

Quantification of edited magnetic resonance spectroscopy: a comparative phantom based study of analysis methods

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Synopsis

A calibrated series of MRS phantoms is used to compare the performance of common spectroscopy analysis tools in the quantification of GABA-edited spectroscopy data. Varied GABA concentration, and simulated spectra provide a ground truth with which to compare.

Introduction

Quantification of metabolites and neurotransmitters has a wide range of applications in neuroscience. Gamma-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system, maintaining the excitation–inhibition balance¹. Its prominent role in both neurotransmission and metabolism has led to extensive study, and a plethora of potential applications for its detection. These include: schizophrenia^{2,3}, epilepsy^{4,5}, diabetes⁶, autism spectrum disorders⁷, anxiety disorders^{8,9}, and depression¹⁰. However, quantifying GABA is challenging: it exists in the brain in mMolar concentrations, and relatively stronger signals, such as NAA, and creatine, will overlap with, and obscure the GABA signal. Spectral editing techniques such as MEGA-PRESS¹¹ simplify the spectrum significantly, but the decomposition of this spectrum remains a non-trivial task. Several software packages have been developed to address this problem, but differences between model basis sets, fitting algorithms and pre-processing of the data gives rise to discrepancy in the reported concentrations. The goal of this study is to assess the robustness of GABA quantification using a calibrated phantom study. While phantoms have inevitable limitations, the establishment of a “ground truth” concentration allows a far more meaningful comparison of results.

Methods

Several series of phantom data sets were created. The first involved pH adjusted liquid metabolite solutions at room temperature. Starting with fixed concentrations of NAA and Creatine, the amount of GABA in the solutions was incrementally increased. Other series were performed similarly but with additional metabolites such as glutamine and glutamate, increasing the complexity of the spectra. Finally, a series of gel phantoms with varying concentrations of several key metabolites NAA, Cre, Glu, Gln and GABA were prepared. Each phantom was scanned on a 3T Siemens Magnetom using the Siemens MEGAPRESS protocol. A 20x20x20mm voxel was selected at isocentre. The sequence parameters were: TR=2000ms, TE=68ms, 160 averages and a 1250Hz receive bandwidth was used to acquire 2048 complex data points. The spectra acquired were analysed with in-house software and several commonly available quantification tools including TARQUIN^{12,13}, JMRUI^{14,15}, LCModel^{16,17}, VeSPA¹⁸, and GANNET¹⁹. As a specific figure of merit the ratio of GABA to NAA was calculated, plotted against the actual concentration ratios for the phantom data series and linear fits were performed. The quantification routines were also tested against simulated spectra generated using FID-A²⁰, and in-house code.

Results

Significant differences in the GABA/NAA ratios reported by different tools were observed. In addition to differences in the values reported for individual spectra, there were also differences in the linearity of the reported vs actual GABA/NAA ratios and quality-of-fit. LCM results showed a tendency to underestimate the relative concentrations of GABA, while Tarquin tended to overestimate it. Gannet also tended to underestimate GABA, and more significantly than LCM. All of the quantification tools performed significantly better for pH adjusted liquid metabolite solutions than for tissue-mimicking gel phantoms. Tests on simulated spectra suggest that the underestimation of GABA may be the result of imperfect editing of GABA over the entire voxel volume for realistic editing and refocusing pulses. For spectra generated using realistic editing pulses but ideal refocusing pulses, the quantification was extremely accurate, but when more realistic refocusing pulses were used, GABA/NAA ratios were underestimated by at least 20% on average, which is slightly better than the experimental results for both our in house software and LCM results, which suggest underestimation of at least 30-40%

Discussion

Significant differences in the concentration ratios reported by different tools when supplied with identical input spectra, and significant discrepancies between reported ratios and actual ratios suggest that more work is necessary to ensure accurate and robust quantification. The tools investigated differ in many ways ranging from differences in the basis sets used, to differences pre-processing and fitting algorithms. More work is needed to elucidate the origins of the differences. From our in house analysis, we found that extensive pre-processing was often detrimental, and that the most accurate and robust results were achieved with a simple numerical peak-area-integration algorithm and minimal pre-processing. The numerical integration outperformed model-based peak fitting routines in terms of consistency and accuracy of the results. Simulations suggest that the observed underestimation of GABA is likely attributable to non-uniform editing efficiency, which may be reduced by newer sequences such as MEGA-sLASER.

Conclusion

More work is required to elucidate the origin of differences observed. Larger phantom studies using different hardware and sequence implementations are desirable as well as systematic comparison of quantification results obtained for in-vivo spectra.

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Figures

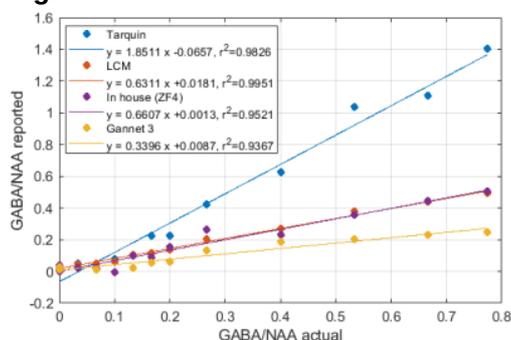


Fig.1: Reported GABA/NAA concentration ratios and linear fits for different tools for a series of liquid metabolite solutions with fixed concentration of NAA (15mM) and CR (8mM) and increasing concentrations of GABA (0–11.6mM). A slope greater than 1 indicates systematic overestimation for Tarquin, while a slope less than 1 indicates underestimation, which appears to be dominant for all other tools. All tools achieve reasonable quality-of-fit with R^2 values ranging from 0.93 (Gannet) to 0.99 (LCM).

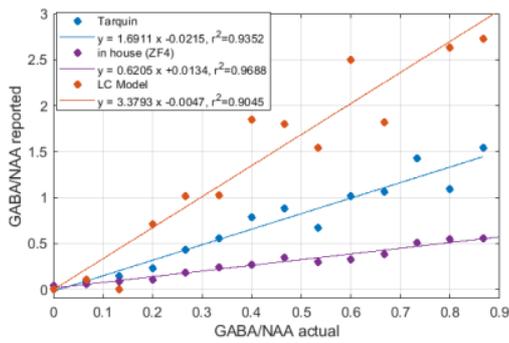


Fig.2: Reported GABA/NAA concentration ratios and linear fits of reported vs actual ratios for different tools for a series of liquid metabolite solutions with fixed concentration of NAA (15mM), Creatine (8mm), Glutamate (12mM), Glutamine (3mM) and increasing concentration of GABA (0--14mM).The increased complexity of the spectra results in reduced R^2 and more scatter in the data points for both Tarquin and LCM, and more pronounced overestimation of GABA, while the quality-of-fit and accuracy of the estimation for our in-house method based on numerical peak integration is virtually unchanged compared to the simple NAA/Cr/GABA series in Fig 1.

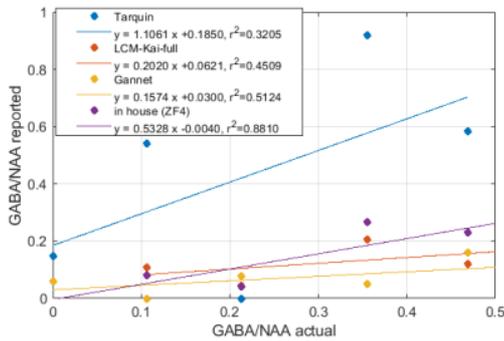


Fig.3: Reported GABA/NAA concentration ratios and linear fits for different tools for a series of 1% agar gel phantoms with varying concentrations of NAA, Creatine, Glutamate and Glutamine and GABA that were warmed to body temperature in a water bath prior to being scanned. Notice the much lower R^2 values for all methods and more significant underestimation of GABA. Again, surprisingly, our in house method achieves the highest R^2 and least underestimation.

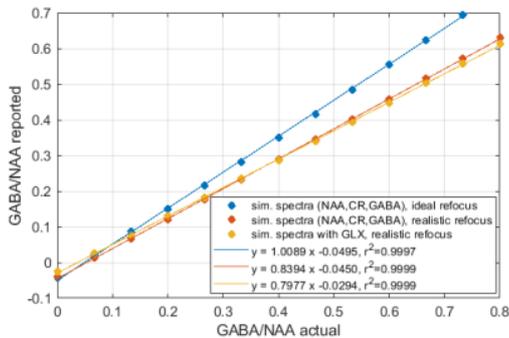


Fig.4: Reported GABA/NAA concentration ratios and linear fits (in house method) for three series of simulated spectra with ideal (Series 1) and realistic (Series 2,3) refocusing pulses, respectively. Series 1 and 2 simulated fixed concentrations of NAA (15mM), Creatine (8mM) and varying concentrations of GABA, while for series 3 Glutamate (12mM) and Glutamine (3mM) were added.

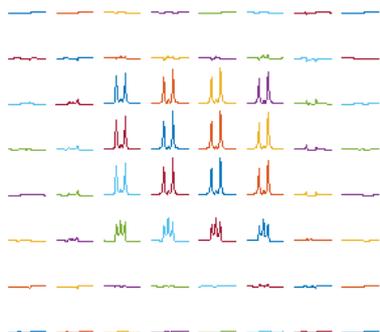


Fig.5: Spatially resolved simulated MEGAPRESS spectra show that the efficiency of the editing pulse is non-uniform and editing is poor in some boundary regions, which may explain underestimation of GABA.