and choline, which had datasets with mean abstinence as long as 5.5 years. Of the 9 studies examining non-abstinent SUD, people with SUD in 4 studies were not experiencing acute drug effects during scanning, 3 studies did not specify participant drug status, and 2 studies stated SUD individuals were experiencing acute drug effects. Of the 28 studies, 26 studies confirmed SUD using DSM criteria, 1 using the Schedule for Affective Disorders and Schizophrenia for School Aged-Children (K-SADS) (Sung et al., 2013), and 1 using an unspecified detailed questionnaire (Chang et al., 1997). The study that used the questionnaire reported that the SUD group had a “history of heavy cocaine use (>3 months of daily use).” Healthy controls in all studies were excluded for SUDs using the DSM (26 studies), K-SADS (Sung et al., 2013), or questionnaire (Chang et al., 1997). People who consumed alcohol and/or nicotine without meeting DSM criteria for dependence were generally not excluded from control groups.

Summary meta-analytic results organized by metabolite and brain region are presented in Table 1 (overall effects) and Table 2 (moderator effects). Results grouped by metabolite and voxel location are presented in more detail below, beginning with the metabolites and regions reresented by the most datasets.

3.1. N-acetyl aspartate (NAA)

3.1.1. Medial prefrontal cortex—Across 21 datasets (616 controls, 654 SUD) in the mPFC (Abe et al., 2013; Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Crocker et al., 2014, 2017; Ernst et al., 2000; Howells et al., 2014; Hulka et al., 2016; Ke et al., 2004; Kim et al., 2018; Nordahl et al., 2002; Salo et al., 2011, 2007; Schmaal et al., 2012; Sung et al., 2013, 2007; Taylor et al., 2007; Wu et al., 2018; Yang et al., 2009), we found significantly lower NAA in SUD vs. controls with a moderately large effect size (g =

−0.44, 95% CI = −0.60 to −0.28, Z = −5.42, p <0.001; heterogeneity: Q = 37.2, I^2 = 44, p =.011; Egger's test: Z = −1.54, p =.13) (Fig. 1). After excluding an outlier dataset (Nordahl et al., 2002), the difference remained significant (g = −0.42, 95% CI = −0.57 to −0.26, Z = −5.26, p <0.001). A significant moderating effect of log TE was also observed, as datasets with longer echo times showed greater effect sizes for NAA in SUD vs. controls (Z = −2.82, p =.005). In a secondary subgroup analysis examining short TE (≤40 ms) and longer than 40 ms TE datasets separately, findings of lower NAA in SUD were significant for both ≤40 ms TE datasets (k = 14, g = −0.34, 95% CI = −0.51 to −0.17, Z = −3.95, p <0.001; heterogeneity: Q = 20.4, I^2 = 32, p =.085; Egger's test: Z = −1.26, p =.21) and >40 ms TE datasets (k = 4, g = −0.86, 95% CI = −1.13 to −0.59, Z = −6.21, p <0.001; heterogeneity: Q = 1.0, I^2 = 0, p =.79; Egger's test: Z = −0.44, p =.66). No effects were found for age, sex, primary drug of use, years used, abstinence status (yes/no), years abstinent, field strength, or normalization method (water vs. creatine).

3.1.2. Frontal white matter—Across 10 datasets (316 controls, 330 SUD) in the FWM (Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Ernst et al., 2000; Howells et al., 2014; Nordahl et al., 2002; Sailasuta et al., 2010; Sung et al., 2007; Taylor et al., 2007), significantly lower NAA was observed between SUD and controls (g = −0.26, 95% CI = −0.51 to −0.01, Z = −2.02, p =.044; heterogeneity: Q = 20.2, I^2 = 57, p =.017; Egger's test: Z = −2.18, p =.029) (Fig. S2). After excluding the dataset exhibiting potential small study bias (which was also an outlier dataset; see Methods) (Sailasuta et al., 2010), however, the effect was no longer significant (g = −0.16, 95% CI = −0.36 to.05, Z = −1.52, p =.13). No effects were found for age, sex, years used, years abstinent, log TE, field strength, or normalization method (water vs. creatine). Notably, all NAA datasets were from studies using short TE (≤ 40 ms) scans. All datasets only examined abstinent individuals.

3.1.3. Basal ganglia—Across 8 datasets (216 controls, 212 SUD) in the basal ganglia (Chang et al., 2005; Cloak et al., 2011; Ernst et al., 2000; Li et al., 1999; Lin et al., 2015; Martinez et al., 2014; Sekine et al., 2002; Taylor et al., 2007), no significant difference was observed in NAA between SUD and controls (g = −0.13, 95% CI = −0.46 to.19, Z = −0.80, p =.43; heterogeneity: Q = 16.5, I^2 = 61, p =.021; Egger's test: Z =0.77, p =.44) (Fig. S3).

3.1.4. Occipital cortex—Across 7 datasets (126 controls, 165 SUD) in the occipital cortex (Abe et al., 2013; Chang et al., 1997; Lin et al., 2015; Nordahl et al., 2002; Sailasuta et al., 2010; Salo et al., 2011, 2007), no significant difference was observed in NAA between SUD and controls (g = −0.13, 95% CI = −0.37 to.11, Z = −1.09, p =.28; heterogeneity: Q = 5.5, I^2 = 0, p =.48; Egger's test: Z =0.41, p =.68) (Fig. S4).

3.2. Choline

3.2.1. Medial prefrontal cortex—Across 20 datasets (602 controls, 645 SUD) in the mPFC (Abe et al., 2013; Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Crocker et al., 2014, 2017; Ernst et al., 2000; Howells et al., 2014; Hulka et al., 2016; Ke et al., 2004; Kim et al., 2018; Nordahl et al., 2002; Salo et al., 2011, 2007; Sung et al., 2013, 2007; Taylor et al., 2007; Wu et al., 2018; Yang et al., 2009), no significant difference was observed in choline between SUD and controls (g =0.06, 95% CI = −0.10 to.22, Z

=0.69, p =.49; heterogeneity: Q = 35.5, I^2 = 46, p =.012; Egger's test: Z =0.07, p =.94) (Fig. S5). After excluding an outlier dataset (Chang et al., 2005), the difference remained non-significant (p =.88). A significant effect of field strength, however, was observed, as datasets with lower field strengths showed greater choline in SUD vs. controls (Z = −2.21, p =.027). A subgroup analysis examining 1.5 T and ≥3 T studies separately found no significant choline difference between SUD and controls at 1.5 T (k = 9, g =0.23, 95% CI = −0.02 to −0.48, Z = 1.82, p =.070; heterogeneity: Q = 17.9, I^2 = 56, p =.022; Egger's test: Z =0.60, p =.55) or 3 T (k = 11, g = −0.08, 95% CI = −0.25 to.08, Z = −0.98, p =.33; heterogeneity: Q = 12.1, I^2 = 3, p =.28; Egger's test: Z = −1.07, p =.29). No effects were found for age, sex, primary drug of use, years used, abstinence status (yes/no), years abstinent, log TE, or normalization method (water vs. creatine).

3.2.2. Frontal white matter—Across 10 datasets (315 controls, 330 SUD) in the FWM (Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Ernst et al., 2000; Howells et al., 2014; Nordahl et al., 2002; Sailasuta et al., 2010; Sung et al., 2007; Taylor et al., 2007), no significant difference was observed in choline between SUD and controls (g = −0.02, 95% CI = −0.18 to.14, Z = −0.27, p =.79; heterogeneity: Q = 10.6, I^2 = 2, p =.30; Egger's test: Z = −0.06, p =.95) (Fig. S6). No effects were found for age, sex, years used, years abstinent, log TE, field strength, or normalization method (water vs. creatine). All datasets only examined abstinent individuals.

3.2.3. Basal ganglia—Across 7 datasets (205 controls, 199 SUD) in the basal ganglia (Chang et al., 2005; Cloak et al., 2011; Ernst et al., 2000; Li et al., 1999; Lin et al., 2015; Martinez et al., 2014; Taylor et al., 2007), no significant difference was observed in choline between SUD and controls (g =0.02, 95% CI = −0.17 to.22, Z =0.14, p =.83; heterogeneity: Q = 4.3, I^2 = 0, p =.64; Egger's test: Z =0.14, p =.89) (Fig. S7).

3.2.4. Occipital cortex—Across 7 datasets (121 controls, 152 SUD) in the occipital cortex (Abe et al., 2013; Chang et al., 1997; Lin et al., 2015; Nordahl et al., 2002; Sailasuta et al., 2010; Salo et al., 2011, 2007), no significant difference was observed in choline between SUD and controls (g =0.01, 95% CI = −0.23 to.26, Z =0.11, p =.91; heterogeneity: Q = 4.6, I^2 = 0, p =.59; Egger's test: Z = −1.35, p =.18) (Fig. S8).

3.3. Myo-inositol

3.3.1. Medial prefrontal cortex—Across 13 datasets (445 controls, 457 SUD) in the mPFC (Abe et al., 2013; Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Ernst et al., 2000; Howells et al., 2014; Hulka et al., 2016; Kim et al., 2018; Sung et al., 2013, 2007; Taylor et al., 2007; Wu et al., 2018), significantly greater myo-inositol was observed in SUD vs. controls (g =0.22, 95% CI =0.04 to.40, Z = 2.34, p =.019; heterogeneity: Q = 20.7, I^2 = 44, p =.055; Egger's test: Z = −0.39, p =.70) (Fig. 2). After excluding an outlier dataset (Cloak et al., 2011), the difference became more significant (g =0.31; 95% CI =0.16 to.45, Z = 4.14, p <0.001). No effects were found for age, sex, primary drug of use, years used, abstinence status (yes/no), years abstinent, log TE, field strength, or normalization method (water vs. creatine). Notably, all myo-inositol datasets were from studies using short TE (≤ 40 ms) scans.

3.3.2. Frontal white matter—Across 8 datasets (286 controls, 305 SUD) in the FWM (Burger et al., 2018; Chang et al., 2005, 1999; Cloak et al., 2011; Ernst et al., 2000; Howells et al., 2014; Sung et al., 2007; Taylor et al., 2007), no significant difference was observed in myo-inositol between SUD and controls (g =0.24, 95% CI = −0.10 to.57, Z = 1.37, p =.17; heterogeneity: Q = 31.5, I^2 = 75, p <0.001; Egger's test: Z = −0.39, p =.69) (Fig. S9). After excluding an outlier dataset (Chang et al., 1999), the difference remained non-significant (p =.48).

3.4. Creatine

3.4.1. Medial prefrontal cortex—Across 13 datasets (483 controls, 459 SUD) in the mPFC (Abe et al., 2013; Chang et al., 2005, 1999; Cloak et al., 2011; Crocker et al., 2014, 2017; Ernst et al., 2000; Hulka et al., 2016; Kim et al., 2018; Schmaal et al., 2012; Sung et al., 2007; Taylor et al., 2007; Wu et al., 2018), significantly lower creatine was observed in SUD vs. controls (g = −0.13, 95% CI = −0.26 to −0.01, Z = −2.04, p =.041; heterogeneity: Q = 5.9, I^2 = 0, p =.92; Egger's test: Z = −0.12, p =.91) (Fig. 3). No effects were found for age, sex, years used, abstinence status (yes/no), years abstinent, log TE, or field strength.

3.4.2. Frontal white matter—Across 7 datasets (267 controls, 276 SUD) in the FWM, no significant difference was observed in creatine between SUD and controls (g = −0.20, 95% CI = −0.47 to.08, Z = −1.41, p =.16; heterogeneity: Q = 15.0, I^2 = 60, p =.02; Egger's test: Z = −3.03, p =.002) (Fig. S10). After removing a study that was driving the significant Egger's test (i.e., causing small sample size bias), the difference remained non-significant (p =.42).

3.5. Glutamate

3.5.1. Medial prefrontal cortex—Across 9 datasets (240 controls, 218 SUD) in the mPFC (Abe et al., 2013; Burger et al., 2018; Crocker et al., 2014, 2017; Howells et al., 2014; Hulka et al., 2016; Schmaal et al., 2012; Wu et al., 2018; Yang et al., 2009), no significant difference was observed in glutamate between SUD and controls (g = −0.19, 95% CI = −0.65 to.27, Z = −0.80, p =.43; heterogeneity: Q = 43.1, I^2 = 81, p = <0.001; Egger's test: Z = −0.03, p =.98) (Fig. S11).

3.6. Glutamate + glutamine (Glx)

3.6.1. Medial prefrontal cortex—Across 7 datasets (204 controls, 198 SUD) in the mPFC (Burger et al., 2018; Chang et al., 1999; Cloak et al., 2011; Ernst and Chang, 2008; Howells et al., 2014; Schmaal et al., 2012; Sung et al., 2013), no significant difference was observed in glx between SUD and controls (g = −0.15, 95% CI = −0.35 to.04, Z = −1.53, p =.13; heterogeneity: Q = 9.2, I^2 = 0, p =.16; Egger's test: Z =0.49, p =.63) (Fig. S12).

3.7. GABA

The neurotransmitter GABA did not have a sufficient number of studies in any brain region to meet our threshold for meta-analysis.

3.8. Effect of quality metrics

For analyzing the moderator effect of COV, the only regional metabolites with $k \geq 14$ were mPFC NAA and choline. For mPFC NAA, the logistic fit for COV was poor and statistically non-significant (R^2 =.25, F = 1.21, p =.35). For mPFC choline, however, the fit was relatively good and significant (R^2 =.55, F = 4.14, p =.038, Fig. S13). As described in Methods, mPFC choline datasets were thus dichotomized into high-quality (mean COV ≤ 15%, k = 11) versus low-quality (mean COV > 15%, k = 9) study subgroups based on the inflection point of the best-fitting logistic curve. Effect sizes were closer to zero in the high quality subgroup but did not differ significantly between the low- and high-quality subgroups (Z =0.54, p =.59; heterogeneity: Q = 34.8, I^2 = 48, p =.010; Egger's test: Z =0.26, p =.80). Secondary analyses of the individual subgroups showed that mPFC choline was not significantly different between SUD and controls in either low-quality (p =.46) or high-quality (p =.94) subgroups.

As mPFC choline showed a significant moderating effect of field strength, as an additional exploratory analysis we compared mean COV values between 1.5 T and ≥3 T studies. 1.5 T studies had qualitatively higher COV values (1.5 T mean COV =0.164 (S.D. =0.036); ≥3 T mean COV =0.136 (S.D. =0.055); Mann-Whitney U = 70, p =.13).

Insufficient data were available to examine the effects of other MRS technical moderators (linewidth, SNR, CRLB). The regional metabolite with the largest number of datasets (NAA in the mPFC) had only 6 studies that reported linewidth, 5 studies that reported SNR, and 3 studies that reported CRLB values.

4. Discussion

In this first-ever (to our knowledge) meta-analysis of MRS studies of methamphetamine and cocaine SUD, we observed **1)** significantly lower NAA in the mPFC and FWM in current or abstinent people with SUD, **2)** significantly higher myo-inositol in the mPFC in current or abstinent people with SUD, and **3)** significantly lower creatine in the mPFC in current or abstinent people with SUD. As the FWM NAA finding included a study with possible small sample bias and was no longer significant after excluding this study, it should be considered provisional. NAA and choline were also examined in the basal ganglia and occipital cortex, but no group effects were found. The largest effect size seen in this meta-analysis was for lower mPFC NAA (g = −0.44). This effect was moderated by echo time (Table 2), such that the difference was larger in studies with TE > 40 ms. The effect, however, was still significant in studies with TE ≤ 40 ms. Effect sizes for FWM myo-inositol and creatine were similar to their corresponding mPFC effect sizes but did not reach statistical significance due to a lower number of available datasets (Table 1). For choline, we did not observe a significant group difference in any brain region, and although moderating effects of field strength and COV-based study quality were observed (Table 2), exploratory post-hoc analyses suggested no significant group differences within any subgroup. No group differences were found for glutamate or glutamate+glutamine (glx). No moderating effects were found for age, sex, primary drug used (cocaine or methamphetamine), years used, years abstinent, or normalization method (water vs. creatine).

The pattern in methamphetamine/cocaine SUD of lower NAA, greater myo-inositol, lower creatine, and no difference in choline most closely resembles the pattern seen in neurodegenerative disorders such as Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Song et al., 2021). Lower NAA and higher myo-inositol are also seen in HIV positive individuals (Chelala et al., 2020) as well as in people with traumatic brain injury (TBI); these conditions, however, also show elevated choline levels (Joyce et al., 2022). The pattern in SUD, furthermore, is unlike that seen in schizophrenia (where both NAA and myo-inositol levels are lower (Das et al., 2018; Iwata et al., 2018; Kraguljac et al., 2012; Whitehurst et al., 2020)) or alcohol use disorder (where mPFC NAA and choline are lower than but mPFC myo-inositol and creatine are not different from controls (Kirkland et al., 2022)). Notably, methamphetamine SUD and AD have numerous shared hallmarks, including neurocognitive deficits, blood-brain barrier dysfunction, and molecular pathogenic mechanisms (Shukla and Vincent, 2020; Zenaro et al., 2017). Methamphetamine SUD may also substantially increase risk for dementia (Tzeng et al., 2020). Furthermore, it is now well-understood that, like AD and MCI, both cocaine and methamphetamine induce neurotoxicity through activation of inflammatory cascades and oxidative radical creation (Clark et al., 2013; Gold et al., 2009; Loftis and Janowsky, 2014; Lopez et al., 2013; Pratico et al., 2002; Song et al., 2021). Why might neuroinflammation result in the observed metabolite profiles of AD/MCI and methamphetamine/cocaine SUDs? As described in the Introduction, the metabolite NAA has diverse functions in the brain and is widely considered to be a marker of neuronal integrity (Maddock and Buonocore, 2012; Moffett et al., 2007) and brain bioenergetics (Clark, 1998). Lower NAA in AD and SUD might thus be interpreted as a sign of neuronal loss or damage. Creatine, like NAA, is also considered to be an index of brain metabolic health due to its role in energy metabolism (Maddock and Buonocore, 2012). Elevated myo-inositol may also be an inflammatory indicator, as it is associated with astrocytic immune activation and even gliosis (Bitsch et al., 1999; Kim et al., 2005). As we did not observe any associations between levels of these metabolites and years of abstinence, it is possible that this profile is not easily reversible (at least for up to 2 years) in SUDs. This negative finding is also consistent with a previous meta-analysis that found no relationship between abstinence and cognitive deficits in individuals with methamphetamine SUD (Basterfield et al., 2019). In contrast, however, a limited number of longitudinal studies suggest some consequences of methamphetamine use (e.g., lower mPFC NAA/Cr, Cho/NAA, and some neurocognitive deficits) may improve after at least one year of abstinence (Iudicello et al., 2010; Nordahl et al., 2005; Salo et al., 2009). Given the lack of longitudinal MRS studies of methamphetamine/cocaine SUDs as well as the fact that all analyses with $k > 10$ in this study only included SUD individuals who were abstinent for up to 2 years, additional longitudinal studies are necessary to determine the extent to which the AD/MCI-like metabolite profile observed here is reversible during more prolonged abstinence.

Most metabolite abnormalities were localized to the mPFC, which showed significant abnormalities in the levels of three metabolites in people with SUD (lower NAA, higher myo-inositol, lower creatine). One reason for this is that there were many more studies of this region than other regions, and thus statistical power for demonstrating significant effects was greatest for the mPFC. This region, however, may also be particularly

vulnerable in people with methamphetamine/cocaine SUD. Importantly, drug seeking behavior and addiction is thought to involve neural activation and plasticity in the human mesocorticolimbic reward system, which originates in the midbrain and projects to the nucleus accumbens, amygdala, hippocampus, and mPFC (Koob and Volkow, 2010). Greater resting state functional connectivity has also been observed within this system in cocaine (Ray et al., 2016) and methamphetamine (Kohno et al., 2014) SUD. As it is possible that hyperconnectivity of this network may help produce the abnormal metabolite profile observed in this meta-analysis, future multimodal studies that combine 1 H-MRS with functional magnetic resonance imaging may examine how these measures are related in SUDs.

4.1. MRS technical considerations

4.1.1. Effect of echo time—Interestingly, the observed finding of lower mPFC NAA in individuals with SUD was moderated by echo time. Specifically, studies with longer echo times showed larger differences in NAA than studies with shorter echo times, although these differences were significant for both short (≤40 ms) and longer TE datasets. Previous studies in schizophrenia have also found relationships between echo time and NAA levels (Bracken et al., 2013; Kuan et al., 2021). The direction of the observed relationship in this study suggests that the T2 relaxation time of NAA is faster in methamphetamine/cocaine SUD than controls. Faster T2 relaxation would mean that NAA signals attenuate more quickly, and NAA levels in SUD would thus appear lower when measured at longer echo times. Like all MRS signals, NAA T2 relaxation time is dependent on its microenvironment. Because it is synthesized in neuronal mitochondria, most mPFC NAA is likely to be localized within neurons. One microenvironmental change that could lead to faster T2 relaxation of NAA would be a reduction in neuronal volumes, especially within axons and dendrites where cell surface to cell volume ratios are higher. Smaller axonal or dendritic volumes could increase the frequency of spin-spin interactions between NAA and less mobile macromolecules and lead to faster relaxation of the NAA signal. Further studies examining T2 relaxation of NAA in the gray matter and white matter of the mPFC are needed to understand the pathophysiological implications of our observation of significantly larger effect sizes for lower mPFC NAA in SUD studies using longer echo times.

4.1.2. Creatine vs. water normalization—We found no significant moderating effects of normalization method for metabolites in the mPFC or any other region. We did, however, observe significantly lower mPFC creatine levels in SUD. This finding calls into question the use of creatine as a reference metabolite in SUD MRS studies of the mPFC. Overall, therefore, we suggest that it may be advantageous to use water-referenced values with conducting MRS studies in methamphetamine/cocaine SUDs.

4.1.3. Effect of field strength—Although no overall difference in SUD was observed for choline, field strength was a significant moderator in that datasets with lower field strengths showed higher positive effect sizes. The reason for this relationship is unclear, although it is possible that it is related to data quality as 1.5 T studies had qualitatively higher COV values than ≥3 T studies (likely due to higher SNR at ≥3 T). It should also be

noted that when 1.5 T and ≥3 T studies were analyzed separately, no significant difference was observed in choline for either analysis.

4.1.4. Relationship with COV—Of the two regional metabolites that had sufficient *k* (≥14) to analyze COV moderator effects using the logistic model, only mPFC choline showed a significant fit to the regression curve. Specifically, a COV threshold of 15% was found that divided datasets into low and high-quality subgroups. No significant difference, however, was found by comparing effect sizes between subgroups. In combination with the overall non-significant choline effect, these results suggest that choline levels are not significantly affected in methamphetamine/cocaine SUD, and that these results are relatively robust to variations in measurement quality.

4.1.5. Overall lack of quality metrics in SUD MRS studies—Notably, because very few studies reported quality metrics, moderating effects of metabolite measurement quality measures (linewidth, CRLB) could not be examined. As these metrics are essential to evaluate MRS scan quality, we recommend that future studies report them along with metabolite levels. When metabolite levels are abnormal, prior MRS meta-analytic work in schizophrenia suggests that effect sizes may be related to these quality metrics, with larger effect sizes observed in studies with better measurement quality (smaller linewidth and lower CRLB) (Smucny et al., 2021).

4.2. Conclusion

In this novel meta-analysis of regional metabolite levels in methamphetamine and cocaine SUD, we found significantly lower NAA, higher myo-inositol, and lower creatine in the medial prefrontal cortex in SUD compared to controls. Given that, to our knowledge, no consensus yet exists for the degree to which these SUDs affect brain metabolite levels (with the possible exception of NAA), the results of our meta-analytic approach shed new light on their neurochemical effects. In particular, the pattern of abnormalities observed in SUDs suggests a potentially meaningful parallel to the neurometabolic abnormalities observed in MCI and AD. Our finding of relationships with echo time and COV suggests that these may be important variables in future MRS studies of SUDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

〈https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases〉 (Accessed 11 March 2022).

Abe C, Mon A, Durazzo TC, Pennington DL, Schmidt TP, Meyerhoff DJ, 2013. Polysubstance and alcohol dependence: unique abnormalities of magnetic resonance-derived brain metabolite levels. Drug Alcohol Depend 130 (1–3), 30–37. [PubMed: 23122599]

Barr AM, Panenka WJ, MacEwan GW, Thornton AE, Lang DJ, Honer WG, Lecomte T, 2006. The need for speed: an update on methamphetamine addiction. J. Psychiatry Neurosci 31 (5), 301–313. [PubMed: 16951733]

Basterfield C, Hester R, Bowden SC, 2019. A meta-analysis of the relationship between abstinence and neuropsychological functioning in methamphetamine use disorder. Neuropsychology 33 (5), 739–753. [PubMed: 31021107]

Bitsch A, Bruhn H, Vougioukas V, Stringaris A, Lassmann H, Frahm J, Bruck W, 1999. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. AJNR Am. J. Neuroradiol 20 (9), 1619–1627. [PubMed: 10543631]

Bracken BK, Rouse ED, Renshaw PF, Olson DP, 2013. T2 relaxation effects on apparent N-acetylaspartate concentration in proton magnetic resonance studies of schizophrenia. Psychiatry Res 213 (2), 142–153. [PubMed: 23769421]

Buonocore MH, Maddock RJ, 2015. Magnetic resonance spectroscopy of the brain: a review of physical principles and technical methods. Rev. Neurosci 26 (6), 609–632. [PubMed: 26200810]

Burger A, Brooks SJ, Stein DJ, Howells FM, 2018. The impact of acute and short-term methamphetamine abstinence on brain metabolites: a proton magnetic resonance spectroscopy chemical shift imaging study. Drug Alcohol Depend 185, 226–237. [PubMed: 29471227]

Chakraborty G, Mekala P, Yahya D, Wu G, Ledeen RW, 2001. Intraneuronal N-acetylaspartate supplies acetyl groups for myelin lipid synthesis: evidence for myelin-associated aspartoacylase. J. Neurochem 78 (4), 736–745. [PubMed: 11520894]

Chang L, Mehringer CM, Ernst T, Melchor R, Myers H, Forney D, Satz P, 1997. Neurochemical alterations in asymptomatic abstinent cocaine users: a proton magnetic resonance spectroscopy study. Biol. Psychiatry 42 (12), 1105–1114. [PubMed: 9426880]

Chang L, Ernst T, Strickland T, Mehringer CM, 1999. Gender effects on persistent cerebral metabolite changes in the frontal lobes of abstinent cocaine users. Am. J. Psychiatry 156 (5), 716–722. [PubMed: 10327904]

Chang L, Ernst T, Speck O, Grob CS, 2005. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am. J. Psychiatry 162 (2), 361–369. [PubMed: 15677602]

Chang L, Munsaka SM, Kraft-Terry S, Ernst T, 2013. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. J. Neuroimmune Pharmacol 8 (3), 576–593. [PubMed: 23666436]

Chelala L, O'Connor EE, Barker PB, Zeffiro TA, 2020. Meta-analysis of brain metabolite differences in HIV infection. Neuroimage Clin 28, 102436. [PubMed: 33383609]

Clark JB, 1998. N-acetyl aspartate: a marker for neuronal loss or mitochondrial dysfunction. Dev. Neurosci 20 (4–5), 271–276. [PubMed: 9778562]

Clark KH, Wiley CA, Bradberry CW, 2013. Psychostimulant abuse and neuroinflammation: emerging evidence of their interconnection. Neurotox. Res 23 (2), 174–188. [PubMed: 22714667]

Cloak CC, Alicata D, Chang L, Andrews-Shigaki B, Ernst T, 2011. Age and sex effects levels of choline compounds in the anterior cingulate cortex of adolescent methamphetamine users. Drug Alcohol Depend 119 (3), 207–215. [PubMed: 21775074]

Crocker CE, Bernier DC, Hanstock CC, Lakusta B, Purdon SE, Seres P, Tibbo PG, 2014. Prefrontal glutamate levels differentiate early phase schizophrenia and methamphetamine addiction: a (1)H MRS study at 3Tesla. Schizophr. Res 157 (1–3), 231–237. [PubMed: 24906219]

Crocker CE, Purdon SE, Hanstock CC, Lakusta B, Seres P, Tibbo PG, 2017. Enduring changes in brain metabolites and executive functioning in abstinent cocaine users. Drug Alcohol Depend 178, 435–442. [PubMed: 28710968]

Das TK, Dey A, Sabesan P, Javadzadeh A, Theberge J, Radua J, Palaniyappan L, 2018. Putative astroglial dysfunction in schizophrenia: a meta-analysis of (1)H-MRS studies of medial prefrontal myo-inositol. Front. Psychiatry 9, 438. [PubMed: 30298023]

Degenhardt L, Sara G, McKetin R, Roxburgh A, Dobbins T, Farrell M, Burns L, Hall WD, 2017. Crystalline methamphetamine use and methamphetamine-related harms in Australia. Drug Alcohol Rev 36 (2), 160–170. [PubMed: 27286742]

Dolder M, Walzel B, Speer O, Schlattner U, Wallimann T, 2003. Inhibition of the mitochondrial permeability transition by creatine kinase substrates. Requirement for microcompartmentation. J. Biol. Chem 278 (20), 17760–17766. [PubMed: 12621025]

Ernst T, Chang L, 2008. Adaptation of brain glutamate plus glutamine during abstinence from chronic methamphetamine use. J. Neuroimmune Pharmacol 3 (3), 165–172. [PubMed: 18521756]

Ernst T, Chang L, Leonido-Yee M, Speck O, 2000. Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. Neurology 54 (6), 1344–1349. [PubMed: 10746608]

Fisher SK, Novak JE, Agranoff BW, 2002. Inositol and higher inositol phosphates in neural tissues: homeostasis, metabolism and functional significance. J. Neurochem 82 (4), 736–754. [PubMed: 12358779]

Gold MS, Kobeissy FH, Wang KK, Merlo LJ, Bruijnzeel AW, Krasnova IN, Cadet JL, 2009. Methamphetamine-and trauma-induced brain injuries: comparative cellular and molecular neurobiological substrates. Biol. Psychiatry 66 (2), 118–127. [PubMed: 19345341]

Hammond GR, Balla T, 2015. Polyphosphoinositide binding domains: key to inositol lipid biology. Biochim. Biophys. Acta 1851 (6), 746–758. [PubMed: 25732852]

Han B, Compton WM, Jones CM, Einstein EB, Volkow ND, 2021. Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among US adults. JAMA Psychiatry 78 (12), 1329–1342. [PubMed: 34550301]

Hedges G, Olkin I, 1985. Statistical Methods for Metaanalysis Academic Press, Orlando, FL.

Hellem T, Shi X, Latendresse G, Renshaw PF, 2015. The utility of magnetic resonance spectroscopy for understanding substance use disorders: a systematic review of the literature. J. Am. Psychiatr. Nurses Assoc 21 (4), 244–275. [PubMed: 26282670]

Hertz L, 2006. Glutamate, a neurotransmitter–and so much more. A synopsis of Wierzba III. Neurochem. Int 48 (6–7), 416–425. [PubMed: 16500003]

Higgins JPT, Thomas J, Chandler K, Cumpston M, Li T, Page MJ, Welch V.Ae, 2020. Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 Cochrane.

Howells FM, Uhlmann A, Temmingh H, Sinclair H, Meintjes E, Wilson D, Stein DJ, 2014. 1)H-magnetic resonance spectroscopy ((1)H-MRS) in methamphetamine dependence and methamphetamine induced psychosis. Schizophr. Res 153 (1–3), 122–128. [PubMed: 24529366]

Hulka LM, Scheidegger M, Vonmoos M, Preller KH, Baumgartner MR, Herdener M, Seifritz E, Henning A, Quednow BB, 2016. Glutamatergic and neurometabolic alterations in chronic cocaine users measured with (1) H-magnetic resonance spectroscopy. Addict. Biol 21 (1), 205–217. [PubMed: 25600822]

Iudicello JE, Woods SP, Vigil O, Scott JC, Cherner M, Heaton RK, Atkinson JH, Grant I, HIV Neurobehavioral Research Center (HNRC) Group, 2010. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. J. Clin. Exp. Neuropsychol 32 (7), 704–718. [PubMed: 20198527]

Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK, Kim J, Gerretsen P, Mimura M, Remington G, Graff-Guerrero A, 2018. Neurometabolite levels in antipsychotic-naive/free patients with schizophrenia: a systematic review and meta-analysis of (1)H-MRS studies. Prog. Neuropsychopharmacol. Biol. Psychiatry 86, 340–352. [PubMed: 29580804]

JASP Team, 2020. JASP (Version 0.13.1) [Computer Software]

Joyce JM, La PL, Walker R, Harris AD, 2022. Magnetic resonance spectroscopy of traumatic brain injury and subconcussive hits: a systematic review and meta-analysis. J. Neurotrauma 39 (21–22), 1455–1476. [PubMed: 35838132]

Ke Y, Streeter CC, Nassar LE, Sarid-Segal O, Hennen J, Yurgelun-Todd DA, Awad LA, Rendall MJ, Gruber SA, Nason A, Mudrick MJ, Blank SR, Meyer AA, Knapp C, Ciraulo DA, Renshaw PF, 2004. Frontal lobe GABA levels in cocaine dependence: a two-dimensional, J-resolved magnetic resonance spectroscopy study. Psychiatry Res 130 (3), 283–293. [PubMed: 15135161]

Kim JE, Kim GH, Hwang J, Kim JY, Renshaw PF, Yurgelun-Todd DA, Kim B, Kang I, Jeon S, Ma J, Lyoo IK, Yoon S, 2018. Metabolic alterations in the anterior cingulate cortex and related cognitive deficits in late adolescent methamphetamine users. Addict. Biol 23 (1), 327–336. [PubMed: 27813228]

Kim JP, Lentz MR, Westmoreland SV, Greco JB, Ratai EM, Halpern E, Lackner AA, Masliah E, Gonzalez RG, 2005. Relationships between astrogliosis and 1H MR spectroscopic measures of brain choline/creatine and myo-inositol/creatine in a primate model. AJNR Am. J. Neuroradiol 26 (4), 752–759. [PubMed: 15814917]

Kirkland AE, Browning BD, Green R, Leggio L, Meyerhoff DJ, Squeglia LM, 2022. Brain metabolite alterations related to alcohol use: a meta-analysis of proton magnetic resonance spectroscopy studies. Mol. Psychiatry 27 (8), 3223–3236. [PubMed: 35508628]

Klein J, 2000. Membrane breakdown in acute and chronic neurodegeneration: focus on choline-containing phospholipids. J. Neural Transm 107 (8–9), 1027–1063. [PubMed: 11041281]

Kohno M, Morales AM, Ghahremani DG, Hellemann G, London ED, 2014. Risky decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence. JAMA Psychiatry 71 (7), 812–820. [PubMed: 24850532]

Koob GF, Volkow ND, 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35 (1), 217–238. [PubMed: 19710631]

Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC, 2012. Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. Psychiatry Res 203 (2–3), 111–125. [PubMed: 22981426]

Kuan E, Chen X, Du F, Ongur D, 2021. N-acetylaspartate concentration in psychotic disorders: T2-relaxation effects. Schizophr. Res 232, 42–44. [PubMed: 34015554]

Li SJ, Wang Y, Pankiewicz J, Stein EA, 1999. Neurochemical adaptation to cocaine abuse: reduction of N-acetyl aspartate in thalamus of human cocaine abusers. Biol. Psychiatry 45 (11), 1481–1487. [PubMed: 10356631]

Lin JC, Jan RK, Kydd RR, Russell BR, 2015. Investigating the microstructural and neurochemical environment within the basal ganglia of current methamphetamine abusers. Drug Alcohol Depend 149, 122–127. [PubMed: 25700612]

Lind A, Boraxbekk CJ, Petersen ET, Paulson OB, Siebner HR, Marsman A, 2020. Regional myo-inositol, creatine, and choline levels are higher at older age and scale negatively with visuospatial working memory: a cross-sectional proton MR spectroscopy study at 7 Tesla on normal cognitive ageing. J. Neurosci 40 (42), 8149–8159. [PubMed: 32994337]

Loftis JM, Janowsky A, 2014. Neuroimmune basis of methamphetamine toxicity. Int. Rev. Neurobiol 118, 165–197. [PubMed: 25175865]

Lopez N, Tormo C, De Blas I, Llinares I, Alom J, 2013. Oxidative stress in Alzheimer's disease and mild cognitive impairment with high sensitivity and specificity. J. Alzheimers Dis 33 (3), 823–829. [PubMed: 23076075]

Maddock RJ, Buonocore MH, 2012. MR spectroscopic studies of the brain in psychiatric disorders. Curr. Top. Behav. Neurosci 11, 199–251. [PubMed: 22294088]

Martinez D, Slifstein M, Nabulsi N, Grassetti A, Urban NB, Perez A, Liu F, Lin SF, Ropchan J, Mao X, Kegeles LS, Shungu DC, Carson RE, Huang Y, 2014. Imaging glutamate homeostasis in cocaine addiction with the metabotropic glutamate receptor 5 positron emission tomography radiotracer [(11)C]ABP688 and magnetic resonance spectroscopy. Biol. Psychiatry 75 (2), 165–171. [PubMed: 24035345]

Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R, 1998. Simultaneous in vivo spectral editing and water suppression. NMR Biomed 11 (6), 266–272. [PubMed: 9802468]

Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM, 2007. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog. Neurobiol 81 (2), 89–131. [PubMed: 17275978]

Nissen JD, Pajecka K, Stridh MH, Skytt DM, Waagepetersen HS, 2015. Dysfunctional TCA-cycle metabolism in glutamate dehydrogenase deficient astrocytes. Glia 63 (12), 2313–2326. [PubMed: 26221781]

Nordahl TE, Salo R, Possin K, Gibson DR, Flynn N, Leamon M, Galloway GP, Pfefferbaum A, Spielman DM, Adalsteinsson E, Sullivan EV, 2002. Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependent subjects: a preliminary proton MRS study. Magnetic resonance spectroscopy. Psychiatry Res 116 (1–2), 43–52. [PubMed: 12426033]

Nordahl TE, Salo R, Natsuaki Y, Galloway GP, Waters C, Moore CD, Kile S, Buonocore MH, 2005. Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. Arch. Gen. Psychiatry 62 (4), 444–452. [PubMed: 15809412]

Petroff OA, 2002. GABA and glutamate in the human brain. Neuroscientist 8 (6), 562–573. [PubMed: 12467378]

Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ, 2002. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. Arch. Neurol 59 (6), 972–976. [PubMed: 12056933]

Ray S, Di X, Biswal BB, 2016. Effective connectivity within the mesocorticolimbic system during resting-state in cocaine users. Front. Hum. Neurosci 10, 563. [PubMed: 27881959]

Rigotti DJ, Inglese M, Gonen O, 2007. Whole-brain N-acetylaspartate as a surrogate marker of neuronal damage in diffuse neurologic disorders. AJNR Am. J. Neuroradiol 28 (10), 1843–1849. [PubMed: 17921226]

Sailasuta N, Abulseoud O, Hernandez M, Haghani P, Ross BD, 2010. Metabolic abnormalities in abstinent methamphetamine dependent subjects. Subst. Abus 2010 (4), 9–20.

Saito RF, Andrade LNS, Bustos SO, Chammas R, 2022. Phosphatidylcholine-derived lipid mediators: the crosstalk between cancer cells and immune cells. Front. Immunol 13, 768606. [PubMed: 35250970]

Salo R, Nordahl TE, Natsuaki Y, Leamon MH, Galloway GP, Waters C, Moore CD, Buonocore MH, 2007. Attentional control and brain metabolite levels in methamphetamine abusers. Biol. Psychiatry 61 (11), 1272–1280. [PubMed: 17097074]

Salo R, Nordahl TE, Galloway GP, Moore CD, Waters C, Leamon MH, 2009. Drug abstinence and cognitive control in methamphetamine-dependent individuals. J. Subst. Abus. Treat 37 (3), 292–297.

Salo R, Buonocore MH, Leamon M, Natsuaki Y, Waters C, Moore CD, Galloway GP, Nordahl TE, 2011. Extended findings of brain metabolite normalization in MA-dependent subjects across sustained abstinence: a proton MRS study. Drug Alcohol Depend 113 (2–3), 133–138. [PubMed: 20739127]

Schmaal L, Veltman DJ, Nederveen A, van den Brink W, Goudriaan AE, 2012. N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study. Neuropsychopharmacology 37 (9), 2143–2152. [PubMed: 22549117]

Sekine Y, Minabe Y, Kawai M, Suzuki K, Iyo M, Isoda H, Sakahara H, Ashby CR Jr., Takei N, Mori N, 2002. Metabolite alterations in basal ganglia associated with methamphetamine-related psychiatric symptoms. A proton MRS study. Neuropsychopharmacology 27 (3), 453–461. [PubMed: 12225702]

Shukla M, Vincent B, 2020. The multi-faceted impact of methamphetamine on Alzheimer's disease: from a triggering role to a possible therapeutic use. Ageing Res. Rev 60, 101062. [PubMed: 32304732]

Smucny J, Carter CS, Maddock RJ, 2021. Medial prefrontal cortex glutamate is reduced in schizophrenia and moderated by measurement quality: a meta-analysis of proton magnetic resonance spectroscopy studies. Biol. Psychiatry 90 (9), 643–651. [PubMed: 34344534]

Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, Green M, Harper D, Ren B, Forester BP, Ongur D, Du F, 2021. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: a meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res. Rev 72, 101503. [PubMed: 34751136]

Sung YH, Cho SC, Hwang J, Kim SJ, Kim H, Bae S, Kim N, Chang KH, Daniels M, Renshaw PF, Lyoo IK, 2007. Relationship between N-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: a proton magnetic resonance spectroscopy study. Drug Alcohol Depend 88 (1), 28–35. [PubMed: 17084995]

Sung YH, Carey PD, Stein DJ, Ferrett HL, Spottiswoode BS, Renshaw PF, Yurgelun-Todd DA, 2013. Decreased frontal N-acetylaspartate levels in adolescents concurrently using both methamphetamine and marijuana. Behav. Brain Res 246, 154–161. [PubMed: 23466689]

Taylor MJ, Schweinsburg BC, Alhassoon OM, Gongvatana A, Brown GG, Young-Casey C, Letendre SL, Grant I, Group H, 2007. Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. J. Neurovirol 13 (2), 150–159. [PubMed: 17505983]

Tzeng NS, Chien WC, Chung CH, Chang HA, Kao YC, Liu YP, 2020. Association between amphetamine-related disorders and dementia-a nationwide cohort study in Taiwan. Ann. Clin. Transl. Neurol 7 (8), 1284–1295. [PubMed: 32608133]

Whitehurst TS, Osugo M, Townsend L, Shatalina E, Vava R, Onwordi EC, Howes O, 2020. Proton magnetic resonance spectroscopy of N-acetyl aspartate in chronic schizophrenia, first episode of psychosis and high-risk of psychosis: a systematic review and meta-analysis. Neurosci. Biobehav. Rev 119, 255–267. [PubMed: 33068555]

Wu Q, Qi C, Long J, Liao Y, Wang X, Xie A, Liu J, Hao W, Tang Y, Yang B, Liu T, Tang J, 2018. Metabolites alterations in the medial prefrontal cortex of methamphetamine users in abstinence: a (1)H MRS study. Front. Psychiatry 9, 478. [PubMed: 30420814]

Yang S, Salmeron BJ, Ross TJ, Xi ZX, Stein EA, Yang Y, 2009. Lower glutamate levels in rostral anterior cingulate of chronic cocaine users - a (1)H-MRS study using TE-averaged PRESS at 3 T with an optimized quantification strategy. Psychiatry Res 174 (3), 171–176. [PubMed: 19906515]

Zenaro E, Piacentino G, Constantin G, 2017. The blood-brain barrier in Alzheimer's disease. Neurobiol. Dis 107, 41–56. [PubMed: 27425887]

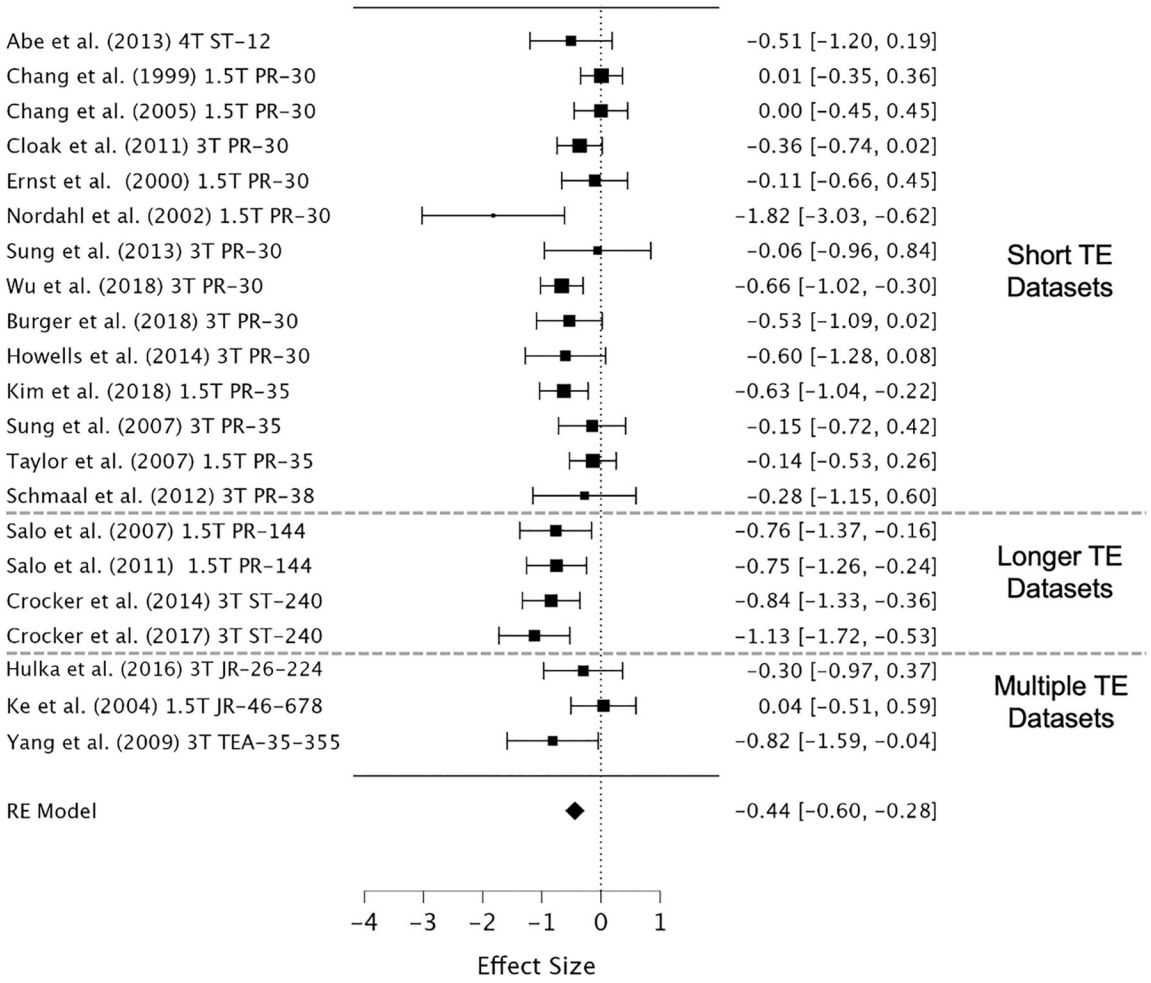

Fig. 1.

Forest plot of 21 datasets reporting medial prefrontal cortex (mPFC) N-acetylaspartate (NAA), ordered from shortest to longest echo times (TEs). Studies with multiple TEs (k=3) are listed at the bottom. Publication, field strength, sequence, and TE are listed at left. Hedge's g and 95% CI are at center and right. First dashed line separates short (≤40 ms) from longer TE datasets. Second dashed line separates longer TE from multiple TE datasets. Note: Plot is scaled differently from plots in Figs. 2 and 3. JR = J-Resolved 2D spectroscopy; PR = PRESS; RE = random effects; ST = STEAM; TEA = Echo Time-Averaged PRESS.

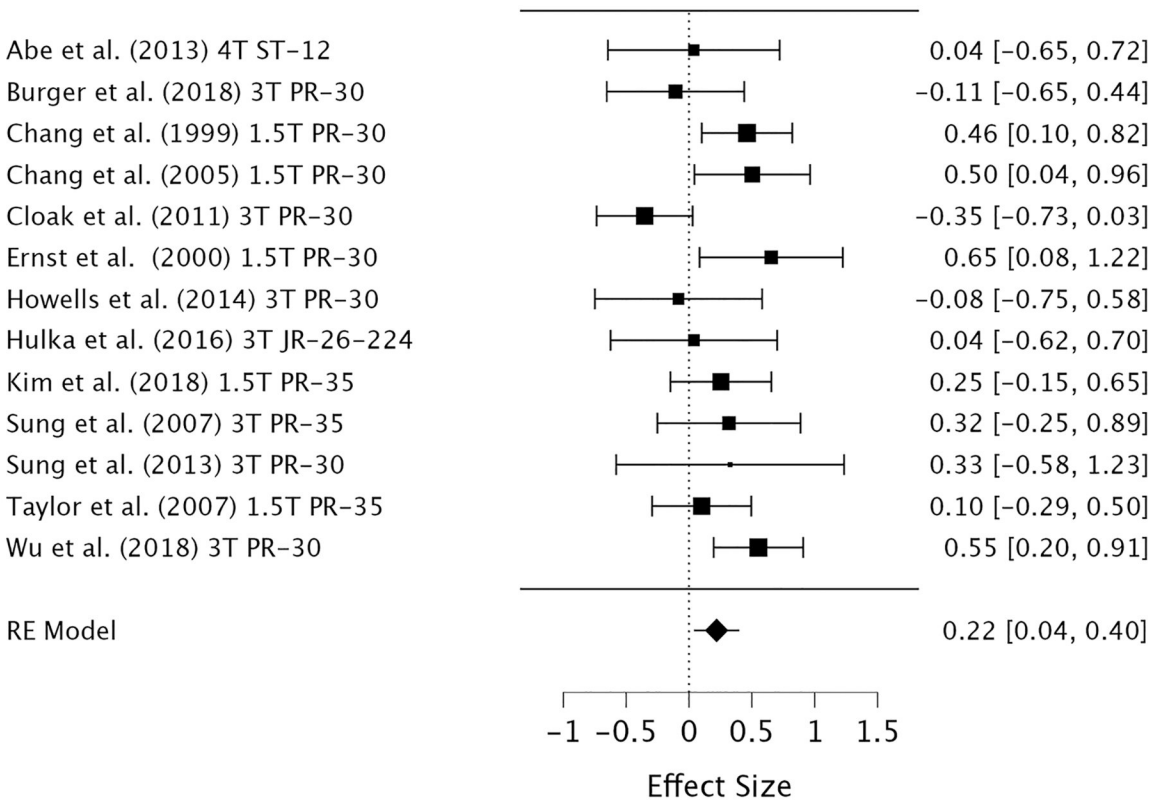

Fig. 2.

Forest plot of 13 datasets reporting medial prefrontal cortex (mPFC) myo-inositol, in alphabetical order by first author. Publication, field strength, sequence, and echo time (TE) are listed at left. Hedge's *g* and 95% CI are at center and right. Note: Plot is scaled differently from plot in Fig. 1. JR = J-Resolved 2D spectroscopy; PR = PRESS; RE = random effects; ST = STEAM.

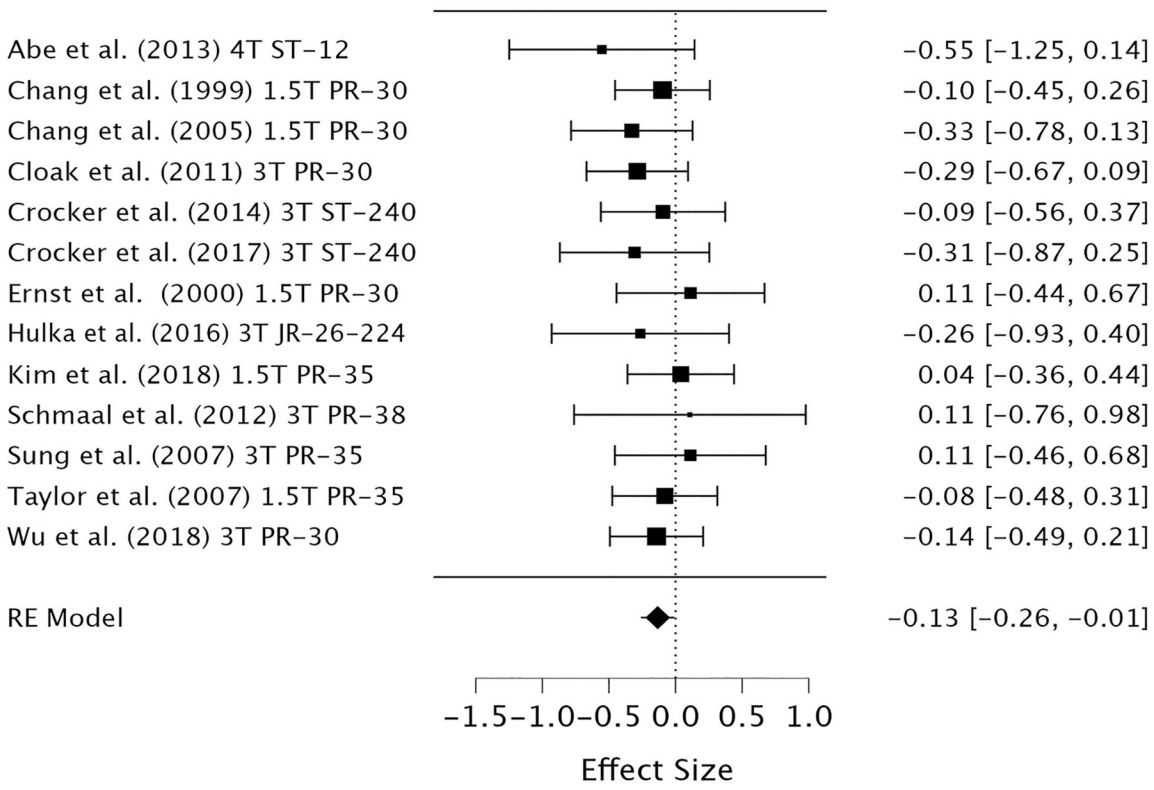

Fig. 3.

Forest plot of 13 datasets reporting medial prefrontal cortex (mPFC) creatine, in alphabetical order by first author. Publication, field strength, sequence, and echo time (TE) are listed at left. Hedge's *g* and 95% CI are at center and right. Note: Plot is scaled differently from plot in Fig. 1. JR = J-Resolved 2D spectroscopy; PR = PRESS; RE = random effects; ST = STEAM.

Table 1

Overall effects results summary. Significant effects are in bold italic. FWM = frontal white matter, Glx = glutamate+glutamine, mPFC = medial prefrontal cortex, NAA = N-acetyl-aspartate.

Metabolite -Region	***k***	***g* (95% CI)**	***p***
NAA -*mPFC*	***21***	***−.44 (−0.60−−0.28)***	***<0.001***
-mPFC [a]	***20***	***−.42 (−0.57−−0.26)***	***<0.001***
-FWM	***10***	***−.26 (−0.51−−0.01)***	***.044***
-FWM[a,b]	9	−0.16 (−0.36−0.05)	0.13
-Basal Ganglia	8	−0.13 (−0.46−0.19)	0.43
-Occipital	7	−0.13 (−0.37−0.11)	0.28
Choline -mPFC	20	0.06 (−0.10−0.22)	0.49
-mPFC[a]	19	0.01 (−0.11−0.13)	0.88
-FWM	10	−0.02 (−0.18−0.14)	0.79
-Basal Ganglia	7	0.02 (−0.17−0.22)	0.83
-Occipital	7	0.01 (−0.23−0.26)	0.91
Myo-inositol -*mPFC*	***13***	***.22 (0.04−0.40)***	***.019***
-mPFC [a]	**12**	**0.31 (0.16−0.45)**	**<0.001**
-FWM	8	0.24 (−0.10−0.57)	0.17
-FWM[a]	7	0.08 (−0.15−0.32)	0.48
Creatine -*mCFC*	***13***	***−.13 (−0.26−−0.01)***	***.041***
-FWM	7	−0.20 (−0.47−0.08)	0.16
-FWM[b]	6	−0.10 (−0.33−0.14)	0.42
Glutamate -mPFC	9	−0.19 (−0.65−0.27)	0.43
Glx -mPFC	7	−0.15 (−0.35−0.04)	0.13

[a] With one outlier dataset excluded.

[b] With one small sample bias study excluded.

Table 2

Significant moderator effects. COV = coefficient of variation, mPFC = medial prefrontal cortex, NAA = N-acetyl-aspartate, TE = echo time.

Metabolite -Region -Moderator	***k***	**Z**		***p***
NAA -mPFC -log TE	21	−2.82		0.005
Metabolite -Region -Dataset Group	***k***	***g* (95% CI)**		***p***
NAA -mPFC -short TE (≤40 ms) datasets	14	−.34 (−0.51−0.17)		0.001
NAA -mPFC -longer TE (>40 ms) datasets	4	−.86 (−1.13−−0.59)		0.001
Metabolite -Region -Moderator	***k***	**Z**		***p***
Choline -mPFC -field strength	20	−2.21		0.027
Metabolite -Region -Dataset Group	***k***	***g* (95% CI)**		***p***
Choline -mPFC −1.5 T datasets	9	0.23 (−0.02−−0.48)		0.070
Choline -mPFC ≥3 T datasets	11	−.08 (−0.25−0.08)		0.33
Metabolite -Region -Moderator Logistic Fit	***k***	$\mathbf{R^2}$	**F**	***p***
Choline -mPFC -COV	20	0.55	4.14	0.038
Metabolite -Region -Moderator Comparison	***k* ≤15% / *k* >15%**	**Z**		***p***
Choline -mPFC -COV≤15% vs. >15%	11/9	0.54		0.59
Metabolite -Region -Dataset Group	***k***	***g* (95% CI)**		***p***
Choline -mPFC -COV≤15% datasets	11	0.01 (−0.16−0.17)		0.94
Choline -mPFC -COV>15% datasets	9	0.10 (−0.17−0.36)		0.46