



## The Path to a Cure Interview with MS imaging scientist Daniel Pelletier

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Although Multiple Sclerosis has been recognized as a disease and studied since the nineteenth century, there is still much we do not understand about it. One of the reasons for the gaps in our knowledge is that the sites targeted by MS – the brain and spinal cord – can't be physically sampled at will without risk to the patient, so tissue samples can only be obtained through a medically necessary biopsy or an autopsy. This has limited scientists greatly in two ways: first, the numbers of samples scientists can acquire is typically small, and second, these samples are not always useful for studying the types of questions that need to be answered.

Fortunately, the development of non-invasive neuroimaging techniques such as magnetic resonance imaging (MRI) has given scientists the ability to see conditions in the brain and spinal cord without intrusion and risk, which has added greatly to our understanding of MS. Future enhancements to imaging technology promise to expand what we know about MS even further. One of the scientists leading the way in innovative uses of imaging to study MS is Daniel Pelletier, MD, of the University of California San Francisco. Boston Cure Project's Hollie Schmidt recently talked with Daniel to get his perspectives on the field's past contributions to MS research and clinical care, and its prospects for further benefiting people with MS in the future.

***Hollie:** It says on the UCSF web site that you're interested in understanding the natural history of MS using neuroimaging techniques, and integrating the advances into the daily care of patients. I think our readers would agree those are very worthwhile interests! Can you tell me how you became interested in studying MS in the first place?*

**Dan:** When I was doing my neurology training, I couldn't help noticing how very young the MS patients were compared with other patients. Some of these patients were exactly my age. They would also have a disease that will, most likely, last for the rest of their life. I was particularly struck by these facts which is why I was moved to work in this field.

*And why have you chosen to approach MS from an imaging standpoint?*

Before I started my medical career, my background was not in biochemistry, or chemistry, or biology, but computer sciences and engineering. During my

medical training I was introduced to Doug Arnold, an MS scientist working on imaging, and when I saw all the computers in his lab and learned about the approaches that he was taking, I thought it would also be a good fit for me. Using imaging to study MS lets me use and extend my background in computer science and physics and combine it with my neurology and MS training. In my lab I'm working with computer science people who are managing all these images, graphics and browsers, so it's a rare but perfect combination.

*What are you working on right now?*

My main focus now is a technique called MR spectroscopy (MRS), which I've been using since 1998. I use it because it can bring more specificity to what we can image in the brain – in other words, it gives us more information about what's there. Conventional MR images are very good at detecting if there's something abnormal, but they lack the ability to tell us what we are seeing exactly.

What we're studying with MRS are small proteins or amino acids that we can measure and use as biomarkers of the brain. In particular we've been studying the amino acid *N*-acetyl aspartate (NAA), a marker that tells us about the presence and integrity of axons and neurons, as well as other markers of interest such as myo-inositol, choline and creatine. In addition, we can now measure neurotransmitters, which are small proteins that are used by neurons to talk to each other, and over time we will gain access to more and more metabolites that will increase our ability to understand the disease. So MR spectroscopy is giving us non-invasive, *in vivo* (in living subjects) tools to measure all kinds of molecules including neurotransmitters, and that's essentially been my focus for the past year and a half. By the way, at this point we're mainly using MRS to better understand the disease, but later we're going to use it to find and understand the effects of treatments. After that – it's a step by step process – we can bring these tools into the clinical world to diagnose MS and evaluate prognosis.

*Let's talk about MRI and its potential to help us understand and treat MS. First of all, there are a number of other technologies available to image the brain, like CT and PET. Why is MRI so widely used in MS?*

First, it offers an excellent picture of the brain, with high resolution. We can look at an MRI and find tiny details that CT is not going to give. The same comparison is true for PET imaging – PET is very useful for looking at the physiology of what's going on, but it doesn't offer the resolution that MRI can bring. Second, MRI is very convenient, is non-invasive, and has virtually no side effects.

*Is there anything MRI is not very good at showing?*

There are definitely areas where we need to do better. MRI has great resolution but it doesn't have the specificity that we need. For instance, at this point we don't have a perfect myelin MRI metric that will give us precise information about which areas are demyelinated and which aren't. So we are looking for ways to create higher contrast between plaque and normal white matter. We also don't yet have the resolution to study gray matter plaques and pathology, and this is definitely a major focus of research these days. Someday we will have the ability to look with far greater detail at the gray matter and this will also help our understanding of MS. So MRI gives us greater resolution but there is more work to do, especially in imaging the smaller structures such as the cortical gray matter.

*What would you say are the most important things that imaging studies have taught us in recent years?*

I think that the ability to see lesions has dramatically changed the way we understand and see MS. For instance, we can diagnose MS much sooner than we were able to years ago. We've also learned that the dynamic of these lesions is extremely high – in other words lesions wax and wane – and we have the ability to study that like never before. More recently we've learned a great deal about tissue loss, and our ability to more accurately measure brain atrophy is helping our understanding of MS and will someday help us tell whether or not our drugs are helping our patients. So we can diagnose MS sooner, we can see lesions, and we have a better grasp of tissue loss and brain atrophy. But as I said, we're not done, we need to do better.

*Of all the recent MS findings that have been produced using imaging technologies, have any surprised you?*

Well, recently we've seen with MRI studies that there are blood perfusion abnormalities in active, acute MS plaques. Specifically, blood flow is increased in these areas. The idea that MS has something to do with the blood vessels and blood flow is new to me, and I'm not sure what it means. I'm definitely surprised by that.

*Looking into the future, I can think of three areas of deep concern to people with MS that imaging has the potential to address. Can you give us your view on imaging's contributions to date in these areas and where future advances will take us? The first area is reducing the uncertainty of diagnosis & prognosis for people with MS.*

I think MRI has helped tremendously with diagnosis, particularly on the patient side. Any MS neurologist or doctor taking care of MS patients should look at the MRI brain scans or films with their patients. It's a very important

exercise in diagnosis because patients can see what's there for themselves. It's harder to say, "I don't have that" when looking at the images. Viewing MRIs together is also helpful in discussing what's going on over time, for instance whether or not there is any new disease activity. Doing this together helps build the relationship overall between a patient and doctor, first because of the time spent together reviewing the images, and second because it's a very concrete exercise and seeing things with their own eyes makes it easier for patients to understand.

Prognosis is more difficult. Years ago we thought that we would be much further along with this than we are today. It's been a little bit disappointing. We certainly would like to predict someone's course 5, 10, 20 years down the road by looking at a conventional image, but I'm not quite sure we're there. But we are going in the right direction. For example, patients whose very first brain scan shows many lesions or what we call a high lesion volume tend to have a higher level of disability five or ten years later. However, the correlation is not perfect and that's why we need to find better metrics. Our ability to measure tissue loss is helping even more in terms of prognosis. Patients who have an increase in brain atrophy over a year or two tend to do worse in terms of disability seven to eight years down the road. So we've made some progress but we're trying to do better.

*Secondly, how is imaging contributing to gauging the effectiveness of treatments, both in clinical trials and in individual treatment decisions?*

Once again, MRI is playing a major role, both in terms of clinical trials and what we do on a daily basis with our patients. During the relapsing-remitting phase, for instance, the use of a contrast agent to detect acute enhancing lesions is useful in telling us there is an active process going on in a patient on the day we do the scan. That's very useful for clinicians. Being able to count lesions or identify new lesions is also very helpful in monitoring progress and treatment response. In clinical trials, we are doing exactly the same things, counting lesions and finding new lesions, but it has to be done in a controlled way, where everyone is doing the same type of imaging and there is a central analysis. We are getting better at using MRI in clinical trials through developing better software and standardization of MRI protocols to produce more homogeneous images. We are also developing measures of brain atrophy that are more reliable and are using that in clinical trials to measure the impact of a given drug. However, one of my goals is to introduce MRS, with its greater specificity, into the context of multi-center clinical trials. With MRS we could measure metabolites such as NAA as a new way of evaluating possible treatment effect. This is coming and I'm working very actively on it.

*A question about atrophy, is it the case then that changes in atrophy are actually noticeable over the time span of a clinical trial?*

This is a very active area of research and there are controversies. The way I look at the data, in the context of a one- or two-year trial, we do see brain atrophy changes, and our measures are sensitive and reproducible enough to detect a treatment effect. However, the effect is small and that requires a very large study – it's not something we can detect with 10 or 20 patients and not something we can detect over two to three months. Also, we have to be very careful with brain atrophy in the short term after introducing a treatment. There can be brain volume changes because of inflammation resolution or water going away, or due to the use of steroids. So brain atrophy is not a short-term kind of metric. But it is useful in a larger clinical trial lasting for a few years. And it's correlated with physical disability and cognitive dysfunction, which is what we ultimately really care about.

*The third area people are often interested in is MRI's contributions to understanding the fundamentals of disease (the why's and the how's regarding the development of MS). For instance, can it help us at all in understanding the causes of the disease?*

The difficulty with using MRI to find the cause of MS is that when we evaluate patients or bring them into the scanner, the disease is already there. Even after just the first clinical attack there may be five or six lesions which may indicate that the disease has been going on for years. Other new areas such as understanding the relationship between the immune system and genetics may help us figure this out. But as for using MR for this, I don't see it at the moment.

*What can MRI tell us about attacks, remissions, and lesions?*

In terms of attacks, I think MRI has given us something new, which is that we see more MRI "attacks" than we see clinical "attacks." There's a ratio of about five to ten brain lesions for each clinical attack. So MRI is helpful because it's more sensitive than clinical observation in detecting activity. But even with MRI we cannot predict where or when in a particular person those brain attacks will come up. There have been some studies involving magnetization transfer imaging (MTI) where we were trying to see whether there's a decrease in the magnetization transfer ratio (MTR) in areas where a gadolinium (Gd) lesion is about to occur. Right now we can track backward from a lesion and often we will see that there was a change in MTR before; however, we can't predict the placement of Gd-enhancing lesions yet using MTR. This tells us that before you actually see a Gd lesion, there might be small detectable changes that are not driven by blood-brain barrier disruption, but right now you cannot use those changes to predict where the lesions are going to be.

Another thing we're learning is that lesions have a lifespan. Generally they appear, then later they disappear. If we have the luxury of scanning someone on a weekly basis, we can see lesions going away over time. Something we've found out with MR is that the longer a lesion shows Gd-enhancement, the more likely it is that the lesion will have axonal damage. The life of a Gd-enhancing lesion is three to four weeks on average, but if it lasts six, eight, ten weeks, it's more likely we will see more severe tissue damage there. Why is this the case – why is the inflammation maintained and why would it persist so long? We don't know. Patients do have an ability to repair their brain, to get rid of inflammation. My opinion is that this is under genetic control, which we are trying to understand by looking at MRI characteristics and genetics together. Seeing the brain with MRI is going to help everybody, including immunologists and geneticists!

*Can MRI tell us what causes a lesion to start forming in a certain spot and what makes it stop growing?*

We don't know much about this other than knowing how lesions are typically distributed – they tend to be around the corpus callosum, they tend to be in the white matter, they tend to irradiate from the ventricles. The cervical spinal cord is more frequently affected than the thoracic cord. We knew that from pathology, and now we know that also from MRI, that lesions have a typical distribution and location. But we don't have the information yet to tell where a lesion is going to appear or why it appears there, unfortunately.

*What information can imaging give us about why are there different subtypes of MS, such as relapsing-remitting, secondary progressive, and primary progressive?*

There have been a lot of studies looking at subtypes – PPMS, SPMS, RRMS – and I believe the MRI contribution has been important. On average the images from a PPMS group will not look like those from a SPMS group. The amount of visible lesion is less in PPMS than SPMS. We also see using MRI that people with PPMS tend to have more lesions in the cervical and spinal cord compared with those who have RRMS. But keep in mind that these are group comparisons. If you look at MRIs from specific patients, it remains hard to tell whether they have RRMS or PPMS.

As for why these different subtypes exist, through MRI studies we have found that in PPMS, the degree of neuro-axonal injury is not correlated with the number of visible white matter lesions. In RRMS the correlation between visible lesions and amount of tissue injury is better. So perhaps this reflects an important difference between the two types that should be explored. For instance, stopping lesion formation in RRMS is still important where in PPMS a more neuroprotective approach might be more beneficial.

*Today there is still a lot of information we can only obtain by analyzing tissue samples from biopsy or autopsy, things like what types of cells are located in an area, what is the tissue structure like, what types of molecules are present, are any viruses there, etc. Will we ever get to the point where we can visualize these things using noninvasive techniques?*

Yes, this is where we're going, and it's where we want to go because it will further increase the specificity that we lack using conventional MRI. MRS is definitely a step in that direction. But better techniques are coming that are complementary to MRS and they involve creating new contrast agents that go beyond the use of gadolinium. One of the major interests recently has been to look at macrophage activity with ultra-small paramagnetic iron oxide (USPIO) particles. These are particles which are internalized only by macrophages so they give us information about that particular type of cell. In the future we will have other MR agents that will target not only specific types of cells but also specific molecules. This is definitely the most promising approach to better define what's going on in acute and chronic lesions, as well as what's happening outside the lesions in the normal appearing white matter. We want to understand the relationship between axonal loss and demyelination, whether the severity of axonal injury is related to lesions or whether another process is going on which is partially or totally independent of lesions. The only way to find that out in MR will be to have specific markers – an axonal marker, a myelin marker, a macrophage marker, and if we were able also to distinguish between glial cells, an oligodendrocyte marker. The field of MR is extremely active in finding those specific markers. This is definitely the way to go and it will happen.

*How long will it take?*

It's going to take years of research, involving the use of animal models, to better validate and understand those methods and metrics. However, once we understand how to use them and have worked through any difficulties, we can bring that to *in vivo* MS research. Recently I've learned that some of these probes are already ready, it's just a matter of being able to use them in humans. As soon as we have that ability, things are going to go very fast. I'm very optimistic!

*Leaving aside the technological challenges for a moment, what are the other major challenges facing you and other scientists working in this area that you'd like to have addressed?*

If we could create an organized network of scientists who use a common core of technology (protocols, sequences, and so on) and machines that were well-calibrated with each other, we could be much more effective in enrolling larger numbers of patients into studies. There's a lot we can learn from a 25-

patient study, but so much more to learn from a 500-patient study, which a single site cannot do. Currently everyone is doing their own MRI research in their own labs, which is good in a way because it results in new ideas, but in addition to that, if we could organize ourselves to do research using new MRI methods in a multi-center setting, that would be fantastic. I'm really open to this idea and I'm hoping that one day we can do it.

Another thing we need is more MRI/histopathological correlations. We need to do more MRIs on autopsy cases from tissue banks, because this is how we're going to understand what our MRI tools are showing us. Once again, to do this right would require a major collaborative effort involving lots of institutions, which will only happen if people want to work together.

*Is there anything else you'd like our readers to know?*

For one thing, they should be proactive and look at their films with their neurologists.

More generally, they need to know that the field of MR is very active. We want to use this non-invasive tool for better diagnosis of MS, we want to know more about prognosis so we can be more aggressive or less aggressive in treating a patient, we want to know if a patient's drug is working, we want to know more about what happens in the disease. Overall, we want to have more of an impact on our patients' daily living.