Improvements in Amide-CEST-MRI: Just the tip of the iceberg

INTERVIEW BY **BLAKE DEWEY**

EDITOR'S PICK FOR JANUARY

In the early days of 2017, we sat down (virtually, of course) to have a conversation with Moritz Zaiss, Johannes Windschuh and Alexander Radbruch. Our topic was their recent MRM paper, "Downfield-NOE-Suppressed Amide-CEST-MRI at 7 Tesla Provides a Unique Contrast in Human Glioblastoma." Chemical Exchange Saturation Transfer (CEST) imaging is an indirect imaging technique for the protons of certain metabolites, where saturation is applied off-resonance (with respect to water). Saturated protons are allowed to exchange with water protons and then imaged using conventional imaging methods. However, frequency selection is not always enough to specifically target a functional group, such as amide groups, which are common in CEST imaging methods, producing a "mixed" contrast. Moritz, Johannes, and Alexander, together with others in their group, have been slowly removing confounding effects in an attempt to isolate the measurement of amide proton transfer. In this paper, they continue their efforts by removing the downfield Nuclear Overhauser Effect (NOE), resulting in clinically relevant findings and correlation with gadolinium uptake in patients with glioblastoma.

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>
> –Moritz Zaiss

MRMH: Moritz, to break the ice a little bit, how did you get started in MR research?

Moritz: Well, I actually did solid state physics for quite a while, but decided to move to a more applied field, and move from solid state to not-so-solid state, which was the human body and especially the brain.

MRMH: And Johannes, what brought you into MR?

Johannes: Well, my way was more direct. I started with hyperpolarized MRI and Moritz got me over to the CEST side of things and that is where I stayed.

MRMH: Finally Alexander, you come from the clinical side of things, but what got you into MR research?

Alexander: Actually, I got fascinated by the images. I was always very interested in physics and built strong relationships with our great physics d epartment in Heidelberg. That's why I decided to study radiology, and ever since I have been working closely together with the physics guys like Moritz and Johannes.

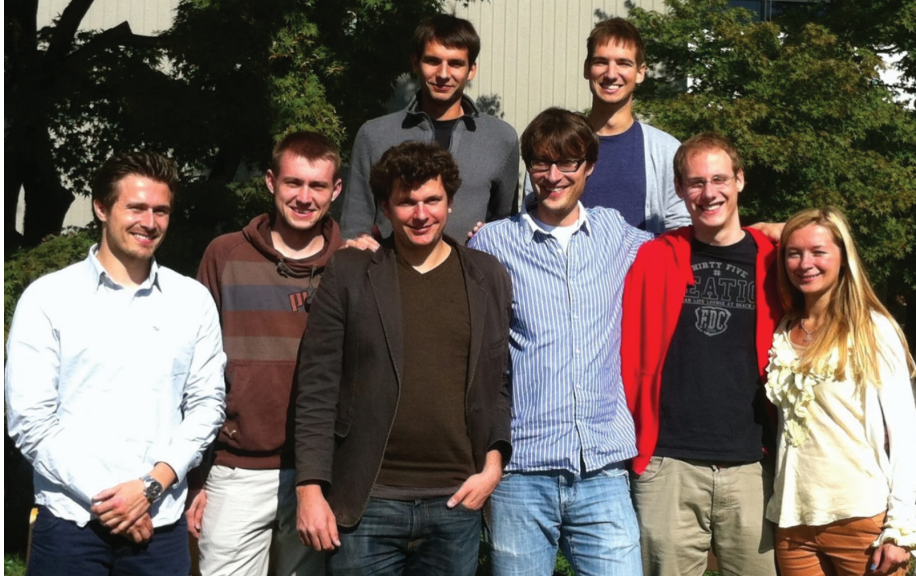
MRMH: That's a great relationship to have. Moving onto your research, can you summarize your method for us?

Moritz: One of the first CEST contrasts detected *in vivo* was amide proton transfer, which we tried to isolate as best as possible in this work. CEST is an indirect measurement via the water pool, which is comparable to estimating the size of an iceberg by using only what is visible above the surface of the water. The apparent height of the visible tip will not only depend on the total shape of the iceberg, but also on the density of the surrounding water, and on the amount of snow on the iceberg. Similarly, the "amide" CEST signal at 3.5 ppm, is in principle affected by water relaxation and concomitant semi-solid MT, and 'some snow' which would be other CEST contributions. The big idea of this work is to separate all of these contributions and isolate the one originally aimed at amide proton transfer. More techni-

Moritz Zaiss

Zaiss M, Windschuh J, Goerke S, Paech D, Meissner J-E, Burth S, Kickingereder P, Wick W, Bendszus M, Schlemmer H-P, Ladd ME, Bachert P, Radbruch A. Downfield-NOE-suppressed amide-CEST-MRI at 7 Tesla provides a unique contrast in human glioblastoma. *Magn Reson Med.* 2017;77:196–208. doi: 10.1002/mrm.26100
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26100/full

Alexander Radbruch



The research group in Heidelberg, Germany.

cally speaking, the peak 3.5 ppm downfield from water seems to originate not only from amide protons, but also from a pool with dipolar-coupled NOE-like behavior, which is not pH dependent. So, we measured the well-known upfield NOE effect and used this to remove the downfield NOE effect and also isolate the pH dependent exchange effect. Then, by correcting for water relaxation, semi-solid MT, and B_1 inhomogeneity influences, we could estimate the total iceberg from the tip of the iceberg. Finally, after all the effort to isolate this amide effect and test it *ex vivo*, we could apply it in glioblastoma patients and what we saw was surprising; the isolated amide contrast showed a very strong correlation to gadolinium uptake not only in the same region – as APT did already before, but really showing very similar structures.

MRMH: What is the strength of this method? How would you convince the Chief of Radiology to use your method?

Alexander: In my experience, it is actually quite easy to convince them to put it into clinical life, if you highlight that we are in desperate need of new sequences. If you look at the criteria for radiological assessment of neurooncology, they say we rely on T_1- or T_2-weighted imaging. If we focus on T_2, we want to know is it invasive tumor or is it only edema? This has major clinical relevance for the patient, as they may be taken to the operating room again, or not, depending on the assessment. We cannot say it is an easy answer with CEST, but it is a new chance to finally have a sequence with *in vivo* access and with the benefit that we don't need contrast agents.

Moritz: I think it is a major strength that without any contrast agent, we see the same regions that are defined on gadolinium-enhanced scans. So, we see something on the metabolic level which corresponds to what we know is an affected region.

MRMH: Now for the hardest question for researchers, what is your method's weakness?

Johannes: We gain so much from the higher field strength at 7 Tesla, but there are always problems. B_1 inhomogeneity is one that we solved with a simple method of measuring at multiple B_1 values, but that increases the measurement time. Measurement time is always of the essence, so this is critical, of course, in the clinic. In addition, we are also dependent on so many points in the Z-spectrum, so this also means even longer measurements.

Moritz: Maybe a last weakness to add is that it is a single slice method and this is a bad thing for clinicians.

MRMH: Is going to multi-slice the next technical step?

Moritz: It's actually in the pipeline. We were able to extend our sequence to 3D, and that can now be used in forthcoming studies.

Johannes: In addition, all of the contrasts have to be evaluated on how to use them. Maybe there are different diseases that are interesting for different contrasts, like NOE.

Alexander: Actually, my task is always to keep my physics friends on track and focus them on what we need in the clinic. I love the potential of 7 T and 9.4 T, but this should also be possible at 3 T.

Moritz: And I argue that you should buy a 7 T, because it is much more fun for the physicists. ■

Johannes Windschuh

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