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Soher, Brian J.; Clarke, William T.; Wilson, Martin; Near, Jamie; Oeltzschner, Georg

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Community-organized Resources for Reproducible MRS Data Analysis

Brian J. Soher¹, William T. Clarke^{2,3}, Martin Wilson⁴, Jamie Near⁵, Georg Oeltzschner^{6,7}

¹Department of Radiology, Duke University Medical Center, Durham, NC, United States

² MRC Brain Network Dynamics Unit, University of Oxford, Oxford, UK

³ Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

⁴ Centre for Human Brain Health and School of Psychology, University of Birmingham, Birmingham, UK

⁵ Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

⁶ Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, United States

⁷ F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States

All authors contributed equally to this letter.

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Corresponding author:

Georg Oeltzschner, PhD

Russell H. Morgan Department of Radiology and Radiological Science

600 N Wolfe St, Park 367H, Baltimore MD 21287

410-614-3431; goeltzs1@jh.edu

In 2021, the de-facto gold-standard *in-vivo* magnetic resonance spectroscopy (MRS) analysis software, LCModel¹, transitioned from proprietary/paid to an open-source/free model. For 29 years, this software has fulfilled the demand for robust analysis workflows, while at the same time restricting access and dissuading continued development. We argue that this moment represents a golden opportunity for MRS developers and users to transition towards collaborative community-sourced workflows and datasets.

NMR spectroscopy preceded MR medical imaging by decades and offers unique potential to noninvasively extract biochemical information. However, the clinical impact of in-vivo MRS is modest compared to functional, diffusion, perfusion, or magnetization transfer imaging. One particular reason is comparably low replicability and comparability of metabolite estimates across MRS groups, which is exacerbated by heterogeneous analysis approaches and poor validation^{2–5}. This hardly comes as a surprise, as MRS spans several highly specialized sub-fields (X-nuclei, spectral editing, spectroscopic imaging), all operating under low-signal-to-noise conditions relative to conventional MRI. Like any inherently quantitative technique, MRS estimates depend on decisions made during preprocessing, modeling, and quantification^{2,3}. Historically, MRS groups tend to use local data analysis infrastructure, often matured over years of research. However, local operational continuity comes at the expense of comparability, reproducibility and repeatability of metabolite estimates across sites, vendor ecosystems, and software environments. Expert consensus recommendations on data acquisition^{6–8}, processing and modeling⁹, macromolecule handling¹⁰, nomenclature¹¹, and reporting¹² have recently been published, recognizing the need for methodological harmonization. These recommendations need to be widely adopted. But shifting established lab-specific workflows to consensus practices requires effort with little incentive (or funding) to individual labs.

We propose a more efficient way of implementing consensus: pooling resources to create communityorganized deliverables like software tools, databases, continued support, and educational material. This paradigm is applicable for single-voxel MRS (where substantial consensus exists), and can serve as a template for spectroscopic imaging, which is methodologically more diverse and consensus formation is less mature. There is precedent in the magnetic resonance community: the fMRI field has been able to build around collaborative open-source platforms (AFNI¹³, SPM¹⁴, FSL¹⁵) from its earliest days. This allowed the community and software developers to identify weaknesses, integrate new methods into mainstream workflows, and boost standardization.

As consensus recommendations emerge, a shift in the MRS field towards community organization has already occurred. Four authors of this article served as inaugural members of the Code & Data Sharing Committee of the ISMRM MR Spectroscopy Study Group, creating community resources and efforts to harmonize spectroscopic data storage into the NIfTI-MRS format¹⁶ and a BIDS¹⁷ MRS extension proposal. Open-source end-to-end analysis software^{18–22} has emerged for a variety of environments (Python, MATLAB, and R), including modular consensus-based preprocessing routines and customizable linear-combination-modeling algorithms. The coalescence of these initiatives occurred at an auspicious moment: the transition of the LCModel software to open-source and free availability.

We challenge the community to look upon this convergence of events as an opportunity for MRS developers and users alike to transition towards community-organized resource building. The ultimate endpoint is an ecosystem of interoperable analysis tools and datasets, created and maintained through community projects and connected by standardized data storage specifications. This will:

- encourage consensus adoption,
- facilitate development and validation of new MRS methods,
- accelerate integration into mainstream usage,
- offer long-term accessibility and maintenance,
- reduce duplicate efforts.

This new generation of analysis software and harmonized data storage can evolve continuously to disseminate consensus, distribute new methods, safeguard accessibility and longevity, and promote critical evaluation. In tandem with increasingly "open data" (in-vivo and synthetic-realistic), validation and benchmarking will become easier and more accessible, providing training and validation data for emerging neural-network-based approaches as a welcome side effect. Importantly, new methods encoding additional information into an MRS acquisition are maturing, for example diffusion-weighted^{23–25}, functional^{26,27}, and multi-parametric MRS²⁸, unlocking access to cell-type-specific microstructure, dynamic metabolism, and individual relaxometry. This new generation of experiments needs a new, innovative generation of multi-spectrum tools, allowing to incorporate physical relationships between spectra and break the barriers of traditional single-spectrum modeling.

The enduring popularity of the LCModel application is proof that the MRS field demands wellstructured analysis methods. Its transition to open-source paves the way for collective resource building in the MRS field. The MRSHub (<u>https://www.mrshub.org</u>) is a free online gathering place for the MRS community to share resources and contribute solutions. We call upon MRS developers to contribute their new methods into this community ecosystem that increases availability and accelerates uptake and validation. We encourage MRS users to take advantage of the modular, consensus-based, open-source pipelines in MRSHub to drive access to reproducible state-of-the-art analysis. This approach will improve access to advanced methods for users at a broader range of institutions and foster adoption of consensus recommendations by researchers and scanner manufacturers alike, ultimately removing barriers to the adoption of MRS in the clinic.

- Provencher, S. W. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn. Reson. Med.* 30, 672–9 (1993).
- Marjańska, M., Deelchand, D. K., Kreis, R. & Team, the 2016 I. M. S. G. F. C. Results and interpretation of a fitting challenge for MR spectroscopy set up by the MRS study group of ISMRM. *Magn. Reson. Med.* 87, 11–32 (2022).
- 3. Marjańska, M. & Terpstra, M. Influence of fitting approaches in LCModel on MRS quantification focusing on age-specific macromolecules and the spline baseline. *NMR Biomed.* **34**, e4197 (2021).
- 4. Zöllner, H. J. *et al.* Comparison of different linear-combination modeling algorithms for short-TE proton spectra. *NMR Biomed.* **34**, e4482 (2021).
- 5. Craven, A. R. *et al.* Comparison of seven modelling algorithms for γ-aminobutyric acid–edited proton magnetic resonance spectroscopy. *NMR Biomed.* e4702 (2022) doi:10.1002/nbm.4702.
- Wilson, M. *et al.* Methodological consensus on clinical proton MRS of the brain: Review and recommendations. *Magn. Reson. Med.* 82, 527–550 (2019).
- Öz, G. *et al.* Advanced single voxel 1H magnetic resonance spectroscopy techniques in humans: Experts' consensus recommendations. *NMR Biomed.* n/a, e4236.
- Deelchand, D. K. *et al.* Across-vendor standardization of semi-LASER for single-voxel MRS at 3T. *NMR Biomed.* n/a, e4218 (2019).
- 9. Near, J. *et al.* Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: experts' consensus recommendations. *NMR Biomed.* **n**/**a**, e4257.

- Cudalbu, C. *et al.* Contribution of macromolecules to brain 1H MR spectra: Experts' consensus recommendations. *NMR Biomed.* 34, e4393 (2021).
- Kreis, R. *et al.* Terminology and concepts for the characterization of in vivo MR spectroscopy methods and MR spectra: Background and experts' consensus recommendations. *NMR Biomed.* n/a, e4347.
- Lin, A. *et al.* Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations. *NMR Biomed.* 34, e4484 (2021).
- Cox, R. W. AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Comput. Biomed. Res.* 29, 162–173 (1996).
- 14. Friston, K. J. *Statistical parametric mapping the analysis of funtional brain images.* (Elsevier/Academic Press, 2007).
- Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W. & Smith, S. M. FSL. *NeuroImage* 62, 782–790 (2012).
- Clarke, W. T. *et al. NIfTI-MRS: A standard format for magnetic resonance spectroscopic data*. 2021.11.09.467912 https://www.biorxiv.org/content/10.1101/2021.11.09.467912v1 (2021) doi:10.1101/2021.11.09.467912.
- 17. Gorgolewski, K. J. *et al.* The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. *Sci. Data* **3**, 160044 (2016).
- Simpson, R., Devenyi, G. A., Jezzard, P., Hennessy, T. J. & Near, J. Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. *Magn. Reson. Med.* 77, 23–33 (2017).
- Clarke, W. T., Stagg, C. J. & Jbabdi, S. FSL-MRS: An end-to-end spectroscopy analysis package. Magn. Reson. Med. 85, 2950–2964 (2021).
- 20. Oeltzschner, G. *et al.* Osprey: Open-source processing, reconstruction & estimation of magnetic resonance spectroscopy data. *J. Neurosci. Methods* **343**, 108827 (2020).

- Soher, B. J., Semanchuk, P., Todd, D., Steinberg, J. & Young, K. VeSPA: integrated applications for RF pulse design, spectral simulation and MRS data analysis. in *Proc Int Soc Magn Reson Med* vol. 19 1410 (2011).
- Wilson, M. spant: An R package for magnetic resonance spectroscopy analysis. J. Open Source Softw. 6, 3646 (2021).
- Posse, S., Cuenod, C. A. & Le Bihan, D. Human brain: proton diffusion MR spectroscopy. *Radiology* 188, 719–725 (1993).
- Palombo, M., Shemesh, N., Ronen, I. & Valette, J. Insights into brain microstructure from in vivo DW-MRS. *NeuroImage* 182, 97–116 (2018).
- 25. Deelchand, D. K., Auerbach, E. J. & Marjańska, M. Apparent diffusion coefficients of the five major metabolites measured in the human brain in vivo at 3T. *Magn. Reson. Med.* **79**, 2896–2901 (2018).
- Mullins, P. G. Towards a theory of functional magnetic resonance spectroscopy (fMRS): A metaanalysis and discussion of using MRS to measure changes in neurotransmitters in real time. *Scand. J. Psychol.* 59, 91–103 (2018).
- Bednařík, P. *et al.* Neurochemical and BOLD Responses during Neuronal Activation Measured in the Human Visual Cortex at 7 Tesla. *J. Cereb. Blood Flow Metab.* 35, 601–610 (2015).
- Kulpanovich, A. & Tal, A. The application of magnetic resonance fingerprinting to single voxel proton spectroscopy. *NMR Biomed.* 31, e4001 (2018).