Meta-analysis and Open-source Database for In Vivo Brain Magnetic Resonance Spectroscopy in Health and Disease

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Abstract:

Proton (^{1}H) Magnetic Resonance Spectroscopy (MRS) is a non-invasive tool capable of quantifying brain metabolite concentrations *in vivo*. Prioritization of standardization and accessibility in the field has led to the development of universal pulse sequences, methodological consensus recommendations, and the development of open-source analysis software packages. One on-going challenge is methodological validation with ground-truth data. As ground-truths are rarely available for *in vivo* measurements, data simulations have become an important tool. The diverse literature of metabolite measurements has made it challenging to define ranges to be used within simulations. Especially for the development of deep learning and machine learning algorithms, simulations must be able to produce accurate spectra capturing all the nuances of *in vivo* data. Therefore, we sought to determine the physiological ranges and relaxation rates of brain metabolites which can be used both in data simulations and as reference estimates. Using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, we've identified relevant MRS research articles and created an open-source database containing methods, results, and other article information as a resource. Using this database, expectation values and ranges for metabolite concentrations and T_2 relaxation times are established based upon a meta-analyses of healthy and diseased brains.
Keywords: Human Brain, Database, Meta-analysis, Proton MRS, *in vivo*, Simulation

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Abbreviations: ^{1}H, proton; 2-HG, 2-hydroxyglutarate, Adc, addiction; ADHD, attention-deficit/hyper activity; Asc, ascorbate; Asp, aspartate; Aut, autism; Bip, bipolar; Canc, cancer; Cho, choline-containing compounds; CPMG, Carr-Purcell Meiboom-Gill; Cr, creatine; CRLB, Cramer-Rao lower bounds; CSF, cerebrospinal fluid; D1, type 1 diabetes; Dem, dementia; Dep, depression; E4, apolipoprotein 4 carriers; Etrm, Essential Tremor; Fib, fibromyalgia; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; Glx, sum of glutamate and glutamine; Gly, glycine; GM, gray matter; GPC, glycerophosphocholine; ISMRM, international society for magnetic resonance in medicine; Lac, lactate; LASER, localization by adiabatic selective refocusing; MCI, mild cognitive impairment; MEGA, Mescher-Garwood; mI, myo-inositol; Mig, migraine; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; NAA, N-acetylaspartate; NAAG, N-acetyl-aspartyl-glutamate; OCD, obsessive compulsive disorder; Pain, chronic pain; PC, perinatal Complications; PCho, phosphocholine; PCr, phosphocreatine; PD, Parkinson's disease; PE, phosphoethanolamine; Pers, personality disorder; PRISMA, preferred reporting Items for systematic reviews and meta-analyses; PRESS, point resolved spectroscopy; Psy, psychosis; PTSD, post-traumatic stress disorder; Schz, schizophrenia; Seiz, seizure disorder; Ser, serine; sI, scyllo-inositol; sLASER, semi-adiabatic localization by adiabatic selective refocusing; STEAM, stimulated echo acquisition mode; SNR, signal-to-noise ratio; Str, stroke; T_2, spin-spin relaxation time; Tau, taurine; TBI, traumatic brain injury; tCho, sum of choline-containing metabolites; tCr, sum of creatine and phosphocreatine; tNAA, sum of N-acetyl-aspartate and N-acetyl-aspartyl-glutamate; TE, echo-time; TI, inversion time; TM, mixing time; TR: repetition time; WM, white matter

1. Introduction:

In vivo MRS can measure levels of metabolites in the brain non-invasively, allowing the abnormal biochemical and cellular processes of disease to be interrogated. The most prominent signals in the ^{1}H spectrum are the methyl singlets associated with N-acetylaspartate/N-acetylaspartylglutamate (tNAA), creatine-containing compounds (tCr), and choline-containing compounds (tCho). Substantial multiplet contributions to the spectrum are also seen from myo-inositol (mI), glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA), glutathione (GSH), and lactate (Lac). A handful of other metabolites can be quantified, including but not limited to: aspartate (Asp); ascorbate (Asc); scyllo-inositol (sI); serine (Ser); glycine (Gly); and taurine (Tau) [1–3]. For each of these metabolites, there exists a diffuse literature of measurements made using different methodologies in healthy controls and various populations of neurologic, psychiatric, and neurodevelopmental disease. Consensus on the physiological ranges for metabolite concentrations and relaxation values has yet to be determined.

Quantification of metabolite levels by MRS is challenging and a variety of methods are used to convert detected signal voltages into concentration-like measurements. These are all relative – that is, they rely upon the collection of a reference signal. Phantom-replacement [4] and synthetic referencing [5] are cumbersome and not widely used, so internal signal referencing predominates [6,7]. Among the potential reference signals, there is no clear and unambiguous 'best' option, each having advantages and disadvantages. Metabolite-metabolite referencing (most commonly to creatine) has the advantage of being simultaneously acquired and relatively unaffected by changing amounts of cerebrospinal fluid (CSF) within the measurement volume [8]. However, metabolite-water referencing is now the consensus-recommended approach, based upon the high SNR of the water signal and its role as the solvent [7,9,10]. Concentrations can be inferred from signal ratios and an assumption of the MR-visible water concentration, and can be expressed in molal (mol/kg solvent), molar (mol/dm^3) or institutional units (i.u.) [7,9–11]. Correction for the varying water signal relaxation rates and

visibilities in gray matter (GM), white matter (WM) and CSF is usually also performed on the basis of segmented structural images [12]. The relaxation of metabolite signals is usually corrected on the basis of literature reference values [12,13].

Generating realistic synthetic *in vivo* spectra is desirable for the development and validation of MRS quantification methods. Simulations that produce spectra that are fully representative of *in vivo* data, in terms of metabolite concentrations, macromolecular background, spectral baseline, artifacts and other nuances of MRS, will improve validation of classical methods and permit the development of deep learning techniques. Density matrix simulations based upon prior knowledge of metabolite chemical shifts and coupling constants [14–19] can generate metabolite basis spectra. However, deriving the metabolite component of a synthetic spectrum from simulated basis sets additionally requires specifying appropriate metabolite concentrations and lineshapes (combining relaxation behavior and field inhomogeneity). The International Society for Magnetic Resonance in Medicine (ISMRM) 'Fitting Challenge' was one of the first efforts to create realistic synthetic spectra to test the performance of different modeling software packages [20], specifying a single metabolite T_2 value of 160 ms and, 'normal ranges,' for metabolite concentrations. While there have been a few disease-specific meta-analyses of MRS literature [21–25], there has not been a meta-analysis of the healthy and 'control' literature nor a cross-diagnosis comparison of the MRS literature. Therefore, in this manuscript we describe an open-source database which can be used to identify trends among the MRS literature and provide a meta-analysis to better inform future efforts to generate synthetic data that represent brain MRS in health and disease.

2. Methods:

In the current study, we have developed a comprehensive open-source database that includes metabolite relaxation and concentration values. This collates the results of nearly 500 MRS papers, tabulating metabolite concentrations and relaxation rates for the healthy brain and a wide range of pathologies. Each entry also includes the publication information, experimental parameters, and data

acquisition methods. To demonstrate the utility of this database, we performed three separate analyses: 1) an investigation into healthy brain metabolite concentrations; 2) a model of how these concentrations change in 25 clinical populations; and 3) a model to predict and account for variable metabolite T_2 results.

2.1 Search Methods:

In building the database, publications were identified to determine eligibility for inclusion according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [26,27]. Searches were conducted on PubMed, Web of Science, and Scopus databases. Separate searches (each search phrase is included in Supplementary Table 1) were carried out to specifically identify publications that either quantified metabolite concentrations or T_2 relaxation times, herein referred to as the concentration study and relaxation studies, respectively. The original search for both was conducted in August of 2021. In order to include literature published throughout 2021, an additional follow-up search was conducted in March 2022. No limitation for publication date was specified for searches; only articles available in English were included. A PRISMA flowchart that reflects the process of building concentration and relaxation databases is shown in Figure 1.

For both the concentration and relaxation studies, only *in vivo* brain ^{1}H-MRS data from primary sources were considered. Duplicate records (i.e., abstracts/titles) identified from more than one database, reviews, meta-analyses, re-analyses, and book chapters were excluded during the "Removed Before Screening" step of the "Identification" stage. Conference posters were generally also excluded at the "Removed Before Screening" step since they are not peer-reviewed (with exceptions made, where information was otherwise scarce). During the "Screening" stage, "Records Excluded" were those identified as the wrong field of study (e.g., NMR Spectroscopy for food science), X-nuclei (e.g., ^{13}C, ^{31}P, ^{17}O, ^{15}N, ^{23}Na, etc.), non-spectroscopy MR methods (e.g., anatomical, functional, diffusion, etc.), or that did not study the brain. For the Concentration study, "Records Excluded" also included animal studies. All reports (i.e., research articles) were able to be retrieved for the remaining screened

records. Finally, during the “Assessed for Eligibility” step, the “Reports Excluded” step reflects articles that did not include the mean and standard deviation for at least one metabolite concentration quantified in molar (moles/liter), molal (moles/g), or institutional units (i.u.), or referenced to total creatine (1/tCr), nor transverse relaxation times T_2 or rates R_2. Mean and standard deviation were calculated for reports listing median and quartile results, using the methods outlined in [28,29] to handle normal and skewed distributions, respectively. Distributions were classified as normal or skewed by comparing the upper and lower quartile-to-median ranges; if the range between the median and the lower quartile was similar to the range between and the median and the upper quartile (<50% difference), then the distribution was classified as normal, otherwise it was classified as skewed. Articles that presented values in the form of bar or scatter plots were included by manually determining mean and standard deviations with the assistance of an in-house Python software package that maps pixel values to figure axes. Authors were contacted by email ` if they collected relevant data, but did not list their results; these included authors that only provided statistical results (e.g., t-statistic, p-value, etc.), non-standard units (e.g., arbitrary units), or normalized measurements (e.g., relative to baseline, z-scored, etc.).

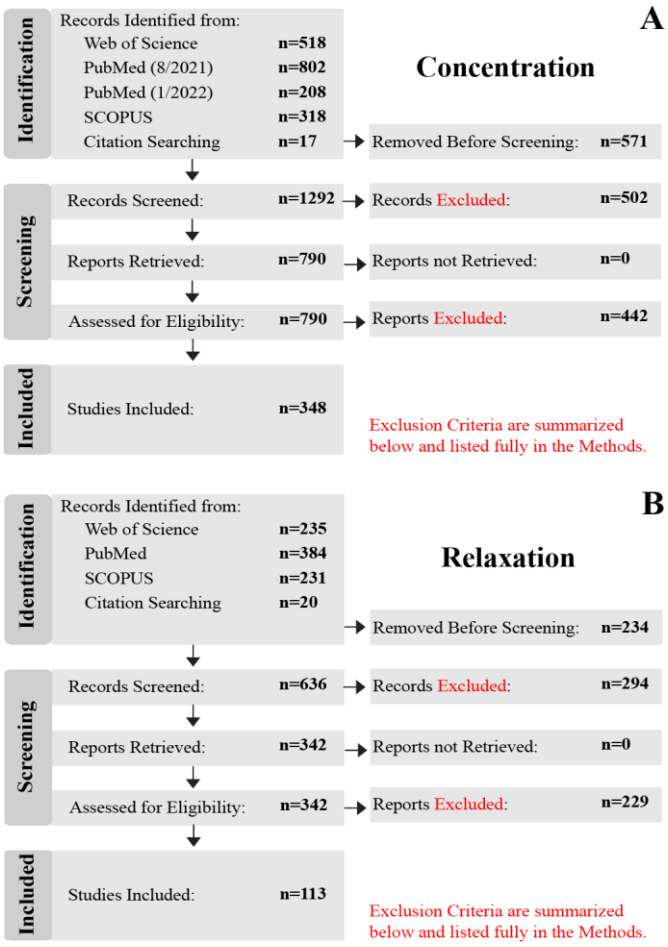

Figure 1: PRISMA flow charts that show the database selection and inclusion process of the **(A)** concentration and **(B)** T_2 relaxation publications. Records "Removed Before Screening" were duplicates (identified from more than one database), reviews, meta-analyses, textbooks, or re-analyses. Conference abstracts were generally excluded, with exceptions made when information for a given metabolite/disease was scarce. "Records Excluded" were those identified as the wrong field of study, non-^{1}H MRS, non-spectroscopy MR methods, non-brain regions, or animal studies (for Concentration study only). "Reports Excluded" during the "Assessed for Eligibility" did not include metabolite concentrations nor relaxation values.

Due to the high volume of articles (10,506) returned for the concentration study, articles were initially limited to 2018-2021. Where necessary, articles were retrieved from earlier years to ensure that three or more studies were included for less commonly studied clinical populations or difficult-to-measure metabolites (e.g., ascorbate) – this provided an abbreviated subset of 1,863 articles in the "Identification" stage. Of the original 1,863 articles, 571 articles were "Removed Before Screening" leaving 1,292 articles. After screening, 790 records remained and the corresponding report was

retrieved. A total of 348 articles were determined to be eligible for inclusion in the database and analysis.

While this work aims to determine MRS features in the human brain, the relaxation study included all species as a handful of metabolites have not yet been well studied outside of animal models. A total of 870 articles were returned by the database searches during the “Identification” stage. Of the original 870 articles, 234 were “Removed Before Screening.” The remaining 636 records were "Screened" and 294 were removed in the “Records Excluded” step. 342 reports were then retrieved and assessed for eligibility. Finally, 113 articles remained and were included in the database and analyses.

Data were analyzed using in-house Python scripts that utilized *NumPy*, *Pandas*, *Scipy*, *Statsmodels*, *Matplotlib*, and *Scikit*-learn [30–35]. The weighted mean and 95% confidence intervals calculated within the healthy and clinical metabolite concentration meta-analyses used a combined effects model. Specifically, combined effects were determined using a Random Effects model [36] which can be advantageous for biological studies where a true value does not exist across studies (e.g., metabolite concentration varies from person to person). If a Random Effects model was not defined or there was not enough data (<8 studies), a Fixed Effect model was used [36] which can similarly identify common effects with less flexibility by assuming a singular true value. Weighting across studies, both for combined effects and meta-regression, used the inverse variance weighting scheme [37] to penalize high-variance studies. While all data are present in the database, meta-analyses were only carried out when 3 or more studies were available for a particular metabolite, group, or field strength.

2.2. Metabolite Concentrations in Healthy Populations:

Studies that investigated healthy individuals or had healthy control groups were used to determine metabolite concentration ranges in healthy populations. Of the 350 studies included, 259 studies investigated a healthy population or included a healthy control group (26% of studies included no healthy subjects). Subjects were classified into early life (<2 years of age), adolescent (5-14 years of

age), young adult (18-45 years of age) and aged adult (>50 years of age). These age ranges allowed for the greatest number of studies to be included in each of the categories while leaving a gap (e.g., 46-49 years of age) to set groups apart. There were 8 [38–44], 19 [45–63], 199 [54,64–258], and 45 [81,97,142,152,156,159,194,196,225,244,259–288] studies within the four age categories (early life, adolescent, young adult, aged), respectively. To determine the concentration ranges, values were separated by metabolite and units (i.u./mM and 1/tCr) reported. Finally, a combined effects model [36] was used to compute the mean and 95% confidence interval (as seen in Figure 2.

2.3. Metabolite Concentrations in Clinical Populations:

Studies that investigated clinical groups and included a healthy control group were included in the clinical population analysis. There were 180 publications [38–43,49–52,54–57,59,62–64,68,69,71,73–75,77,78,80,82,84,87,91,92,94–98,100,101,103,104,106,107,110,111,113,116–118,120,124,128,129,136–142,144,146,148–151,153,155,160–165,170,173,174,176,178,179,181–183,185–189,191,192,196–200,202–205,207,209,210,213,218,220–222,224,227,229,230,232,235,237,240,242,243,246–248,250–255,257–261,263,264,267–273,276,277,279–313] consisting of 25 unique clinical groups. To determine the concentration ranges, values were separated by metabolite and units reported. Each clinical population was then modeled as a linear change relative to their respective control group by using the 'ratio of means' method [314,315]. A value of 1.0 would indicate no difference between the clinical and control groups. Finally, a combined effects model [36] was used to compute the mean and 95% confidence interval (as seen in Figure 3).

2.4. T_2 Meta-regression Model:

Studies that investigated healthy subjects or included a healthy control group were included in the T_2 relaxation analysis. Of the 113 included studies, 76 studies [3,13,316–389] were included in the analysis. All the studies' results were separated by metabolite for the analysis to produce 629 values. Next, a multiple meta-regression was employed with 6 input variables: 1) metabolite; 2) field strength;

3) localization pulse sequence; 4) T_2 filter, 5) tissue type; and 6) subject species. Metabolite was a categorical variable that included 14 metabolites, with some of them further differentiated by moiety (Asp, tCr CH_2, Cr CH_3, GABA, Gln, Glu, Gly, tCho, GSH, Lac, mI, NAA CH_3, NAAG, Tau). Field strength was a continuous variable from 1.5 T through 14.1 T. Localization pulse sequence was a categorical variable that included Point Resolved Spectroscopy (PRESS), Stimulated Echo Acquisition Mode (STEAM), or either Localization by Adiabatic Selective Refocusing (LASER) or semi-LASER (sLASER). 'T_2 filter' was a categorical variable indicating whether the data were collected with a Carr-Purcell Meiboom-Gill (CPMG) multi-echo sequence or not. Tissue type was a categorical variable which was characterized as GM (voxel composition >80% GM), WM (voxel composition >80% WM), or mixed (all other cases). Subject species was a categorical variable that specified human or not human. The output was a continuous T_2 value in milliseconds. Continuous variables were scaled between 0 and 1. Categorical variables were dummy coded creating for use within the regression model. The model was iteratively re-run leaving one datapoint out each time for prediction (i.e., 629 individual leave-one-out regression models were run).

3. Results:

3.1. Database:

The database currently contains 461 publications with each entry containing the publication information, experiment details, parameters of the data acquisition, and the mean and standard deviation of the results. A complete list of the information available from each entry in the database is given in Table 1. We used the PRISMA guidelines to ensure an unbiased and wide-reaching approach was taken to identify and screen publications. The database is open-source and available online at https://github.com/agudmundson/mrs-database.

3.2. Healthy Metabolite Concentrations:

The physiological ranges of brain metabolites were determined within the each of the four age categories for both i.u./mM and 1/tCr. The resulting weighted mean and 95% confidence intervals for young and aged adult concentrations, for both i.u./mM and 1/tCr, are shown in Figure 2. The weighted

mean, 95% confidence intervals, and other summary statistics for healthy infant, adolescent, young adult, and aged populations are available at https://github.com/agudmundson/mrs-database.

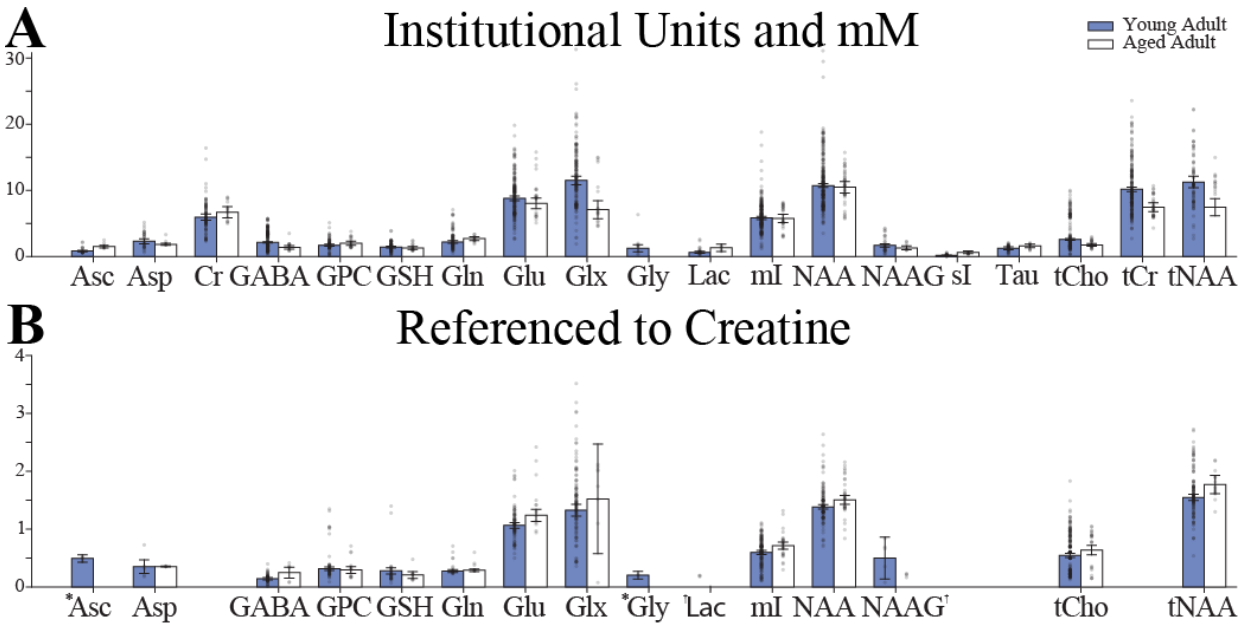

Figure 2: Brain metabolite concentrations in younger (18-45 years, in blue) and older (>50 years, in white) healthy adults from studies that reported results as: **(A)** Molar, molal, and Institutional Units; **(B)** Creatine-referenced. An * indicates the use of a Fixed Effects Model rather than a Random Effects Model. A † indicates a combined effects model was not defined.

3.3. Clinical Metabolite Concentrations in pathological conditions:

While clinical studies that did not include a control group were included in the database, the main focus was on studies that had direct comparisons, to minimize confounds involving technical variations among studies. Rather than computing effect sizes, linear changes were used to be directly interpretable to generate concentrations for future simulations. Figure 3 depicts levels of commonly investigated metabolites measured in diseased populations. The mean linear change, 95% confidence intervals, and other summary statistics for each metabolite in the 25 clinical populations is available at https://github.com/agudmundson/mrs-database.

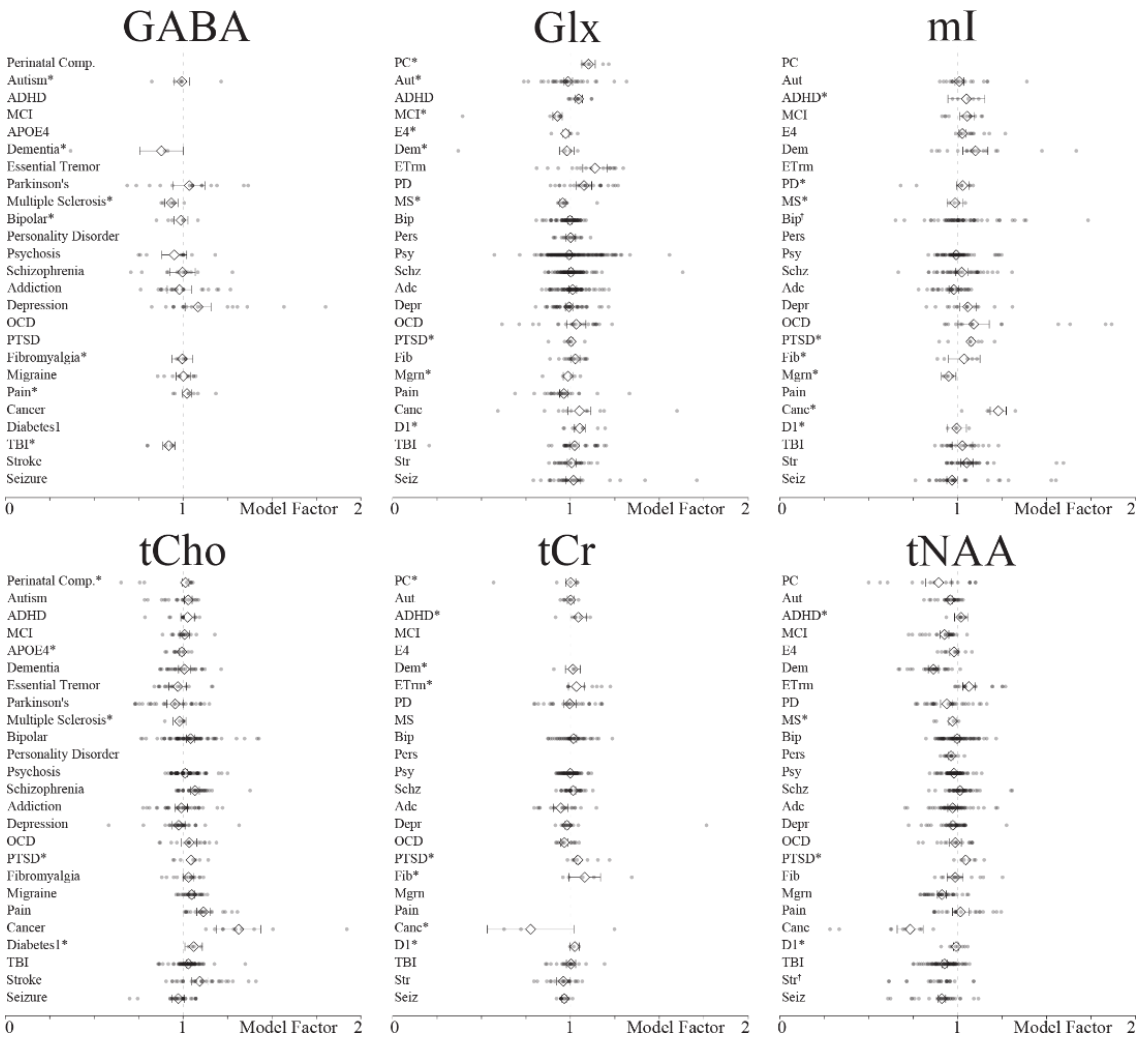

Figure 3: The six most commonly investigated metabolite concentrations modeled in diseased populations. Data from metabolite and metabolite complexes are combined (e.g., Cr and tCr, Glu and Glx). An * by the group classification indicates the use of a Fixed Effects Model rather than a Random Effects Model. A † indicates a combined effects model was not defined. PC = perinatal complications; Aut = autism; ADHD = attention-deficit/hyper activity; MCI = mild cognitive impairment; E4 apolipoprotein 4 carriers; Dem = dementia; Etrm = essential tremor; PD = Parkinson's disease; MS = multiple sclerosis; Bip = bipolar; Pers = personality disorder; Psy = psychosis; Schz = schizophrenia; Adc = addiction; Depr = depression; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; Fib = fibromyalgia; Mgrn = migraine; Pain = chronic pain; Canc = cancer; D1 = type 1 diabetes; TBI = traumatic brain injury; Str = stroke; Seiz = seizure disorder.

3.4. T_2 relaxation:

The iterative leave-one-out models achieved a median adjusted R^2 of 0.782 (Q1 = .7817; Q3 = 0.7819). Predictions for these models yielded a median error of 26.61 ms (Q1 = 12. 06 ms; Q3 = 54.66 ms) with 16.23% error (Q1 = 7.51%; Q3 = 27.29%). Figure 4 shows the actual value plotted with the marker size representing the weight within the model and the meta-regression model for 3 of the most

common metabolites, NAA, Cho, Cr. The full model is available at https://github.com/agudmundson/mrs-database.

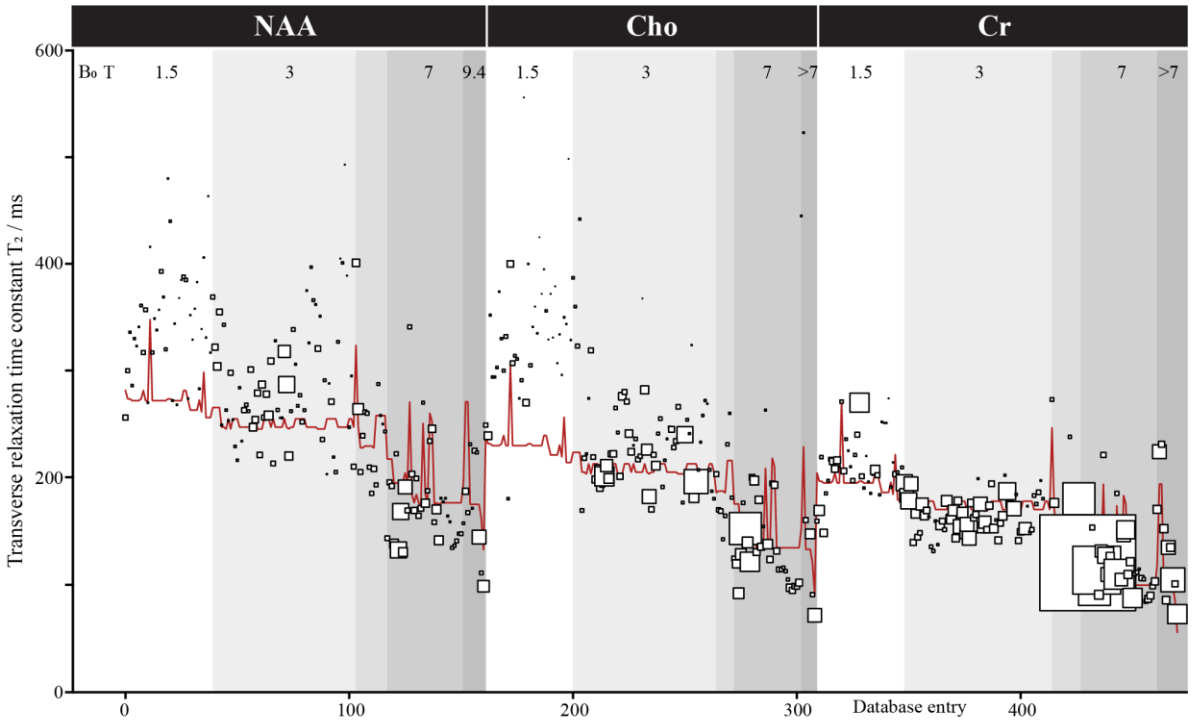

Figure 4: Transverse relaxation time meta-analysis. Only results for NAA, Cho, and Cr are shown for ease of visualization, but a total of 629 values for 14 metabolites were included in the database and modeled. Metabolite, field strength, localization, T_2 filter, species, and tissue type were included as factors in the model. Database entries are sorted here by these factors in that order. Each study is represented by a square of size reflecting the modeling weight (based on the inverse of variance). The red line shows the model.

4. Discussion:

4.1 Open-source Database:

Using a systematic approach, we provide the first database for MRS results and corresponding methods. As this database is freely available through the cloud-based website GitHub, new entries can be continually added and existing entries can be updated with more information through collaborative efforts. This database is valuable for quickly identifying trends as results across multiple studies can be interrogated. As with the meta-analyses performed here, future analyses may interrogate brain region, software, or other methodological decisions.

Citation:	**Voxel:**
Name in Database	Dimensions (x, y, z)
Publication Year	Volume
Author(s)	Anatomical Region
Journal Volume	Hemisphere
Title	Tissue Fractions (Mean/Standard Deviation)
Digital Object Identifier	
	Acquisition:
Study Populations:	Localization Sequence
Study Index	Water Suppression
Population	Acquisition Bandwidth
Control Group	Number of Datapoints
Treatment or Conditions	Number of Transients
Visit or Session Number	Repetition Time (TR)
Total Number of Subjects	Echo Time (TE)
Number of Subjects Analyzed	Inversion Time (TI)
Number of Male Subjects	T_2 Filter
Number of Female Subjects	
Age (Mean/Standard Deviation)	**Analysis:**
	Preprocessing Software
Hardware:	Fitting/Quantification Software
Scanner Manufacturer	Segmentation Software
Scanner Model	Partial Volume Correction
Magnetic Field Strength	Relaxation Correction

Table 1. Information available for entries in the database.

4.2 Physiological Ranges of Brain Metabolites in the Healthy Adults:

The primary goal of this meta-analysis was to summarize levels of MRS-accessible metabolites with a large data mining and unification approach. This was not the first effort to provide typical concentration values or ranges – physiological ranges of metabolites have been proposed previously for the healthy brain using data from multiple species [390,391]. Here, a comprehensive approach was taken to unify measures across hundreds of human studies and appropriately weight them to establish the physiological ranges of 19 brain metabolites and metabolite-complexes. The focus here on recent publications (<5 years old) biased the analysis toward data quantified using more current and advanced

methodologies. Reassuringly, many values here reflect similar ranges to those previously proposed [20,390,391].

Methodological heterogeneity within the MRS literature certainly limits any quantitative meta-analysis. The extent to which such effects negatively impact this analysis vary. For example, the clinical effects are all quantified within-study (i.e., each study is characterized in terms of a fractional group difference), so first-order effects associated with different tissue corrections shifting the mean concentration values are not a concern; however, second-order effects (where less valid corrections might lead to a group-bias) are still a concern. The main concentration analysis does conflate data quantified with a variety of methods. The variance observed in the meta-analysis results thus includes measurement variance as well as methodological variance within the literature. Where the combined/random effects models 'compare' categories with biased sampling among the methods represented, this approach may be misled by methodological biases.

The metabolic profile provided here represents progress towards effective and accurate simulation of realistic synthetic data. The development of data analysis methodologies is limited by a lack of ground truths – methodological performance is usually assessed in terms of modeling uncertainty (CRLB) or within- or between-subject variance (standard deviation). Notably, these metrics do not reflect a true measurement error, tending to ignore measurement bias and conflate sources of variance. Ultimately, synthetic data that accurately represent all features of *in vivo* data allow comprehensive evaluation of sources of variance and bias in MRS methods. Beyond validation of traditional analysis methods, such synthetic data are integral to developing deep learning and machine learning algorithms for MRS data analysis and quantification.

4.3. Physiological Ranges of Brain Metabolites in Clinical Populations:

Here, a linear model demonstrating the relationship between healthy and clinical populations was presented. Results for the six most frequently quantified metabolites can be seen in Figure 3. As far as we know, this is the first study to provide a basis to determine physiological and pathological

ranges of brain metabolites in such a wide array of clinical populations. Many of the cohort effects summarized, and those highlighted in Figure 3, agree with previous systematic reviews and disease-specific meta-analyses [21–25,392]. For example, our analysis reproduced the widely recognized elevated choline in tumors [22] and elevated mI and decreased NAA in aging and Alzheimer's Disease [21,392–394]. Neurometabolic changes in tNAA and tCho also appear to have some value in discriminating between clinical syndromes with similar symptomology, such as Parkinson's Disease and Essential Tremor [395–397]. It is notable that, although tCr is often used as an internal reference, it is not markedly stable across the disease populations, and can show changes across aging [398,399]. By synthesizing meta-analytic information across a range of disorders, this resource may allow the development of future tools to discriminate between clinical conditions.

4.4. Multiple Meta-Regression to Explain Heterogeneity of Metabolite T_2 Relaxation Results:

T_2 relaxation is an important aspect of *in vivo* MRS data and should be carefully considered when simulating data. Unfortunately, apart from the 3 most common methyl singlets (i.e., tNAA, tCr, tCho), T_2 ranges have not been well established. This can be seen as most relaxation-corrected absolute quantification methods rely on a small handful of references and must make approximations for tissue differences, pulse sequence effects, or even for metabolites that have not been studied for the given acquisition protocol. The goal of this analysis was to produce a model that could provide metabolite T_2 ranges for simulation. To do this, we leveraged data from multiple metabolites across different species that were measured using a variety of acquisition schemes. While results between studies can be seen to have a high degree of variability, the multiple meta-regression model was able to account for a large degree of the variance. The model included 6 variables: 1) metabolite, 2) field strength, 3) localization pulse sequence, 4) T_2 filter, 5) tissue type, and 6) subject species. Following a leave-one-out validation approach, nearly 80% of the variance could be attributed to the 6 factors. The major factors that explain variance in T_2 are field strength, with shorter T_2 at higher field; metabolite, with Cr having shorter T_2 than Cho and especially NAA; species, with longer T_2 in rodents; and T_2-filter (although

CPMG filters are only used in a minority of studies). The error in prediction was low, with approximately 25% of the prediction errors less than 10 ms, 50% of prediction errors less than 25 ms, and nearly 75% of prediction errors under 50 ms. High prediction errors came primarily from a small subset of papers that appear to represent outliers in the dataset suggesting predictions may provide reliable estimates when simulating understudied metabolites. We did not attempt to quantify 'study quality' as a potential weighting factor, other than through cohort size. The main factor that is not included in the model (although addressed to some degree by the 'tissue factor') is brain region of measurements, where iron-rich regions are known to show shorter T_2s [400–402]. It will also be important to measure T_2 data in clinical populations and across the lifespan to further solidify the existing body of literature.

The context of generating the metabolite components of synthetic spectra, which this meta-analysis builds toward, requires metabolite basis functions, metabolite amplitudes, as well as metabolite linewidths. By surveying the metabolite T_2 literature, we sought to better understand the 'pure-T_2' of metabolite linewidths in the absence of local field inhomogeneity. One model of *in vivo* lineshapes is to assume T_2 as the Lorentzian linewidth component and to assign inhomogeneity broadening to a Gaussian linewidth component – the data compiled here can inform such a model. It is also appropriate to consider transverse relaxation weighting of metabolite amplitudes when assembling synthetic spectra "acquired" at typical TEs.

5. Conclusion:

Here, we provide a new database containing brain metabolite results from nearly 500 MRS publications. This database is freely available online where users can view and contribute their own data. Moving forward, this database can function as a community resource allowing deeper interrogation and understanding of how acquisition protocol, software analysis tools, brain region, population, etc. impact and/or bias results.

Using the database, we have determined physiological ranges of 19 brain metabolites and metabolite-complexes across the lifespan of healthy individuals. We further modeled disease effects relative to healthy controls to allow for determining concentration ranges for 25 psychiatric and neurologic diseases. Finally, we have performed a meta-regression to determine appropriate ranges for T_2 in MRS simulations. The determined ranges will be invaluable for informing the generation of synthetic data for evaluating analysis tools and deep learning datasets. Additionally, these ranges may serve as a reference to clinical researchers that are unaware of the expected values for a given metabolite or may be considering how MRS can fit within their study design.

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