MRSI consensus

Q. Given that online processing/analysis is still poorly implemented even for single-voxel spectroscopy, how likely are vendors to implement these recommendations for integration on clinical scanners? Do you think the prospect of nice metabolite maps could finally lead to investment in this?

A. Just showing nice metabolite maps will not be sufficient to get the manufacturers to put in the engineering effort, the research community also needs to demonstrate clinical efficacy.

[B.J.S.] To get manufacturer investment, you have to look at their point of view, which is return on investment. They want to see a 'product' that they can sell for some reasonable profit. If we can show one or a few clinical uses that 1) clinicians want, and 2) are reimbursable (thus OK by the hospital where clinicians work), and 3) can be sold to many (100s – 1000s) of sites (as opposed to 10-20 only), then manufacturers will 'invest' in making our method work at a product level. Mind you, they may not use the full featured development MRS(I) method that piloted this product. They might instead use a very tightly focused version of the method that is more robust in a clinical MR environment.

[O.C.A.] There is larger demand for in vivo metabolic imaging from specialists outside the Radiology departments (neurologists, neuro-oncologists, neurosurgeons, psychiatrists). These specialists are the end-users of this information and if they like it they will push the radiologists to perform these measurements, and in turn the radiologists will push the manufacturers.

[S.P.] As discussed, vendor implementation is based on return on investment. If MRSI remains difficult to use, unreliable and clinical value remains limited, the enthusiasm for implementation remains low. If MRSI remains difficult to use and clinical value is shown for a specific application, enthusiasm for implementation will be high. If MRSI becomes easy to use and reliable, but clinical value remains limited, the enthusiasm for implementation will still increase as it leverages clinical studies in pursuit of showing significance. I suggest that we invest in both showing clinical utility and technical development with a focus on reliability.

Q. should we invest in mapping QC parameters along with quantified metabolite maps as well (for clinical use)? Or should be remove data with poor QC parameters in the map and put the value to 0?

A. In the paper we recommend both. For clinician review, however, they are not going to spend the time looking at quality maps, so we recommended removing the poor quality voxels, while still keeping the spectra to allow for a more detailed evaluation.

[O.C.A.] Another approach is to remove bad voxels and replace their values not with zero, but with values that are calculated based on the surrounding voxels. This can work if only isolated or a small cluster of voxels has low quality.

[S.P.] Both options should be provided as more experienced users will reexamine poor data to extract information.

Q. QC- we should just look at metabolites or also at the water signals? What criteria, what parameters?

and

Q. Any minimum criteria to be reported for quality?

A. This topic is also discussed in the paper, with the water linewidth being suggested as a measure for studies of lesions where there may be a loss of all (detected) metabolites. Specific quality criteria were not provided beyond stating that those metabolite measures typically used for single voxel MRS equally apply. However, we also acknowledge that this remains an area where better analysis methods and standardized criteria are needed.

Q. Do radiologists need specialized training for MRSI to get accepted in the clinical workflow?

A. While this question was not considered in the paper a general opinion seems to be that high-resolution metabolite images are readily accepted by clinicians but that some training would be of benefit, mainly to recognize the many artifacts that can occur. There is undoubtedly further training needed for the more sophisticated MRS measurements (e.g. 2HG, GABA…). If we can implement the quality improvements suggested and robust quality evaluation, the concerns over artifacts should diminish.

[S.P.] MRSI will gain greater acceptance if it can be integrated without specialized training. It should be read like a PET scan.

Q. What are the suggested methods for harmonization of MRS data across study sites?

A.

[W.B.] I am not 100% sure if I understand correctly ... which method we should harmonize or how we should harmonize? Assuming that it is the first one I would suggest some whole-brain MRSI or at least 3D-MRSI protocol with slab selection (no boxes or single slices), but somewhat reduced brain coverage to make shimming easier.[B.J.S.] I agree that the topic “harmonization” is very broad. If we want to talk about just hardware/acquisition, the SVS community (Oz, Deelchand, etc.) have shown that if an MRS sequence is written/run with the exact same gradients, rf, and timings for GE, Philips, Siemens, then the resultant spectra are quite consistent and repeatable across vendors and longitudinally. This should also be a primary goal for the MRSI community, whatever sequences the MRSI community pushes forward for acceptance. Practically, this will encourage use of MRSI in multi-site, cross-vendor clinical trials, and it will make creating and analyzing repositories of shared MRS data easier to compare.

As for processing, some publications have shown that results differ for the same data run on different software packages and even on the same package for different settings and constraints. The best way to minimize variability due to software is to use the same software and settings for an entire cohort. I don’t know how to get different sites to do this generally, but on a project by project basis it could be specified.

[O.C.A.] A bottleneck for harmonization of MRSI is reconstruction. It will be hard to harmonize with off-line reconstruction based on Matlab. If reconstruction is better integrated with the scanners there will be easier to do harmonization.

I think Andrew has this nice paper with multi-vendor implementation of EPSI which is a step in the direction of harmonization,

Sabati, M., S. Sheriff, M. Gu, J. Wei, H. Zhu, P. B. Barker, D. M. Spielman, J. R. Alger and A. A. Maudsley (2015). "Multivendor implementation and comparison of volumetric whole-brain echo-planar MR spectroscopic imaging." Magn Reson Med **74**(5): 1209-1220.

[S.P.] This paper also shows that there are vendor-specific constraints for implementing echo-planar gradient waveforms and ADC objects. My own experience with different vendors shows that differences in gradient duty cycle and gradient waveform handling (e.g. gradient memory limitations) can be a challenge. While the SVS harmonization efforts have been primarily limited by maximum B1, MRSI has more constraints.

LCModel and related approaches have become somewhat of a standard for spectral quantification for SVS. For MRSI the major constraint is processing time. However, it should be possible to find common grounds on minimum requirements for model-based fitting as described in the excellent consensus paper on SVS analysis.

[D.S.] We had to deal with the issue of data 'harmonization' in the context of a two-site study with a 3T GE at one site (NYC) and a 3T Siemens at another (Mexico City). Although the data were to be acquired using SV MEGA-PRES, the approach would be just as relevant for MRSI. We started by accepting that what was stated above is true even for MRSI, namely that

> "*If we want to talk about just hardware/acquisition, the SVS community (Oz, Deelchand, etc.) have shown that if an MRS sequence is written/run with the exact same gradients, rf, and timings for GE, Philips, Siemens, then the resultant spectra are quite consistent and repeatable across vendors and longitudinally*."

Then we considered how to ensure the comparability of the heterogeneous data in practice. This required consistent signal intensity normalization. So, what we did what to make a large 10 mM aqueous solution of NAA that we put into two identical plastic bottles and sealed for running monthly at each site for QA/QC. The study is still ongoing, but we plan at some point to take the same 4 healthy individuals and scan them on the two instruments. Finally, we settled on using internal water for intensity normalization, and to use the same post-processing software to process the spectra and fit the peaks of interest. With that approach, we believe that we will have identical pairs of that from the two instruments that would enable us to derive "calibration factors" by which spectral intensity or areas from one scanner can corrected by to make them numerically comparable with those from the other scanner. We'll know in about two years if this "harmonization" is any good.

Q. Can we discuss the top choices for clinical applications?

A. The paper reviews clinical applications where a) the spatial information of MRSI is of value and b) the metabolic information can reveal abnormalities not necessarily visible by structural MRI. As for single voxel MRS, brain cancer is considered an important application area, for diagnosis and treatment planning and monitoring. The other areas discussed are epilepsy, TBI, MS, and mitochondrial disorders, while more specialized sites or research studies could include psychiatric disorders, pain disorders and neurodegenerative diseases.

Q. What are the recommendations for MRS in 1.5 T

A. Sorry, but our paper was strongly focused on 3T and higher. The underlying reason is that we considered methods that can produce metabolite images of sufficient spatial resolution

for the results to be considered as a “MRI” modality, meaning that detection sensitivity is an important consideration.

[S.P.] We should address the feasibility of MRSI at 1.5T, at least for the major singlets, lactate and lipids.

Q. I wonder about your 5mm isotropic in 10min at 3T. Even for NAA/Crn/Cho that's pretty challenging.

A. I agree these numbers are challenging with conventional MRSI methods, but with the use of constrained reconstructions this should be achievable. For example, see the papers on SPICE (ZP Liang et al.).

[W.B.] There are papers where this scale of resolution has been reported:

(4.4x4.4x6 in ~5min at 3T)Moser P, et al. Magn Reson Med. 2020 Jun;83(6):1920-1929 ... but this is indeed Hamming-weighted

(2.6x2.6x3 in ~5min at 3T) Lam F et al. Magn Reson Med. 2020 Feb;83(2):377-390 ... but I am not sure how this is smoothed (difficult to say with the imposed regularization)

[O.C.A.] I think the Spice developers are the only ones that showed smaller than 5x5x5 mm3 in under 10 mins. These results need to be reproduced by other groups, but assuming that Low Rank can help improve the SNR for recon of fast high res data backing up from 2.6x2.6x3 in 5 mins to 5x5x5 mm3 in 10 mins should be feasible. I think NAA/Cho/Cr should be possible, maybe Glx/Ins will be borderline.

[S.P.] I think that Spice needs further validation. For example, by simulating data where the MRI provides no spatial support for reconstructing MRSI data. Also, sensitivity to B0 inhomogeneity needs to be investigated. In my lab, we acquire 3D PEPSI with 0.34 cc nominal voxel size in 3 min at 3T using elliptical sampling in ky and kz, and Hamming k-space filters. One parameter that is not harmonized across studies is the spectroscopic readout duration. As Provencher pointed out, truncating the readout biases the quantification. It is not clear to me how much SNR is gained using FID vs short TE MRSI and perhaps I missed a study that published a direct comparison. Possible differences are due to inefficiencies of the refocusing RF pulse and signal saturation in multi-pulse sequences. These can be mitigated.

Q. Perhaps an intermediate goal should be optimizing methods for deployment in multicentre clinical trials, which would somewhat more controlled and tractable than the clinical domain?

[W.B.] I agree that this is the logical next step. Only with such - successful - multi-site (not necessarily multi-vendor) studies one can really attract attention by clinicians and make real pressure on vendors.

[O.C.A.] I think Andrew has this nice paper with multi-vendor implementation of EPSI. For large multi-center studies would need multi-vendor implementation and participation.

Sabati, M., S. Sheriff, M. Gu, J. Wei, H. Zhu, P. B. Barker, D. M. Spielman, J. R. Alger and A. A. Maudsley (2015). "Multivendor implementation and comparison of volumetric whole-brain echo-planar MR spectroscopic imaging." Magn Reson Med **74**(5): 1209-1220.

Q. Is there a way that as a society, we could put pressure on the vendors to do technological development in this area? Every time I talk to vendors, they tell me they get pressure to develop techniques in other areas, but no one is calling for developments in MRS. Obviously that's not true, but I'm wondering if we need to amass some numbers.

A. To my knowledge the ISMRM does not have a history of this type of advocacy effort. It could also be difficult to get an indication of the demand.

[W.B.] "Obviously that's not true"? Of course it is true, when compared to other things that Siemens puts some effort into. The interest for MRSI has to come –at least mostly– from clinicians and not from developers. I think MRS research community doesn't really count.

We have to bring this to ECR, RSNA.... and get some attention there. ISMRM is generally the wrong audience.

[S.P.] The end-users of MRSI are specialists like neurologists, neuro-oncologists, neurosurgeons, psychiatrists which many of them demand this type of information. If they like it, they will demand and put pressure on the imaging centers to provide this and the radiologists will push the manufacturers.

[O.C.A.] We have to get other specialists besides radiologists involved, and many treating clinicians are interested more in the biochemistry that is measured by MRS than in the structural MRI. As end user and consumers of these data the treating clinicians can be a great leverage to counter the push back that we usually hear from radiologists about MRSI, and they could help and put weight on the demand that fast and robust methods be implemented by manufacturers.

Q. Our neuroradiologists are resistant to MRS because it is not reimbursed. A lot of this is about the $$$.

A. Agreed. While not discussed in this paper, some reimbursement is possible in the US (see below) but this remains a changing situation. The MRSI can be bundled as part of the generic MRI clinical order, but getting additional reimbursement can be difficult.

[W.B.] What is actually the prerequisite for reimbursement? In Austria the system is anyway special. There is a fixed amount of money that is reimbursed irrespective of what is being done (so essentially most protocols contain T1, T2 and FLAIR). That's it. Only at our university more is reimbursed or if one has a private insurance. Then, even MRS is reimbursed (according to my boss).

[B.J.S] There's a good review about MRS reimbursement in abstract 2509 from ISMRM 2009. As I've heard the 'reimbursement story', MRS had a reimbursement code for a while, then it was challenged and went away. However, you can still get reimbursed for MRS if your site (in the US) can justify it whatever insurance group you are billing. Usually this means that your business office, and specifically the billing group, needs to have already set up an agreement about billing beforehand. And they might need their hands held by the research group that provides the service while they are trying to get the justification set up. So, in general, only sites that have active MRS expertise, and a good relationship between clinicians and researchers, and a good relationship between the researchers and the hospital business office can get this set up to work frequently and smoothly. I'm not saying that it can't be done, but it does take time, a lot of work and patience in the current environment (US).

[D.S.] The CPT CODE 76390 for MR BRAIN SPECTROSCOPY remains on the books. Reimbursement for MRS depends on the insurance company. Those that reimburse do so for specific procedures that they spell out, while others do not reimburse at all. Aetna is among insurance companies that reimburse for specific procedures that the must be pre-certified (they must be called to approve). This is Aetna's current policy (quite similar for other insurance companies that reimburse):

Policy

Aetna considers magnetic resonance spectroscopy (MRS) (also known as NMR spectroscopy) medically necessary for the following indications:

- Assessing prognosis in hypoxic ischemic encephalopathy
- Distinguishing low grade from high grade gliomas
- Evaluate a brain lesion of indeterminate nature when the MRS findings will be used to determine whether biopsy/resection can be safely postponed
- Distinguishing recurrent brain tumor from radiation-induced tumor necrosis.

Aetna considers magnetic resonance spectroscopy (MRS) (also known as NMR spectroscopy) experimental and investigational for all other indications, including the following (not an all-inclusive list) because there is a lack of evidence of its efficacy in the medical literature.

- Adrenoleukodystrophy
- Breast cancer
- Cerebrovascular diseases/disorders/injuries
- Dementia and movement disorders (e.g., Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, Huntington disease, motor neuron disease, normal-pressure hydrocephalus, Parkinson disease/Parkinsonian syndromes, vascular dementia)
- Dermatomyositis
- Detection and quantification of hepatic steatosis in living liver donors
- Detection of esophageal squamous cell carcinoma
- Differentiatiation of primary central nervous system lymphoma (PCNSL) from other focal brain lesions
- Epilepsy (including juvenile myoclonic epilepsy, and temporal lobe epilepsy)
- Evaluation of migraine pathophysiology and identification of biomarkers in migraine
- Head trauma
- Low back pain
- Lyme neuroborreliosis
- Metabolic and mitochondrial diseases
- Monitoring hepatocellular carcinoma and liver cirrhosis development
- Mucopolysaccharidosis
- Multiple sclerosis
- Polymyositis
- Prognosis of consciousness recovery in individuals with vegetative state
- Prostate cancer
- Psychiatric disorders (e.g., attention-deficit/hyperactivity disorder, autism spectrum disorders, bipolar disorder, depression, emotional dysregulation, obsessive-compulsive disorder, and schizophrenia)
- Radiation encephalopathy
- Sport-related concussion
- Substance use disorders
- Traumatic brain injury

To get a detailed look from within the insurance company of the diagnostic value of MRS is I strongly suggest reading the BACKGROUND to the Aetna policy at:

http://www.aetna.com/cpb/medical/data/200_299/0202.html