QSM: A breakthrough method to assess iron in white matter MS lesions

INTERVIEW BY **Luke Xie, Ryan Topfer** AND **Nikola Stikov**

EDITOR'S PICK FOR AUGUST

A new paper on quantitative susceptibility mapping (QSM) in multiple sclerosis is one of our Editor's picks for the August issue of Magn Reson Med. Junior author Cynthia Wisnieff was not available due to her busy medical school schedule, so we asked the paper's senior authors, Dr. Yi Wang and Dr. David Pitt to discuss their exciting work with us.

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>
> –David Pitt

MRMH: Can you give us a brief overview of QSM and your paper?

Yi: QSM offers a method to localize and quantify the underlying source of magnetic susceptibility changes, such as iron in MS lesions, by deconvolving the phase from gradient echo (GRE) data. The breakthrough in this difficult (ill-posed) deconvolution has been made possible using Bayesian inference with anatomic knowledge such as from structural images. For QSM applications in MS, we looked at pathology to determine the QSM specificity to iron, which is associated with inflammation. We compared the iron maps obtained from QSM with immunohistochemistry of post-mortem MS brains. Using QSM we found: 1) bright rims near the lesion periphery reflect iron, 2) lesion volume extended beyond the T_2 weighted imaging volume reflects iron, and 3) lesions with positive QSM volume reflect iron.

MRMH: What role does iron play in MS?

David: Earlier studies have looked at iron accumulation in deep nuclei, including the basal ganglia—they found a good correlation between disability and the amount of iron in the deep nuclei. But these studies were all carried out with T_2^* imaging. More recent studies using QSM have found that iron can accumulate in white matter lesions, which opened up a whole new field of investigation. It turned out that this iron was present mostly in inflammatory cells: macrophages and microglia. Iron uptake then makes these cells pro-inflammatory, which means that they are more damaging to the tissue. So now by detecting iron, we can have a window for examining inflammatory activity. Previously, we could detect new lesions only when they were gadolinium-enhancing, i.e. for 3-4 weeks until the blood brain barrier closes again and the enhancement is lost. Now, with QSM, inflammation is visible for much longer, although, it is a different type of inflammation. We can now get an idea of whether low-grade inflammation is present for any given lesion.

MRMH: How long is a standard QSM protocol and what are its main challenges?

Yi: It takes 5-7 minutes. More importantly, QSM can

Yi Wang

Wisnieff C, Ramanan S, Olesik J, Gauthier S, Wang Y, Pitt D. Quantitative susceptibility mapping (QSM) of white matter multiple sclerosis lesions: Interpreting positive susceptibility and the presence of iron. *Magn Reson Med* 2015;74:564-570. DOI: 10.1002/mrm.25240

http://onlinelibrary.wiley.com/doi/10.1002/mrm.25420/full

The team at Cornell, including lead author Cynthia Wisnieff (center).

be easily implemented on any site, since it's just a 3D multi-echo GRE sequence. The key thing is that you have to save the complex data. And thus QSM is really a post-processing technique, so it doesn't add any cost in terms of data acquisition. However, the QSM processing is not trivial. The raw phase is wrapped and is difficult to interpret. It needs to be unwrapped and the background phase needs to be removed in present QSM.

MRMH: How do you plan to follow up on this work?

David Pitt

Yi: We are actively translating our findings into the clinics. For example, we have found in MS patients that the lesion susceptibility value measured from QSM increases significantly as a lesion changes from Gd enhancing to non-enhancing. This data indicates that QSM can accurately discriminate between enhancing and non-enhancing lesions in multiple sclerosis without Gd injection. Therefore, QSM could be an alternative or complement to existing gadolinium enhancement techniques. We are also continuously developing the QSM technique for MS applications. For example, we are now looking into combining QSM with another myelin specific biomarker, such as myelin water fraction, to enable better discrimination between iron and myelin.

David: Looking at long-term inflammatory effects with QSM is very exciting. With this tool, we can now ask what multiple sclerosis drugs can do to inflammation in existing lesions. So far, drug studies have only looked at whether drugs can prevent the formation of new lesions. Currently, we are performing in-vitro studies and in-vivo QSM studies to see how long it takes for the iron-positive lesions to change into low-iron lesions, what we believe indicates a reduction in lesional inflammation. Something else that is on the horizon is the iron content in normal appearing white matter in chronic disease. It turns out that in long-standing MS, the iron is slowly lost from oligodendrocytes in myelinated white matter. This iron loss is not well understood but it is very possible that it affects function of oligodendrocytes and compromises myelin integrity in normal appearing white matter, thereby contributing to progressive MS. QSM can become a tool to monitor this loss of iron, and to assess progression in MS. This would be very exciting.

MRMH: Thank you for your time! We look forward to hearing more about your work in the upcoming issues of Magnetic Resonance in Medicine! ■

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