In vivo proton MR Spectroscopy of the healthy and diseased human brain

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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*. In the last decade, the field has made substantial methodological progress. Standardization and accessibility have been particularly prioritized, leading to the development of universal pulse sequences, methodological consensus recommendations, and the development of open-source analysis software packages. This review article summarizes progress over the last decade. One remaining challenge is methodological validation with ground-truth data. Therefore, in addition to reviewing progress, we have conducted a meta-analysis of physiological concentration ranges and relaxation rates of brain metabolites by developing a database summarizing nearly 500 peer-reviewed spectroscopy manuscripts. Expectation values for metabolite concentrations and T_2 relaxation times are established based upon a meta-analyses of healthy and diseased brains.

Table of Contents:

1. Introduction

2. Recent Developments in MRS Acquisition and Analysis Methods

    2.1 Single-voxel MRS

    2.2 Multiple-voxel MRSI

    2.3 Data Analysis and Quantification

    2.4 Deep Learning

    2.5 Database and Meta-analysis Motivations

3. Methods

    3.1 Search Methods

    3.2. Metabolite Concentrations in Healthy Populations

    3.3. Metabolite Concentrations in Clinical Populations

    3.4. T_2 Meta-regression Model

4. Results

    4.1. Database

    4.2. Healthy Metabolite Concentrations

    4.3. Clinical Metabolite Concentrations in pathological conditions

    4.4. T_2 relaxation

5. Discussion

    5.1 Physiological Ranges of Brain Metabolites in the Healthy Adults

    5.2. Physiological Ranges of Brain Metabolites in Clinical Populations

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

6. Conclusion

7. References

8. Glossary

1. Introduction

Proton (^{1}H) Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that has been used for more than 30 years to study metabolites *in vivo* in the human brain. This topic was last comprehensively reviewed for readers of *Progress in NMR Spectroscopy* in 2006 [1]. Since that time, the field of MRS and magnetic resonance spectroscopic imaging (MRSI) has seen substantial progress, both in development of methodology as well as in clinical and neuroscience application studies. A number of other advances in the field of brain MRS have occurred over the last 18 years, including the use of hyper-polarized ^{13}C [2] and also deuterated substrates [3], both of which show promise for clinical research applications. However, this article is limited to only ^{1}H MRS studies of indigenous compounds. The purpose of this manuscript is twofold: to review recent progress in MRS and MRSI, and to provide a database of MRS literature and quantitative reference values for synthetic data.

In the previous review article [1] it was noted that MRS was not routinely used as a diagnostic tool in radiological practice, which remains the case today. There are multiple reasons for this, but steps have been made towards overcoming some of the obstacles limiting routine use both clinically and in research applications. One major issue was a lack of consensus on both techniques and applications for MRS in clinical use which led to the formation a consensus group consisting of expert spectroscopists, radiologists, and other physicians in 2011. In 2014, the group outlined the clinical utility for an array of brain diseases and outlined what research steps would need to be taken in order to advance the field towards common diagnostic use [4]. Many of the technical hurdles associated with MRS were addressed in a series of follow-up consensus articles which also suggested steps moving continued progress [5,6,15,7–14]. In addition to methodological consensus, standardization within the field has become a priority, leading to the development of vendor-harmonized pulse sequences and the development of open-source preprocessing and quantification software packages [8–10,16,17]. Deep learning (DL) techniques for MRS have recently emerged and may soon be available with the growing ability to simulate realistic *in vivo* data. To better recount these accomplishments, the progress in ^{1}H-

MRS can be classified into acquisition vs. analysis, and amongst acquisition, further into single-voxel vs. MRSI techniques.

2. Recent Developments in MRS Acquisition and Analysis Methods

2.1 Single-voxel MRS

A significant development in single-voxel MRS has been the emergence of the semi-adiabatic localized by adiabatic selective refocusing (sLASER) pulse sequence [18] as the recommended method for single-voxel MRS [9,14]. sLASER is similar in concept to the previously described point resolved spectroscopy (PRESS) sequence [19], but replaces each PRESS refocusing pulse with a pair of adiabatic inversion pulses, overcoming issues of limited PRESS refocusing pulse bandwidth and spatial inhomogeneity of the B_1 transmit field, both issues that become greater at ultra-high field (Figure 1). Adiabatic pulses involve both frequency and amplitude modulation of the radiofrequency (RF) profile, and some pulses, including frequency offset corrected inversion (FOCI) and gradient offset independent adiabatic (GOIA), also make use of modulation of the slice selective field gradient amplitude [20,21] which allows for high bandwidth performance with reduced peak RF power [16].

At the high end, development of 7T MRS continues, and *in vivo* human brain spectra at ultra-high field strength (9.4T) have also been recorded [22–29]. At lower field strengths (1.5T and 3T), the detected metabolites are mainly limited to the larger ‘metabolite-complex' signals from: choline-containing compounds, phosphocholine (PCho), and glycerophosphocholine (GPC); creatine-containing compounds, creatine (Cr) and phosphocreatine (PCr); total N-acetylaspartate (tNAA), the sum of N-acetylaspartate (NAA) and N-acetyl-aspartyl-glutamate (NAAG), *myo*-inositol (mI) and Glx, the sum of glutamate (Glu) and glutamine (Gln) [30]. At 7T and higher, a number of additional compounds are quantifiable, including ascorbate (Asc), aspartate (Asp), GABA, glutathione (GSH), glycine (Gly), lactate (Lac), phosphoethanolamine (PE), serine (Ser), taurine (Tau), and *scyllo*-inositol (sI), leading to approximately 18 different compounds that can be quantified [29,31,32]. Notably, another 20 or so compounds have also been reported to be detectable by MRS in pathological or

perturbed physiological conditions, and/or after administration of exogenous substances [23,33,42–44,34–41]. For compounds that are detectable at all field strengths, it has been shown that the signal-to-noise ratio (SNR) increases, despite simultaneous increasing linewidths, and uncertainty estimates (Cramer-Rao lower bounds, CRLBs) decrease with increasing B_0. Reaffirming earlier predictions and results [45], increased quantification precision can be seen from 3T and 4T to 7T [31,46–48] and from 7T to 9.4T [25]. The greatest benefit of higher field may be in separating compounds that have significant overlap at lower field strengths, e.g. NAA from NAAG, or glutamate from glutamine [30,45]. For instance, one study showed an almost 3-fold reduction in CRLBs for Glu and Gln when going from 3T to 7T [46]. Figure 2 shows example spectra from the brain at 1.5T, 3T, and 7T using stimulated echo acquisition Mode (STEAM) and 9.4T using sLASER in white matter (WM), demonstrating the improvements in spectral resolution that occur as B_0 increases.

With increased spectral resolution, higher SNR and shorter-TE acquisitions at higher field strengths, the broad mobile macromolecular (MM) signals underlying the metabolite spectrum in the human brain have received greater attention, and have been characterized at various field strengths [27,49–53]. Gray matter (GM) and WM differences in MM signal amplitude have also been recorded [54,55]. These MM signals largely originate from amino acids within cytosolic proteins [56,57] and a fitting model was proposed [58] for the MM spectrum using chemical shift histograms of amino acid resonances from the Biological Magnetic Resonance Data Bank [59]. Interest in investigating the impact of MM signals in metabolite quantification has soared in the past decade for accurate and reliable quantification of metabolite concentration [60–62]. Various modeling methods have been implemented to handle MM signal in the spectrum, including using an experimentally acquired MM spectrum or using parameterized MM models [63–65]. Figure 3 shows a comparison of both these methods in modeling a metabolite spectrum acquired at 3T from the human brain. Such differences in the fitting routine induce a substantial difference in the estimated metabolite concentration, especially

in those metabolites overlapped with MM peaks [60]. Use of experimentally acquired MM is shown to result in more accurate results [32,62,63,65–70] as recommended by the recent MM consensus [6].

A major growth application of MRS has been single-voxel MRS of the inhibitory neurotransmitter GABA [71], largely by J-difference editing [72] at 3T. The Mescher-Garwood (MEGA) editing scheme combined with PRESS localization (MEGA-PRESS) [73] is the most broadly available and implemented as a product by major vendors (Figure 4). However, MEGA-sLASER [74] is likely to supersede MEGA-PRESS, because its high-bandwidth slice-selective pulses reduce the signal loss caused by destructive effects of spatial inhomogeneities in coupling evolution. Multi-metabolite editing using Hadamard-encoded J-difference editing schemes, such as Hadamard encoding and reconstruction of MEGA-Edited Spectroscopy (HERMES) [75] can accelerate edited MRS by allowing measurements of GABA and the antioxidant glutathione (GSH) simultaneously [76]. Most recently, the Hadamard editing resolved chemicals using linear-combination estimation of spectra (HERCULES) [77] pulse sequence combined a multi-step editing scheme with multi-spectrum modeling to detect a full neurometabolic profile at 3T (Figure 5).

2.2 Multiple-voxel MRSI

Development of MRSI techniques for the human brain has continued since the 2006 review article [1], most notably in techniques for reducing scan time (i.e. ‘fast-MRSI’), improving spatial resolution, reconstruction techniques, removing artifacts, and the use of higher magnetic field strengths. At the time of the last review, the majority of MRSI studies in the literature used conventional phase-encoding in 2 or 3 dimensions to map out distributions of metabolites. However, these methods become extremely time consuming when high spatial resolution and extended brain coverage are required.

Two of the older approaches for reducing MRSI scan time are either to use echo-planar spectroscopic imaging (EPSI) which applies an alternating read gradient during data acquisition (and speeds up acquisitions by an order of magnitude) [78,79], or the use of parallel imaging techniques,

such as Sensitivity Encoding (SENSE) or Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA) [80,81] which can accelerate by factors of 2-4 typically. EPSI can be combined with parallel imaging for further acceleration [82–85]. While these methods work quite well, they do also have some problems. EPSI is demanding on gradient performance, which usually limits the maximum spectral width possible, and both EPSI and parallel imaging methods are prone to artifacts. For these reasons, other approaches have been explored: many different k-space trajectories are possible when applying read gradients during data acquisition, including spirals [86,87], circles, or concentric rings [88,89]. Acquisitions may also be segmented, i.e. so that two or more shots are required to cover all of k-space in the readout direction(s), or (in the case of EPSI) the odd- and even- echoes are processed separately to minimize artifacts from imbalance between positive and negative gradient acquisitions. While this reduces artifacts, it also halves the spectral width available. The concentric ring approach offers high spectral width and efficient sampling, but collecting outer gradient rings is limited by gradient performance. More recently, k-space has been covered by collecting multiple smaller rings (in multiple shots) whose origin is shifted from one scan to the next [90], overcoming this limitation.

MRSI scan times can also be reduced through random under-sampling of k-space, as is now commonly used in MRI for scan time reduction – known as ‘compressed sensing’ (CS) [91]. With appropriate iterative reconstruction techniques, the missing k-space data can be estimated in order to generate a final spectroscopic imaging that would otherwise contain ‘truncation artifacts’ due to the missing k-space points [92–94]. Typically, this involves low rank (LR) estimation of constrained models which may require lengthy reconstruction times. The non-linearity of such reconstruction techniques may lead to the failure to detect small signals of similar amplitude to the noise. However, at least for now, this approach, combined with fast readouts and parallel imaging acceleration, seems to be the best way to achieve high-resolution spectroscopic images with whole brain coverage and clinically acceptable scan times. Figure 6 shows an example of whole-brain MRSI acquired at 3T using a CS/LR reconstruction of SENSE-accelerated three-dimensional (3D) Free Induction Decay (FID)

MRSI data measured in a healthy volunteer at 3T (adapted with permission from reference [94]) where the spatial distribution of metabolites (e.g. higher tCho in frontal regions thalamus and insular cortex, higher tCho, tCr and mI in cerebellum, and higher Glx in gray matter compared to white matter) nicely matches that previously determined using EPSI or other MRSI techniques [95,96].

A simple way to reduce scan time is to reduce the repetition time (TR). In fact, it has long been known in high resolution NMR that the shortest TR also gives the best sensitivity per unit time, so long as the correct flip angle (the 'Ernst angle') is used [97]. In recent times, this has been recognized as the most efficient way to collect MRSI data, achieved by making the acquisition readout no longer than required for a desired frequency-domain resolution, and minimizing the duration of other sequence elements (water, lipid suppression modules etc.) and the echo-time (TE), which can be particularly short for FID, rather than echo, readouts [98]. For MRSI at 7T, FID readouts avoid problems associated with slice-selective refocusing pulses, such as high specific absorption rate, sensitivity to transmit B_1 inhomogeneities, and large chemical shift displacement effects [98–100]. They do however result in spectra with large first-order phase-errors, which complicates spectral analysis. Most recent implementations of high-resolution MRSI at either 3T or 7T use a combination of these approaches – FID-MRSI, sparse-sampling, parallel reconstruction, and sophisticated reconstruction algorithms – in order to achieve wide spatial coverage within reasonably short scan times (Figure 7).

An interesting recent development for MRSI (EPSI) at 7T is frequency-selective refocusing [101]. This has a number of advantages; first of all, pure phase spectra can be obtained because a spin-echo is formed. Secondly, by only refocusing a specific spectral region, unwanted signals (e.g. from residual water and lipid) are removed. Thirdly, compared to slice-selective refocusing pulses, the bandwidth (and hence RF power requirements) of frequency-selective refocusing pulses are much lower. Intriguingly, it has also recently been shown that, with the use of a pair of adiabatic frequency-selective pulses with well-defined inversion (refocusing) profiles, the evolution of coupled spin systems (e.g. such as GABA, or the oncometabolite 2-hydroxyglutarate (2-HG)), can be manipulated

by changing the refocusing frequency, also allowing the mapping of these low concentration compounds via J-difference editing [101]. Edited MRSI is an active topic of research, with several papers being published using a more conventional 'MEGA editing' approach incorporated into MRSI acquisitions at 3T and 7T [102–104]. Such experiments employ subtraction to remove larger signals, they are quite sensitive to any system instabilities or patient motion, and either prospective or retrospective correction schemes may be needed to minimize subtraction artifacts [102,104].

One further technical development that promises to significantly improve data quality, particularly for MRSI, is the use of localized shim coil arrays to correct B_0 magnetic field inhomogeneities. Traditionally, active shimming for MRS is performed using either linear or higher-order (usually 2nd, but sometimes 3rd order) spherical harmonic corrections via shim coils embedded into the magnet and gradient coil assembly. While this approach works well for MRI or single-voxel MRS, it does not have enough degrees of freedom to correct all the magnetic field variations that are found within the human head due to tissues of different magnetic susceptibilities (brain, bone, air spaces). Over the last few years, it has been demonstrated that multiple local shim coils can provide superior field homogeneity over a larger volume of tissue (which is a critical factor for MRSI quality) compared to the standard scanner-based shim coils [105–107]. These coils can either be separate shim arrays (e.g. placed just outside the RF receiver coil) or combined directly with the multi-channel RF receiver coils, i.e. the same coil element is used simultaneously to receive the RF signal as well as to carry a direct current that is used to improve local magnetic field homogeneity.

2.3 Data Analysis and Quantification

A number of MRS data analysis software packages have emerged for use in analyzing *in vivo* brain MRS, many of them released open-source [108–114]. They offer modular methods for preprocessing and image co-registration and tissue-corrected quantification of metabolite levels. Additionally, several of these packages include algorithms to perform linear-combination modeling, which remains the primary method for spectral fitting, and is now recommended by expert consensus

for most *in vivo* applications [14]. The 'LCModel' package [115], the primary linear-combination modeling algorithm in the field for over 25 years, has recently transitioned from being a closed-source commercial product to an open-source resource. As in other neuroimaging modalities, it is increasingly recognized that the choice of analysis pipeline, fitting algorithm, and fitting parameters have substantial influence on quantitative MRS results [116–118]. The discrepancies between a now increasing number of available fitting algorithms, and newly emerging deep learning methods, have generated interest in validation using realistic synthetic data that offers ground-truth values [116].

2.4 Deep Learning

The application of DL methods to MRS shows great potential for many aspects of MRS data analysis, e.g., for improving data quality, but also for directly estimating metabolite levels without linear-combination modeling. Fully connected or convolutional neural networks (CNNs) have been used to perform frequency and zero order phase correction of frequency-domain data [119,120]. CNNs have also been shown to have success in removing spurious echoes by using a short-time Fourier transform to produce a two-dimensional (frequency x time) spectrogram representation of data [121]. Fully connected auto-encoders can differentiate metabolite from broad macromolecular signals in the time-domain [122]. Convolutional auto-encoders have been used to enhance quality and perform full preprocessing routines in the frequency domain [123,124]. CNNs have been trained to directly quantify relative metabolite concentrations from frequency domain signals [125]. Recurrent neural networks have not been used as much, but in one case were shown to have some diagnostic value using long short-term memory (LSTM) and Bidirectional LSTM models [126]. Despite these advances, the field of MRS has been cautious and these methods have yet to be widely used in application studies. However, it is clear that deep learning will offer tools for MRS with further validation.

2.5 Database and Meta-analysis Motivations

Generating realistic synthetic *in vivo* spectra is desirable for validation of MRS analysis methods, but it is an enduring challenge because a ground-truth is always lacking for *in vivo* measurements. 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 DL techniques. Density matrix simulations based upon prior knowledge of metabolite chemical shifts and coupling constants [110,112–114,127,128] can generate metabolite basis spectra for such synthetic data. 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 [116], specifying a single metabolite T_2 value of 160 ms and normal ranges for metabolite concentrations based on experience. Therefore, the goal of the remaining portion of this review is to describe a database and provide a meta-analysis of the MRS literature to better inform future efforts to generate synthetic data that represent brain MRS in healthy and disease.

3. 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.

3.1 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 [129,130]. Searches were conducted on PubMed, Web of Science, and Scopus databases. Separate searches were carried out to specifically identify publications that either quantified metabolite concentrations or measured 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. An additional follow-up search was then conducted March 2022 to ensure all publications through the end of 2021 were included. No limitation for publication date was specified for searches and only articles available in English were included. A PRISMA flowchart that reflects the process of building concentration and relaxation databases is shown in Figure 8.

For both the concentration and relaxation studies, only *in vivo* brain ^{1}H-MRS data from primary sources were considered. Reviews, meta-analyses, re-analyses and book chapters were excluded. Conference posters were typically excluded since they are not peer-reviewed (with some exceptions where information was otherwise scarce). Finally, to be included, manuscript results had to include a mean and standard deviation. For studies that reported statistical results (t-statistics, p-values, etc.) without values, authors were contacted by email for inclusion. Median and quartiles were converted to mean and standard deviation using the methods outlined in [131,132] 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.

For the concentration study, only human subjects research was included. Articles were included if they reported 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). Due to the high volume of articles (10,506) returned for the concentration study, articles were initially limited to 2018-2022. 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.

Articles were included in the relaxation study that reported at least one metabolite T_2 relaxation value in time or R_2 rate in 1/time. 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.

After removing articles according to inclusion/exclusion criteria, articles' titles and abstracts were reviewed for relevance. Once confirmed relevant, article full texts were downloaded to make a final decision on inclusion/exclusion, as summarized in Figure 7.

For the concentration study, of the original 1,863 articles, 571 articles were removed prior to screening leaving 1,292 articles. After screening, 790 articles remained and were retrieved and assessed for relevance. A total of 350 articles were determined to be eligible for inclusion in the database and analysis.

For the relaxation study, of the original 870 articles, 234 were removed prior to screening and 636 articles were further screened. 342 articles 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 [133–138]. 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 [139] 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 [139] 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 [140] 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.

3.2. 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 [141–147], 19 [148,149,158–166,150–157], 199 [23,67,174,264–273,175,274–283,176,284–293,177,294–303,178,304–313,179,314–323,180,324–333,181,334–343,182,344–353,183,354–359,165,184–193,167,194–203,168,204–213,169,214–223,170,224–233,171,234–243,172,244–253,173,254–263], and 45 [183,205,360–369,207,370–379,234,380–389,251,279,294,343,346,349] 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 [139] was used to compute the mean and 95% confidence interval (as seen in Figure 9).

3.3. 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 [141,142,157,305,306,308,310–312,317,321,322,328,160,329–333,335,337,339–341,161,342,345,350–354,359–361,162,362,364,365,368–374,163,377,378,380–387,165,388–397,166,398–407,167,408–414,169,171,143,174,175,178,179,181,183–185,187,188,144,190,192,193,195–201,145,203,204,207–211,213–215,146,217,219,220,223,227,229–231,233,235,150,237,238,240,243,247,249,250,253,254,256,151,257–261,263,264,267,268,270,153,272–276,278,280,282,288,289,156,291–294,296,297,299,300,302,303] 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 [415,416]. A value of 1.0 would indicate no difference between the clinical and control groups. Finally, a combined effects model [139] was used to compute the mean and 95% confidence interval (as seen in Figure 10).

3.4. 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 [25,27,422–431,32,432–441,45,442–451,52,452–461,417,462–471,418,472–481,419,482–487,420,421] 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 1.5T through 14.1T. Localization pulse sequence was a categorical variable that included PRESS, STEAM or adiabatic (e.g., 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).

4. Results

4.1. 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.

4.2. 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 9. 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.

4.3. 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 10 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.

4.4. T_2 relaxation

The model 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 11 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.

5. Discussion

5.1 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 [33,488]. Here, a comprehensive approach was taken to unify measures across hundreds of human studies and appropriately weighted 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 [33,116,488].

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.

5.2. Physiological Ranges of Brain Metabolites in Clinical Populations

Here, a linear model demonstrating the relationship between healthy and clinical populations was presented. 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 agree with previous systematic reviews and domain-specific meta-analyses. For example, our analysis reproduced the widely recognized elevated choline in tumors [489], and elevated mI and decreased NAA in Alzheimer's Disease [490,491]. Neurometabolic changes may also have some value in discriminating between clinical syndromes with similar symptomology, such as Parkinson's Disease and Essential Tremor [492–494]. By synthesizing meta-analytic information across a range of disorders, this resource may allow the development of future tools to discriminate between clinical conditions.

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

Here, a model is presented that could account for a large degree of the variance in published T_2 relaxation results. 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. As such, 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. 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). High prediction errors came primarily from a small subset of papers that appear to represent outliers in the dataset. 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, with iron-rich regions tending to show shorter T_2s. 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. Ultimately, this model provides a rigorous foundation for including T_2 relaxation within simulations and unifying the disparate data currently available.

6. Conclusion

In the 16 years since the last *Progress in NMR Spectroscopy* review article on brain proton MRS, much progress has been made in terms of technical developments and data collection in a large number of studies. Over the last few years, a series of consensus articles has been published on both recommended techniques for acquisition and analysis, as well as potential clinical applications [5,6,15,7–14]. While MRS is used in the clinical environment in some academic medical centers, its use is not widespread due to: relative lack of support from vendors (particular in adoption of recent technical developments); access to technologist and radiologist training; lack of Food and Drug Administration-approved software for data analysis and visualization; and also lack of insurance reimbursement. Additionally, patterns of metabolic changes that are specific to disease-state and that impact clinically significant differential diagnosis have not been established. However, MRS in the human brain is well established for clinical research where it is commonly used to better understand brain metabolism in health and disease, as well as for monitoring the effects of treatment. Here, we review recent progress and provide a new database organizing brain metabolite results from almost 500 publications. This database is freely available online where users can view and contribute data. Using

the database, we have determined physiological ranges of 19 brain metabolites and metabolite-complexes across the lifespan, modeled disease effects, and model factors that influence T_2 relaxation.

7. References

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8. Glossary

^{1}H: proton

^{13}C: carbon-13

2-HG: 2-hydroxyglutarate

3D: three-dimensional

Adc: addiction

ADHD: attention-deficit/hyper activity

Asc: ascorbate

Asp: aspartate

Aut: autism

B_0: static magnetic field

B_1: radiofrequency pulses

Bi-LSTM: bidrectional long short-term memory

Bip: bipolar

Canc: cancer

Cho: choline-containing compounds

CNN: convolutional neural network

CPMG: Carr-Purcell Meiboom-Gill

Cr: creatine

CS: compressed sensing

CRLB: Cramer-Rao lower bounds

CSDE: chemical shift displacement effects

D1: type 1 diabetes

Dem: dementia

Dep: depression

DL: deep learning

E4: apolipoprotein 4 carriers

EPSI: echo-planar spectroscopic imaging

Etrm: Essential Tremor

Fib: fibromyalgia

FID: free induction decay

FOCI: frequency offset corrected inversion

GABA: gamma-aminobutyric acid

Gln: glutamine

Glu: glutamate

Glx: sum of glutamate and glutamine

Gly: glycine

GM: gray matter

GPC: glycerophosphocholine

GOIA: gradient offset independent adiabatic

GRAPPA: generalized autocalibrating partial parallel acquisition

HERCULES: hadamard editing resolves chemicals using linear-combination estimation of spectra

HERMES: hadamard encoding and reconstruction of MEGA-edited spectroscopy

ISMRM: international society for magnetic resonance in medicine

Lac: lactate

LASER: localization by adiabatic selective refocusing

LR: low rank

LSTM: long short-term memory

MCI: mild cognitive impairment

MEGA: Mescher-Garwood

mI: myo-inositol

Mig: migraine

MM: macromolecules

MR: magnetic resonance

MRS: magnetic resonance Spectroscopy

MRSI: magnetic resonance spectroscopy imaging

MS: multiple sclerosis

NAA: N-acetylaspartate

NAAG: N-acetyl-aspartyl-glutamate

NMR: nuclear magnetic resonance

OCD: obsessive compulsive disorder

PainL 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

RF: radiofrequency

Schz: schizophrenia

Seiz: seizure disorder

SENSE: sensitivity encoding

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_1: longitudinal relaxation time

T_2: transverse 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

TM: mixing time

TR: repetition time

WM: white matter

Figures and Tables:

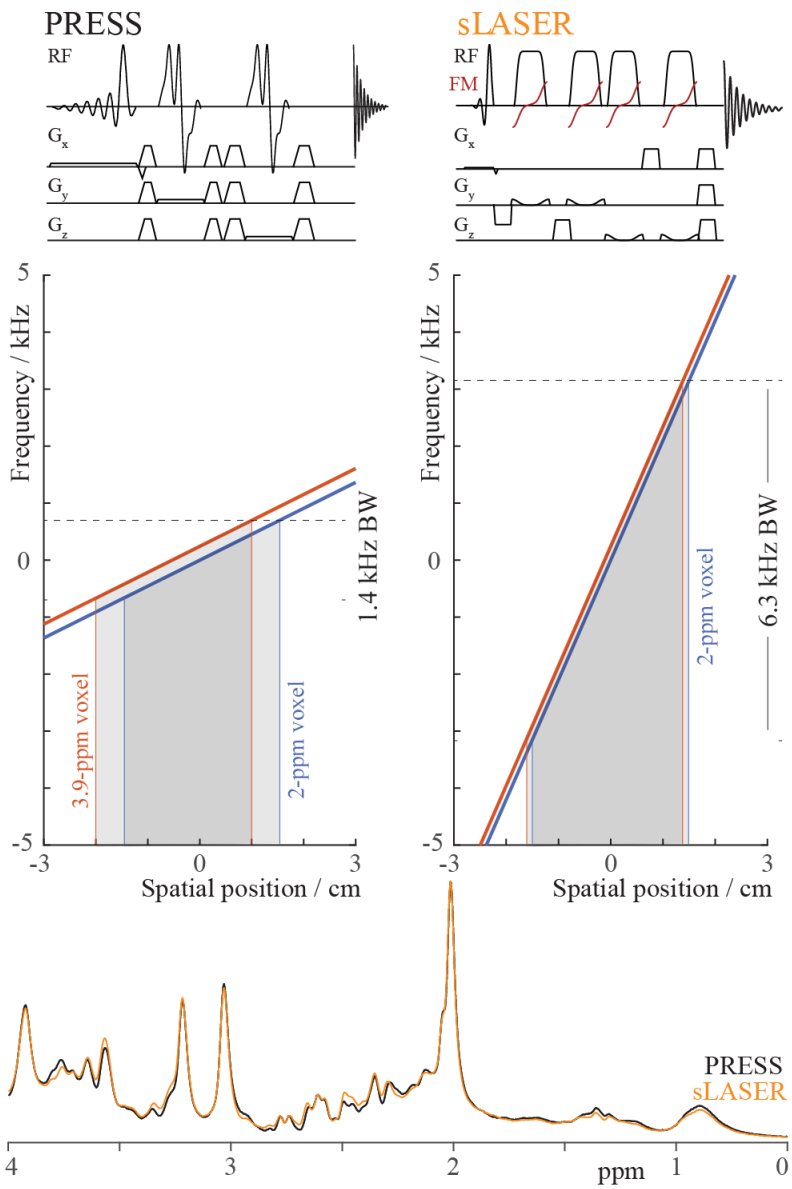

Figure 1: PRESS and sLASER pulse sequences for single-voxel MRS. In PRESS, conventional amplitude-modulated slice-selective 90˚ and 180˚ pulses are used to form a spin-echo from a cuboid inside the sample. In sLASER, after a conventional 90˚ excitation pulse, refocusing is achieved by two pairs of adiabatic, frequency-modulated 180˚ inversion pulses which typically have much higher bandwidth than 180˚ refocusing pulses for the same peak RF power. Here, the conventional pulses in the PRESS sequence have a 1.4 kHz bandwidth, versus 6.3 kHz for the sLASER sequence. The corresponding chemical shift displacement effects (CSDE) for a $(3\ \text{cm})^3$ voxel at 3T are shown in the middle row; for PRESS the CSDE is ~0.5 cm between resonances at 2 ppm and 3.9 ppm; for sLASER the CSDE is ~0.1 cm. The bottom row shows example spectra from one normal volunteer recorded from centrum semiovale white matter (TR 2 s, TE 30 ms, 20 cm^3, scan time ~4 minutes) with both PRESS and sLASER; superficially the spectra are very similar, although there are differences in some of the coupled resonances around 2.5 ppm.

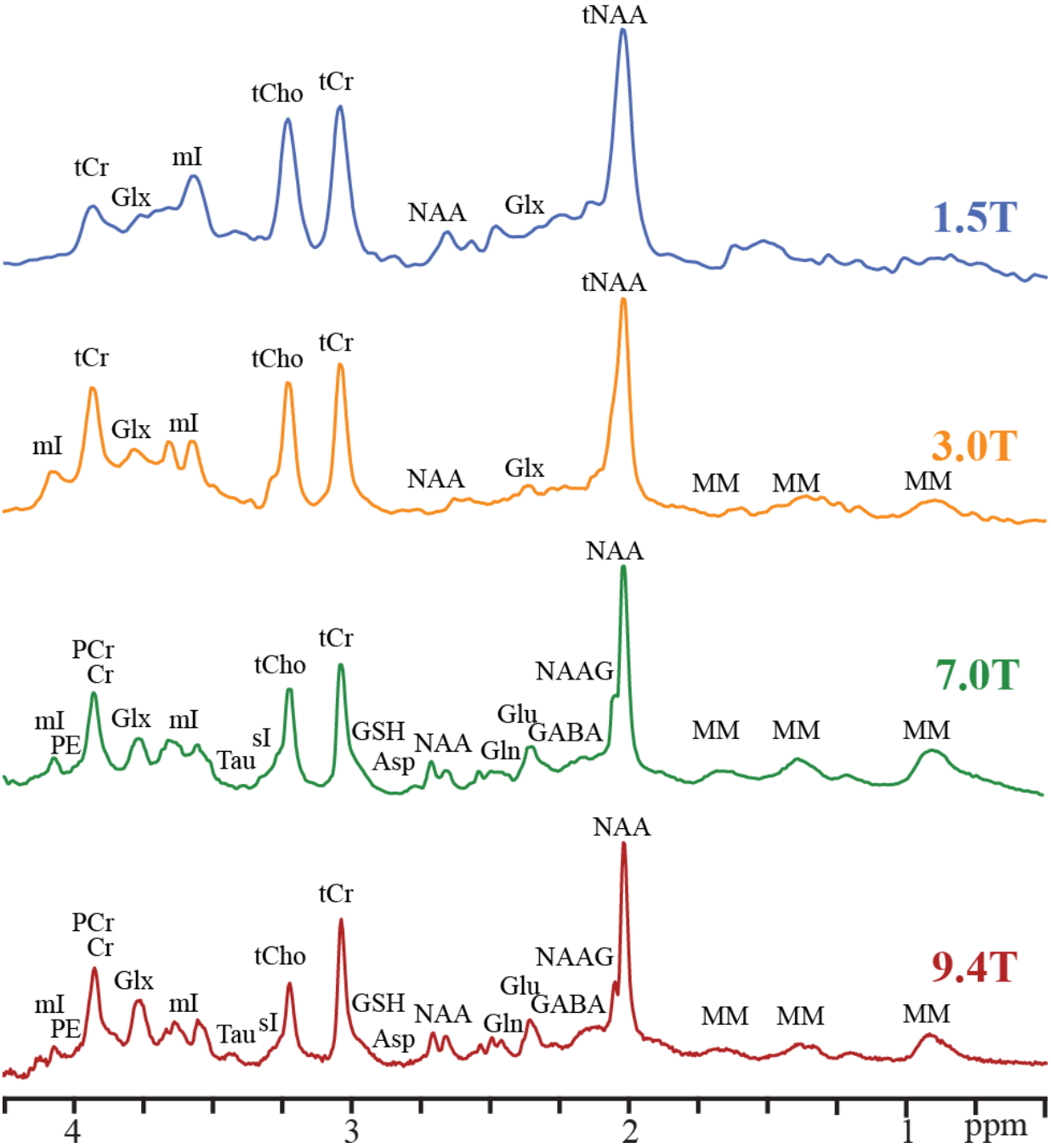

Figure 2: Spectra from white matter of the normal adult human brain recorded at four different magnet field strengths (1.5T, 3.0T, 7.0T, and 9.4T). 1.5T and 3T spectra are recorded with STEAM localization with 128 averages (TR 3s, TM 14 ms, TE 20 ms, 8 cm^3). The 7T spectrum is recorded with STEAM localization with 128 averages (TR 3s, TM 33 ms, TE 14 ms, 12 cm^3). The 9.4T spectrum is recorded with sLASER localization with 64 averages (TR 6s, TE 34 ms, 8 cm^3).

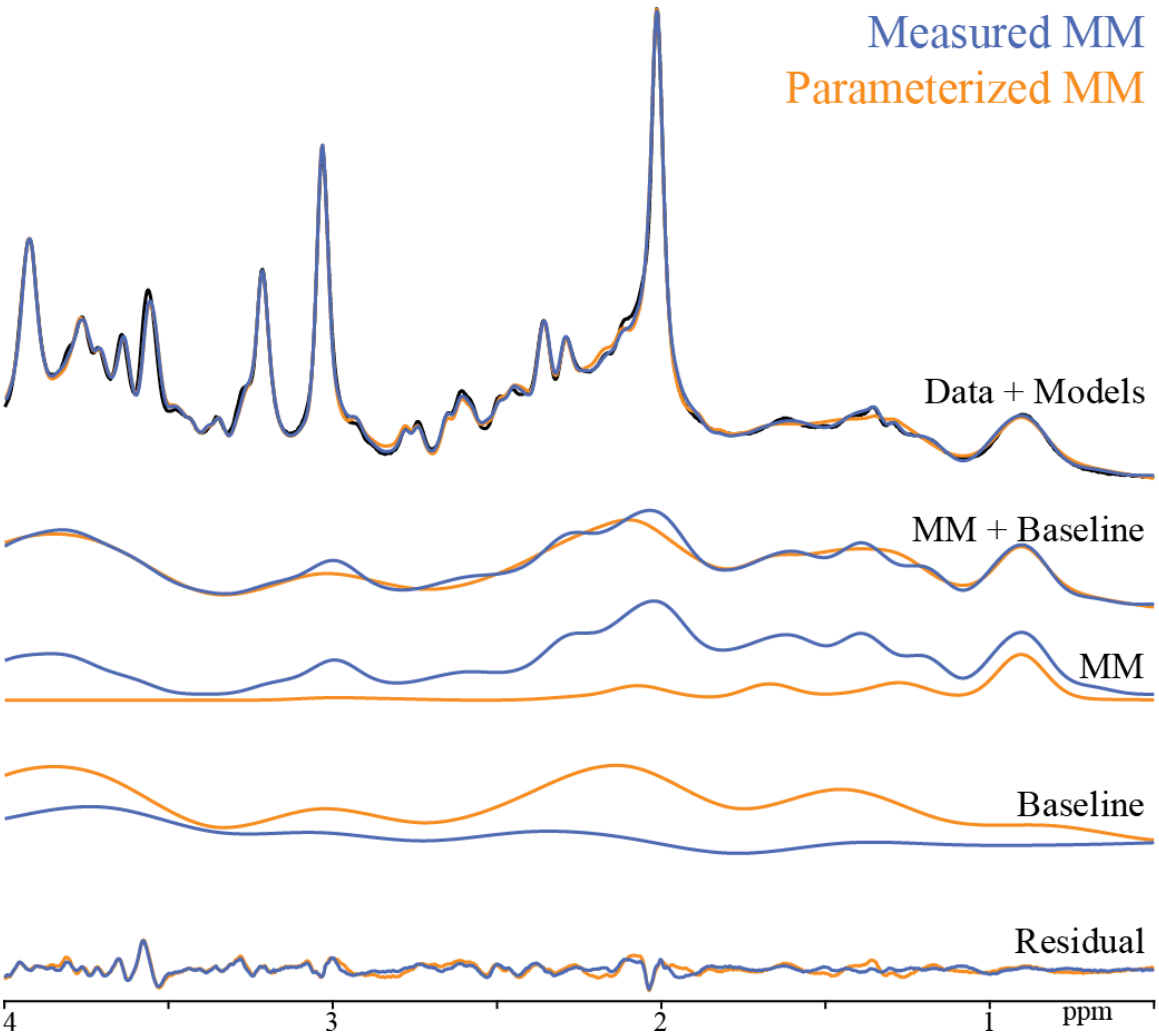

Figure 3: Macromolecular contributions to the human brain spectrum. In addition to narrow signals from metabolites, spectral models must incorporate broader functions to account for baseline distortions and macromolecular signals (which can either be addressed with measured MM spectrum or a parametrized function).

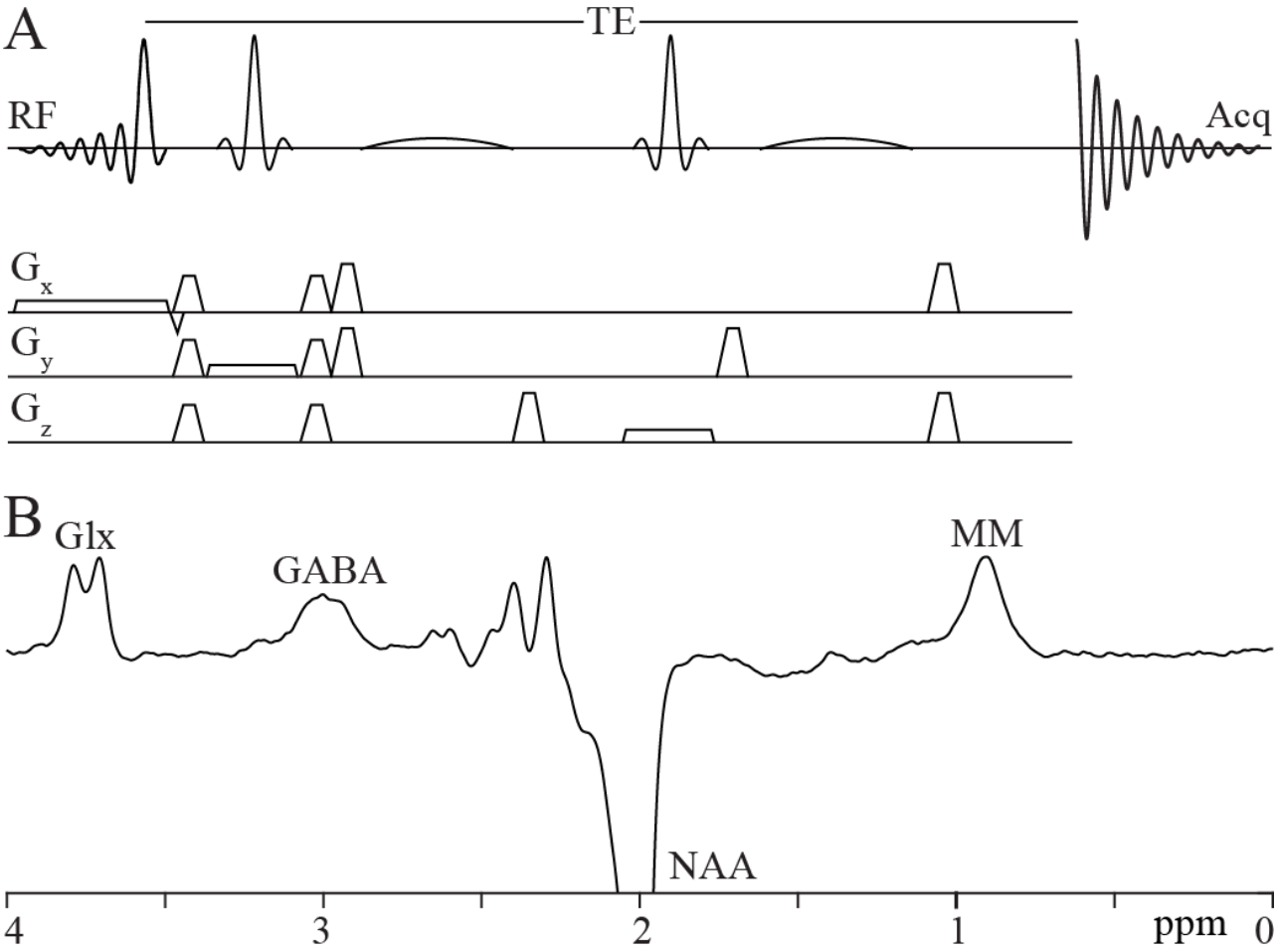

Figure 4: (A) The MEGA-PRESS pulse sequence. Two frequency-selective editing pulses are included during PRESS localization sequence. Scans are performed with the editing pulses placed on-resonance (at 1.9 ppm) and off-resonance (at 7.5 ppm) with respect to the coupled spins of the target molecule to be selected for editing. Note that for maximum editing sensitivity the editing pulses should be separated by TE/2. **(B)** An example of a GABA-edited MEGA-PRESS spectrum from the normal human brain (TR 2 s, TE 68 ms, voxel volume 27 cm^3, scan time approximately 10 minutes). As well as the edited GABA peak at 3 ppm, additional signals are seen from Glu and Gln, NAA, and a MM at 0.9 ppm.

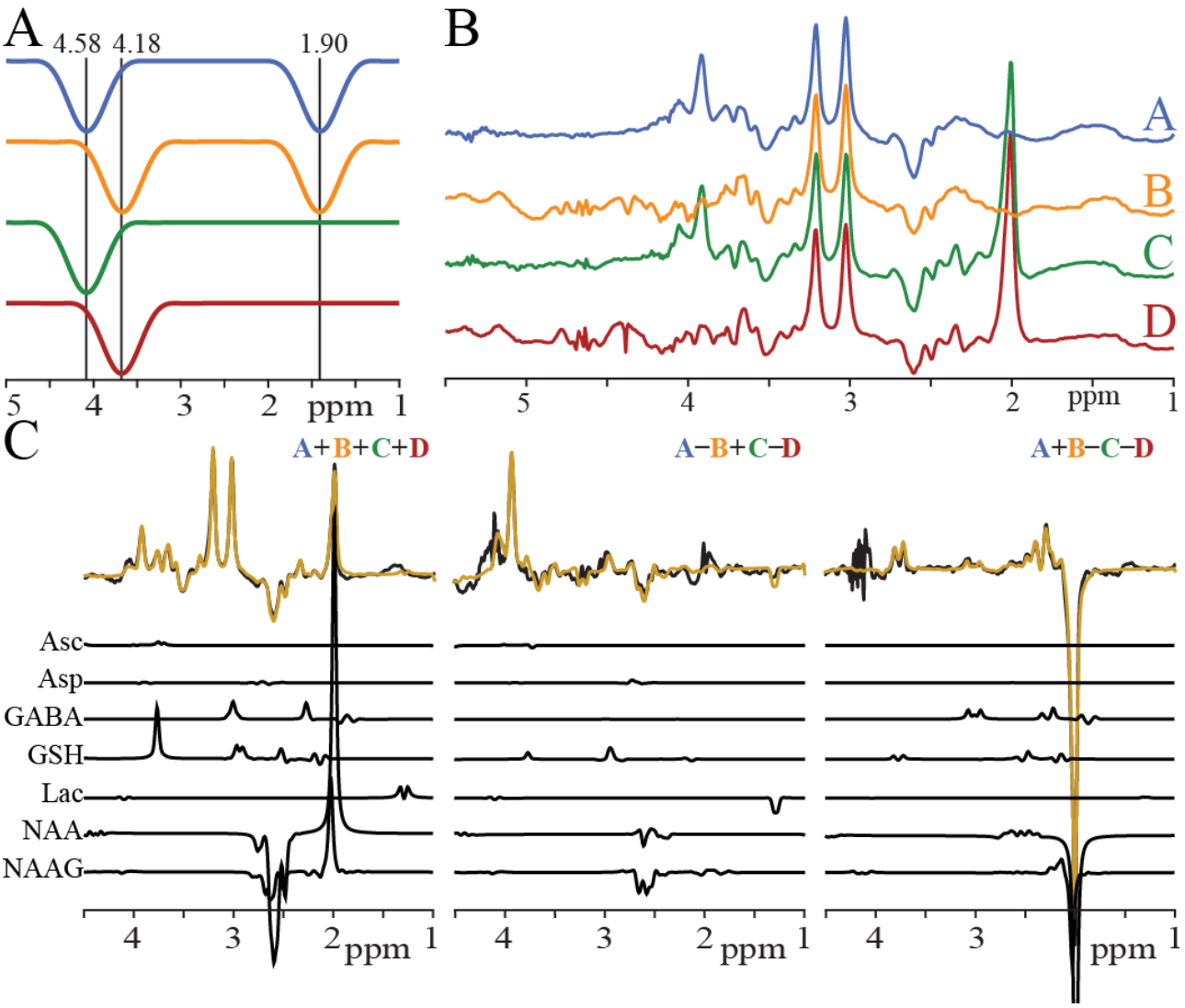

Figure 5: (A) The HERCULES spectral editing scheme (using the pulse sequence of Figure 4). Four scans (A, B, C, D) are recorded with editing pulses applied at different frequencies (A at 4.58 ppm and 1.90 ppm, B at 4.18 ppm and 1.90 ppm, C at 4.58 ppm only, D at 4.18 ppm only). **(B)** HERCULES A, B, C and D spectra are shown from the occipital lobe of normal human brain at 3T (TR 2s, TE 68 s, 27 cm^3, scan time ~10 min), **(C)** Hadamard combinations of the 4 subspectra, showing signals, including Asc, Asp, GABA, GSH, Lac, NAA and NAAG, which can be quantified by simultaneous spectral modeling.

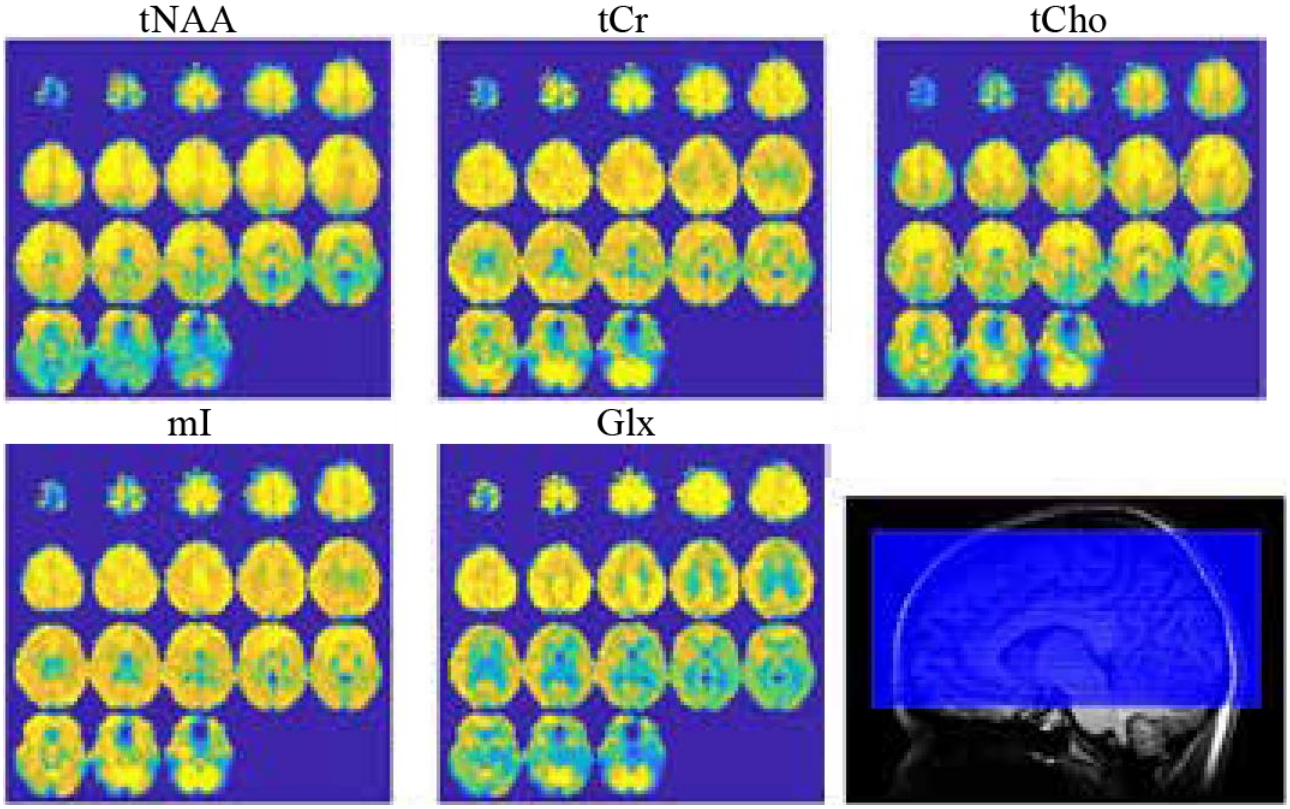

Figure 6: Metabolic images generated from CS/LR reconstruction of SENSE accelerated 3D FID-MRSI data measured in a healthy volunteer at 3T. 5 mm isotropic spatial resolution was obtained in 20 min scan time with an acceleration factor of 3.5. Maps of tNAA, tCr, tCho, mI, and Glx are shown. The sagittal T_1-weighted image (bottom right) shows the location of the excitation slab (blue overlay). Adapted with permission from Klauser et al., 2022 [94].

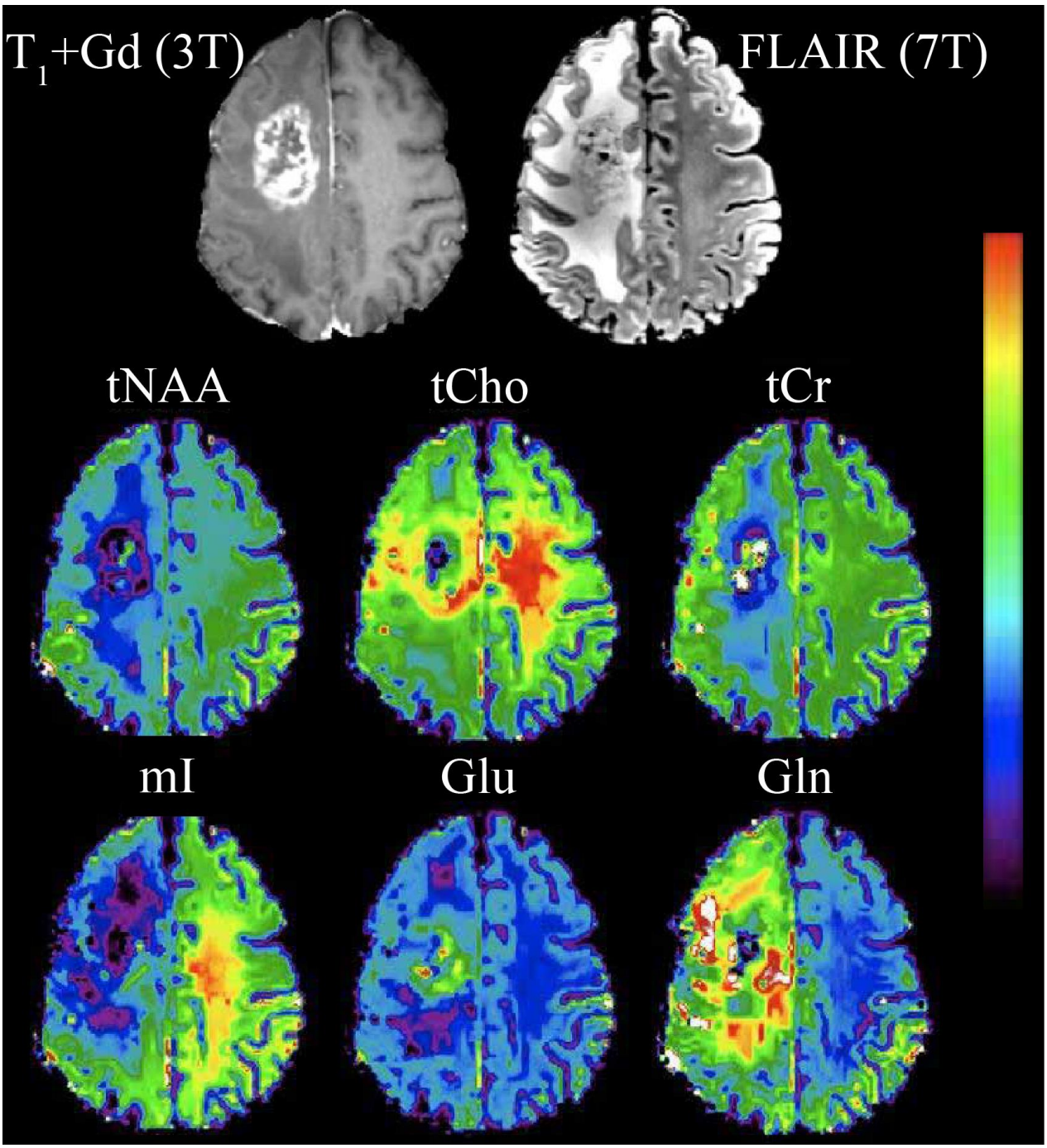

Figure 7: An example of 7T MRSI in a patient with a recurrent diffuse grade II astrocytoma in the right frontal lobe. In this single slice acquisition, voxel size was 3.4 × 3.4 × 8 mm^3 and scan time ~12 minutes. The top row shows anatomical T_1-weighted images post-gadolinium and FLAIR MRI. The middle row shows images of total NAA, choline and creatine, while the bottom row shows images of *myo*-inositol, glutamate and glutamine. The tumor and surrounding edematous regions show decreased tNAA, and well as increased tCho (typical for tumor regrowth) in a ring-like distribution around the enhancing region. Gln is also elevated in the right hemisphere. Interestingly tCho and mI appear mildly elevated in the left frontal lobe which may indicate tumor infiltration, even though this is not depicted on the anatomical MRI scans. Adapted with permission from Hangel et al., 2019 [99].

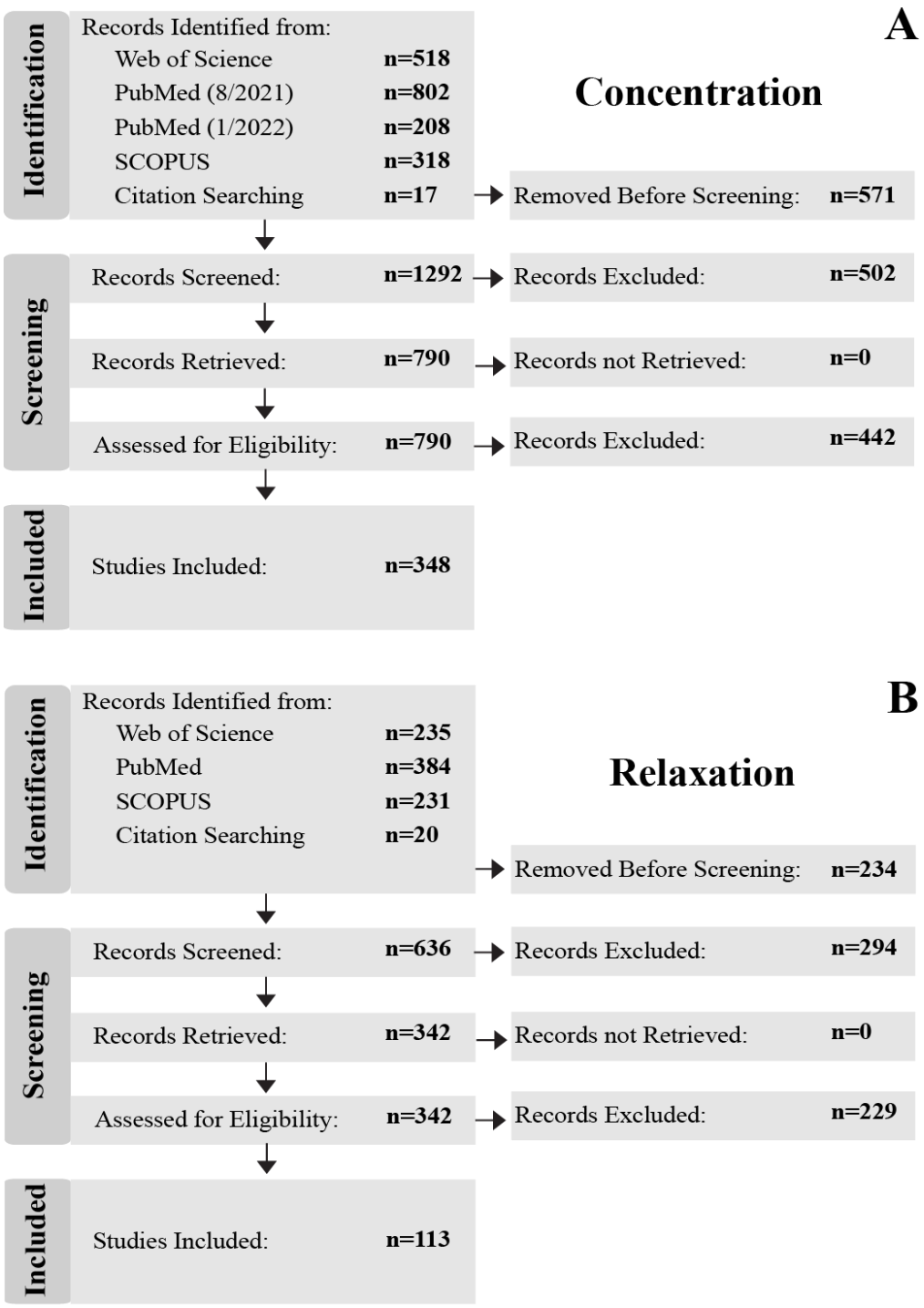

Figure 8: PRISMA flow charts that show the database selection and inclusion process of the **(A)** concentration and **(B)** T_2 relaxation publications.

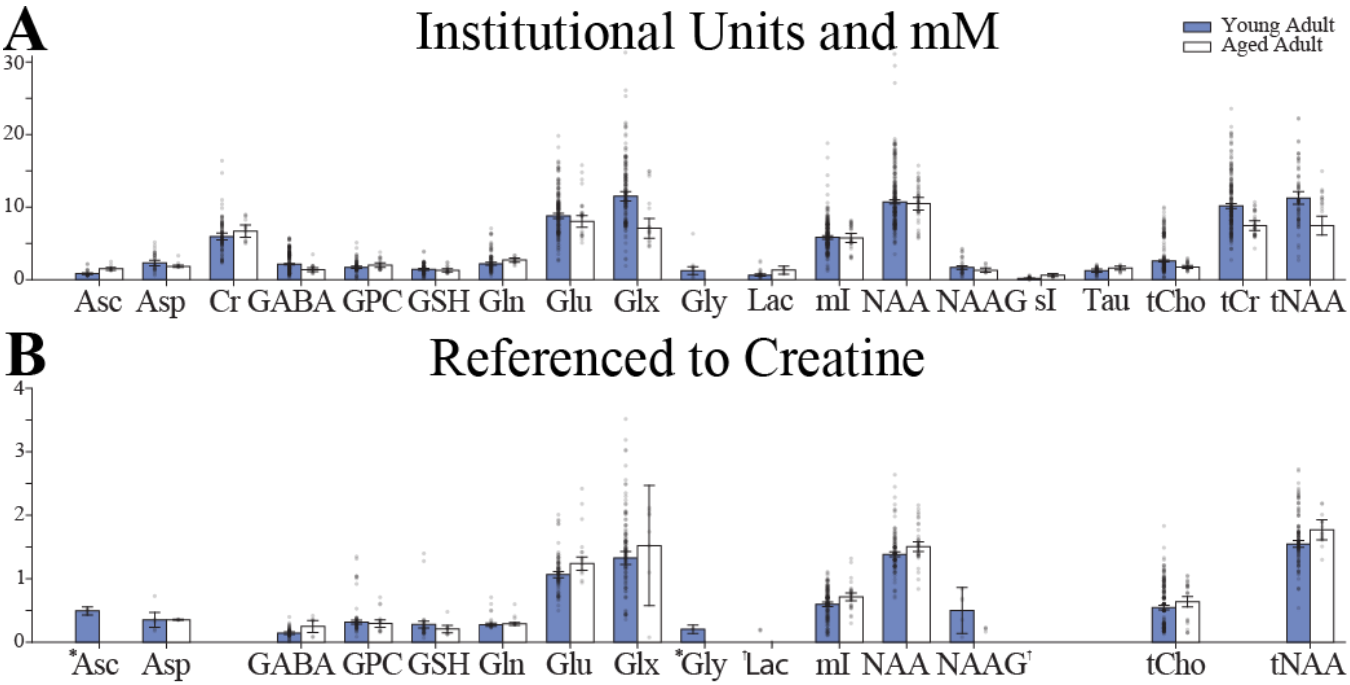

Figure 9: Brain metabolite concentrations in younger (18-45 years, in blue) and older (>50 years, in white) healthy adults from studies that reported results as: **(A)** Molar, molal, and Institutional Units; **(B)** Creatine-referenced. An * indicates the use of a Fixed Effects Model rather than a Random Effects Model. A † indicates a combined effects model was not defined.

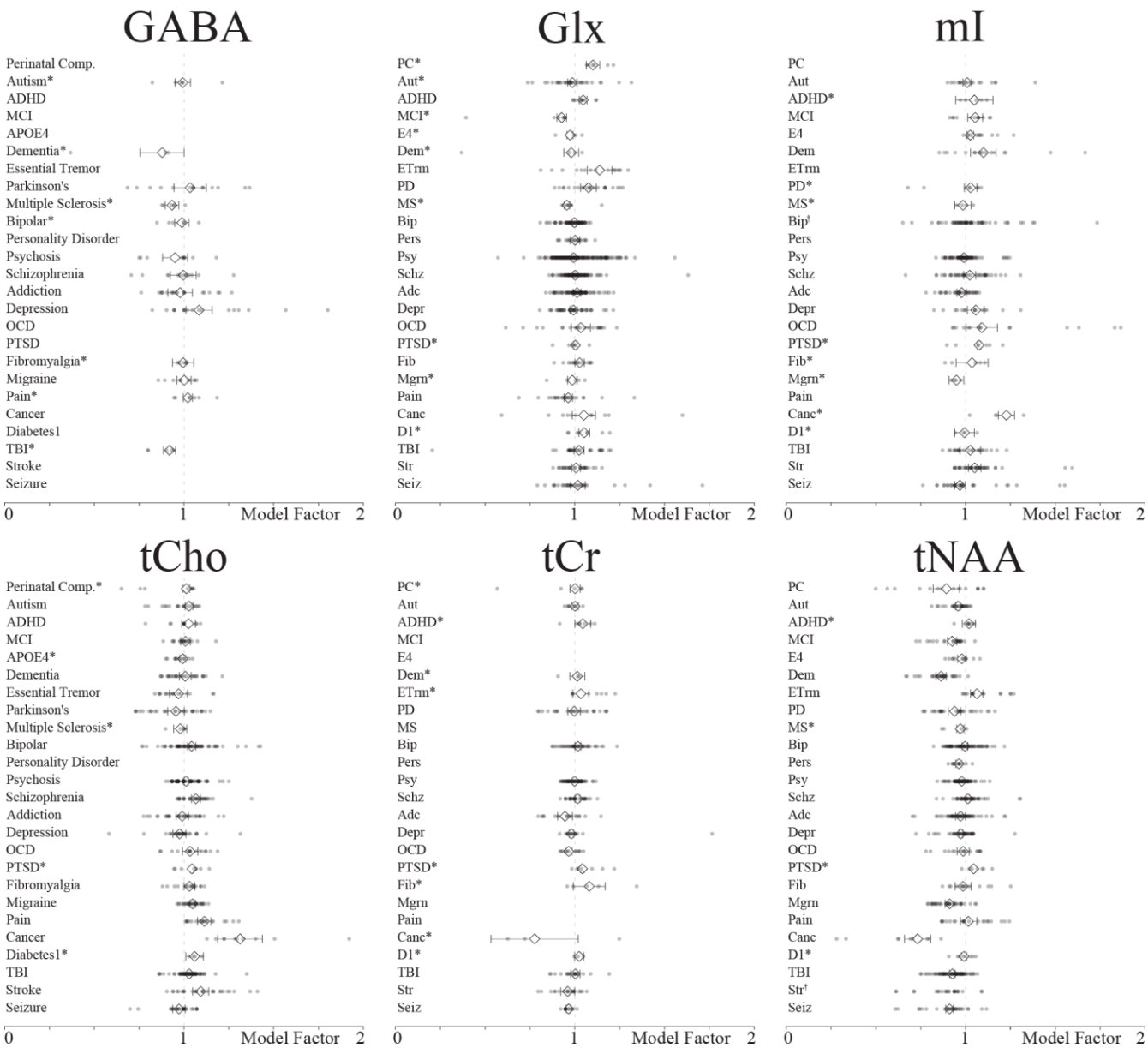

Figure 10: Commonly investigated metabolite concentrations modeled in diseased populations. Data from metabolite and metabolite complexes are combined (e.g., Cre and tCr, Glu and Glx). An * by the group classification indicates the use of a Fixed Effects Model rather than a Random Effects Model. A † 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.

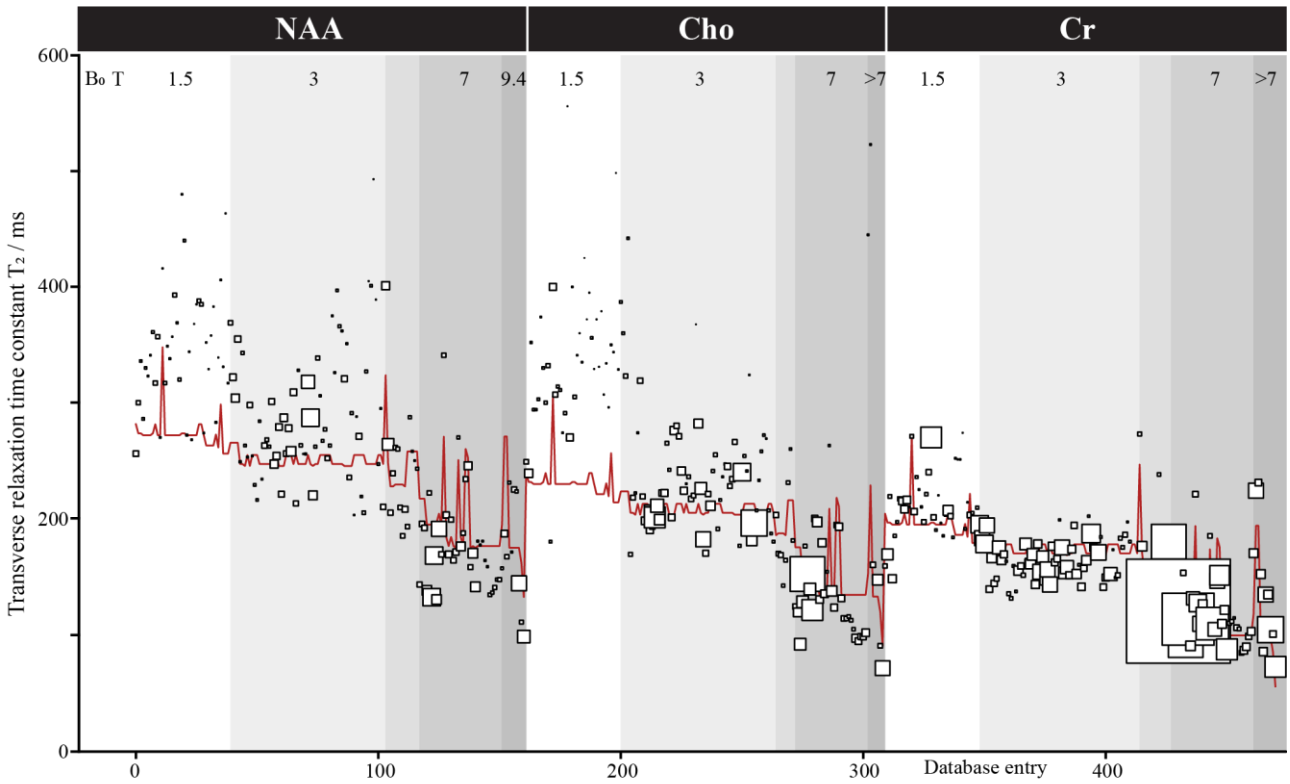

Figure 11: Transverse relaxation time meta-analysis. Only results for NAA, Cho, and Cr are shown for ease of visualization, but a total of 629 values for 14 metabolites were included in the database and modeled. Metabolite, field strength, localization, T_2 filter, species, and tissue type were included 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.

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 Averages
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.