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Early Development of Arterial Spin Labeling to Measure Regional Brain Blood Flow by MRI

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Abstract

Two major avenues of work converged in the late 1980's and early 1990's to give rise to brain perfusion MRI. The development of anatomical brain MRI quickly had as a major goal the generation of angiograms using tricks to label flowing blood in macroscopic vessels. These ideas were aimed at getting information about microcirculatory flow as well. Over the same time course the development of *in vivo* magnetic resonance spectroscopy had as its primary goal the assessment of tissue function and in particular, tissue energetics. For this the measurement of the delivery of water to tissue was critical for assessing tissue oxygenation and viability. The measurement of the washin/washout of "freely" diffusible tracers by spectroscopic based techniques pointed the way for quantitative approaches to measure regional blood flow by MRI. These two avenues came together in the development of arterial spin labeling (ASL) MRI techniques to measure regional cerebral blood flow. The early use of ASL to measure brain activation to help verify BOLD fMRI led to a rapid development of ASL based perfusion MRI. Today development and applications of regional brain blood flow measurements with ASL continues to be a major area of activity.

Keywords

Perfusion MRI; magnetization transfer; functional MRI; blood flow tracers

Background to the Development of Arterial Spin Labeling

It is an honor to be invited to contribute to this exciting volume of Neuroimage to celebrate the 20th anniversary of the introduction of BOLD fMRI. The goal of this contribution is to give a personal history of the early development of the set of MRI techniques that are sensitive to regional cerebral blood flow known as arterial spin labeling (ASL). The history is weighted to that work which directly influenced the experiments performed at Carnegie Mellon University that first demonstrated the basis of ASL.

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MRI is Functional From the Start

In his landmark paper inventing MRI in 1973, Paul Lauterbur already saw the potential for function in MRI (Lauterbur, 1973). This paper demonstrated the way external contrast agents would affect images, as well as listed the range of information that might be accessible, such as spectroscopic and diffusion information. By 1978, the first human brain images were being obtained (Clow and Young, 1978; Holland et al., 1980), and by 1981 the early patient results that indicated MRI would have contrast to white and grey matter as well as sensitivity to detect brain tumors, stroke and multiple sclerosis were published (Doyle et al, 1981, Young et al, 1981). Around this time, Lauterbur and colleagues published the first fully three dimensional images of a fixed human brain and stated again that MRI would be useful for detecting flow and diffusion (Kramer et al, 1981). These predictions were based on the well established Stejskal-Tanner techniques in NMR to measure diffusion and the pioneering work of Singer and colleagues in the late 1950's that began to demonstrate how NMR could detect flow in humans (Singer, 1959). An important paper by Moran in 1982 laid down the modern theoretical framework for detecting flow through large vessels with MRI (Moran, 1982). Early human results demonstrated the effects of flow in large vessels on MRI (Crooks et al., 1982, Bradley and Waluch, 1985, Wedeen et al 1985, Dumoulin and Hart, 1986, Dixon et al 1986). The early work developing angiography demonstrated that water flowing in blood could be tagged in MRI either by magnitude or phase techniques and separated from non-flowing tissue.

The work on angiography was based on detecting large vessels that led to coherent flow over macroscopic (compared to the voxel size) distances. Thus, MRI had already established techniques to monitor velocity of blood in large vessels prior to any work attempting to measure regional blood flow or perfusion. This is an important distinction that is often blurred by the use of the term blood flow. Macroscopic flow through vessels is very important but it is not the relevant parameter for understanding delivery of water out of the capillary bed into tissue. Perfusion or regional blood flow is used to designate delivery of water out of the micro-circulatory system into tissue. The incoherent movement of water in the capillary bed that arrives at tissue over small distances (as compared to the voxel size) could not be measured by the angiographic techniques. This distinction was made clear by Le Bihan and colleagues as they attempted to use diffusion weighted MRI to extract information about perfusion (Le Bihan et al., 1986). Similar ideas were also developed by Bydder and Young and colleagues to attempt to measure regional blood flow in brain (Fish, D.R. et al, 1988). However, these attempts to extend ideas that had been so useful for angiography and diffusion weighting have not yet proven robust for measuring perfusion.

The Spectroscopists Contribute to Perfusion MRI

The early development of *in vivo* spectroscopy by the Radda, Shulman and Chance/Leigh groups led to the training of a group of investigators that had deep interests in the physiology of tissue energetics and the development of MR techniques. They acquired the first generation animal magnetic resonance systems that enabled spectroscopy and imaging to be performed. This group included such luminaries as Ackermann at Washington University, Balaban at NIH, Ogawa at Bell Laboratories, and Ugurbil at University of Minnesota. The attraction of performing imaging and spectroscopy attracted many

established spectroscopists such as Jim Hyde at Medical College of Wisconsin, Tom James/Michael Moseley/Michael Weiner groups at UCSF, and Chien Ho at Carnegie Mellon University/University of Pittsburgh. Finally, the pioneering work of Maudsley and Brown developing chemical shift imaging (Brown et al, 1982, Maudsley et al, 1983) began to attract imaging groups such as Rosen and Brady at Massachusetts General Hospital (MGH) to characterize tissue energetics. From this group of spectroscopists emerged important contributions to imaging including BOLD (Ogawa et al, 1990a, Ogawa and Lee, 1990, Ogawa et al. 1990b, Ogawa et al, 1992, Bandettini et al, 1992, Kwong et al, 1992), magnetization transfer contrast (MTC) (Wolff and Balaban, 1989), the demonstration that diffusion MRI could detect stroke and white matter fiber orientation (Moseley et al, 1990a, Moseley et al 1990b), and early cell tracking by MRI (Yeh et al, 1993). A remarkable series of contributions!

The work of Joe Ackermann and colleagues at Washington University and the work in the Britton Chance/Jack Leigh group at University of Pennsylvania using NMR spectroscopy to measure regional blood flow were very influential for our work on ASL. In 1985 and 1987 Ackerman's group published in two areas that made it clear that magnetic resonance could contribute to measuring brain activity. The first used an energetic measure directly relevant to mapping neural activity and the second demonstrated that tissue perfusion could be measured with an MR detectable agent using well established tracer kinetics. The brain energetics work was an attempt to translate deoxyglucose measures of glucose uptake from PET to NMR by monitoring the build up of deoxy-glucose-6-phosphate using ^{31}P NMR (Deuel et al, 1985). The use of ^{31}P NMR to study brain activation remains an area of interest in MRI (Du et al, 2008). The blood flow tracer that Ackermann and co-workers used to measure tissue perfusion was deuterium oxide, pointing towards water as a useful label for MR measurements of tissue perfusion (Ackerman et al, 1987, Kim and Ackerman, 1988). While this work was aimed at monitoring tumor blood flow, the principles of tracer kinetics had been applied to the brain since Ketty's original work and numerous brain blood flow tracers such as radioactive water and radioactive microspheres were in widespread use. Thus, Ackerman's idea of using water to make MR measurements of perfusion could be readily translated to the brain.

Shortly after the work of the Ackermann group, Leigh and Chance and colleagues demonstrated that trifluoromethane could be detected with ^{19}F MR and might be a useful tracer for perfusion measurements (Eleff et al, 1988). The idea to apply tracer kinetics to MRI of the brain was also pursued by Rosen and colleagues at MGH. They demonstrated that the passage of lanthanide chelates could be sensitively detected due to susceptibility effects as the chelate passed through the vasculature of the brain (Villinger et al. 1988, Rosen et al, 1990). This enabled a relative measure of regional blood flow and blood volume at the resolution of MRI. The first MRI of human brain activation was based on detecting changes in blood volume using contrast agent bolus techniques (Belliveau et al, 1991). Of course, there has been a great deal of work developing contrast agent bolus tracking techniques and this is now a critical technique for perfusion assessment by MRI, especially when applied to stroke. All of these first MRI perfusion tracers required addition of external contrast agents constraining the range of applications.

Measuring Regional Blood Flow at Carnegie Mellon

Getting the Work Going at Carnegie Mellon

I had the good fortune of being recruited in 1987 to my first independent faculty position by Chien Ho. Chien had just established the Pittsburgh NMR Center for Biomedical Research as a joint endeavor between Carnegie Mellon University and the University of Pittsburgh. My laboratory and the animal MRI equipment (first generation 4.7T, 40 cm Bruker and first generation 7T Bruker animal imaging system) were located in the Mellon Institute at Carnegie Mellon University. The Mellon Institute has a remarkable history in NMR having been home to the early career of Paul Lauterbur. In addition, John Pople did his Nobel Prize winning work on quantum computation, first aimed at understanding NMR chemical shifts, in the Mellon Institute. The laboratories of Axel Bothnerby (Bothnerby et al, 1984), Joe Dadok (Dadok and Sprecher, 1974), Miguel Llinas (Llinas et al, 1970), and Chien Ho (Ho and Perussi, 1994) all made important contributions to structure determination in biological systems using unique NMR resources in the Mellon Institute. Indeed, the Bothnerby/Dadok 600 MHz NMR project was a landmark in development of high field NMR. Irving Lowe had just moved from the University of Pittsburgh into the Mellon Institute to join the Pittsburgh NMR Center. Amongst many seminal contributions, Irving was first to perform Fourier transform NMR (Lowe and Norberg, 1957) and solid-state magic angle spinning (Lowe, 1959) and had turned his attention to MRI. The Mellon Institute is truly a place where NMR giants walked.

We set out right away to determine if we could measure brain blood flow with MRI. I had spent a postdoctoral fellowship with Bob Balaban studying cardiac energetics at NIH and my goal was to address questions about regulation of mitochondrial metabolism in brain. These studies needed a MR compatible way to measure where and when the brain was active to guide localization of the metabolic studies. It was well established that measuring changes in brain blood flow was an excellent surrogate marker for changes in regional brain activity. I had the good fortune of having three outstanding colleagues in this work; Don Williams, who was a master of getting the early Bruker MRI scanners to work; John Detre, had come as a postdoctoral fellow with Chien Ho to study metabolism using ^{13}C NMR and he joined in on the blood flow work; and Cliff Eskey, a graduate student co-advised by Rakesh Jain and myself, wanted to measure tumor blood flow.

We tried everything. John took up Chance's fluorinated gas idea (Detre et al, 1990a, Detre et. al 1990b, Walsh et al, 1993) and Cliff worked on Ackermann's D_2O techniques (Eskey et al, 1992). John also used D_2O in the cat to make what may be the first MRI images of brain blood flow (Detre et al 1990c). We also took a crack at LeBihan's IVIM ideas using a very strong homebuilt diffusion sensitizing gradient. None of the approaches to imaging perfusion competed with the resolution of the spin-warp MRI from the rat brain. All were relatively insensitive to changes in blood flow, indeed, always the biggest changes occurred when the animal was sacrificed. John could always be heard laughing as he pointed out that we had developed yet another MR technique that could detect death! Sadly, we did not pay more attention to the diffusion changes with death (we attributed the slowing of diffusion to a temperature drop). Moseley would shortly point out the usefulness of the change in

diffusion for stroke (Moseley et al., 1990a). Nor did we notice the change in T_2 or T_2^* with deoxygenation of hemoglobin upon death (we were imaging with spin echoes and short TEs rather than gradient echoes). Ogawa would soon discover BOLD (Ogawa et al., 1990a). Two big misses at our fingertips! This goes to show how many interesting experiments were “in the air” in the late 1980’s in MRI.

The Turn to Using Endogenous Water as the Perfusion Tracer

My graduate work with Mel Klein and Michael Weiner had been consumed by developing and applying magnetization transfer techniques to measure enzyme kinetics in intact tissue (Koretsky et al, 1986). The ideas were well established in NMR and relied on perturbing a resonance with either a saturation pulse or an inversion pulse and watching that magnetization transfer due to chemical exchange to another resonance. The work focused on measuring creatine kinase and ATP synthesis. Application of magnetization transfer techniques *in vivo* has many challenges such as involvement of competing reactions and the role of metabolites that are below the detectability of NMR (Balaban and Koretsky, 2011). During this work we realized that as long as the perturbation was applied continuously, levels of metabolites far below the detection limit of NMR could be detected through their exchange with a larger, detectable metabolite pool (Koretsky et al, 1985). In the case of continuous saturation, exchange can be detected from the small pool to the large pool as long as the exchange rate constant is on the order of $1/T_1$ or R_1 for the detectable metabolite. The concentration of the saturated metabolite is not important as long as it can be saturated and has a distinct chemical shift. Another way to state this is if the rate constant for exchange multiplied by T_1 is on the order of one, it does not matter how small the metabolite pool is that gets saturated! This has been used to great affect lately by Jun Shen and colleagues at NIH to monitor a growing list of enzyme exchange reactions *in vivo* (Xu et. al., 2009) Amplification of molecules that are at low concentration via exchange with molecules that are at much higher concentration is the basis for MTC (Wolff and Balaban, 1989) and is the key to a new generation of contrast agents (so called CEST agents) that are designed to be detected due to having protons that are in exchange with water (Ward et al, 2000).

Our brain blood flow measurements using fluorinated gases and deuterium oxide in rat gave us values of blood flow of about 1 ml/min/gm tissue, in agreement with other invasive techniques. Since the density of tissue is about 1 gm/ml that makes the apparent exchange constant for water due to blood flow about 0.017 sec^{-1} (density of tissue (gm/ml) divided by blood flow (ml/sec/min)= apparent exchange constant (sec^{-1})). The T_1 of tissue water was about 1.6 sec at 4.7T and so this apparent exchange constant times T_1 of water is about 0.027. Small, but with my background of hunting for low concentration metabolites via exchange this was close enough for me to imagine using magnetization transfer techniques to measure regional blood flow. It was possible to merge tracer kinetic modeling with magnetization transfer modeling to modify the Bloch equations to describe the effect of regional blood flow on tissue water relaxation. The prediction was that we would detect about a 2–3% change in the apparent water T_1 due to blood flow as long as the tissue and blood magnetization were perturbed with respect to one another. With some arm twisting, I convinced Don Williams to try and see if we could detect perfusion in the rat brain within

this framework of magnetization transfer. Rather than chemical exchange, it would be perfusion leading to magnetization transfer that would be detected due to perfusion of water from the microcirculation into the tissue. Our first attempts were to see if we could detect the modulation of T_1 of a thin slice of water from the brain due to changes in blood flow. In this case the tissue water was assumed to be inverted with respect to the blood water which would flow into the tissue from outside the slice with its full magnetization. Indeed, some early work looked promising.

As we were starting these experiments, John Detre left Pittsburgh to complete his neurology training at the University of Pennsylvania. He kept his fingers in MRI research with Jack Leigh. I was happy to hear that John would be working with Jack. Jack made remarkable contributions to the development of spectroscopy for studying biomedical problems. When I was a graduate student, Joe Murphy-Boesch and I had stumbled upon a novel MR coil tuning scheme that greatly improved sensitivity of coils being used for imaging or in vivo spectroscopy which we called balanced matching (Murphy-Boesch and Koretsky, 1983). I first met Jack when he came on a site visit for a Mike Weiner grant at UCSF and he immediately appreciated our new tuning scheme. Indeed he was the first, apart from my mentors Mike Weiner and Mel Klein, to appreciate this work. Sadly, Jack passed away in March, 2008.

Move the Spin Label to the Neck

John Detre called one day excited about a conversation he just had with Jack Leigh. John had been reading “Cerebral Blood Flow” by James Wood (Wood, 1987) which had a chapter on steady-state blood flow measurements. Based on an analogy to the short lifetime of PET isotopes, they decided that endogenous water could be used as a steady-state perfusion tracer by continuously saturating the magnetization of flowing water at the neck until a steady-state develops. I had just had a conversation with my old friend Greg Karczmar, who also suggested moving the spin labeling to the neck. Indeed, this was consistent with the magnetization transfer framework Don and I had been working with but with the added advantage that the flowing blood could be continuously labeled to reach a steady-state in brain magnetization. In this case the blood water would be saturated and perfusion would lead to a decrease in the tissue magnetization. Rather than measure a transient effect as we were trying with the slice selective experiment, continuous labeling would lead to a larger and steady-state change. Thus, continuous saturation of blood flowing into the tissue would give us amplification in direct analogy to detection of small metabolite pools in chemical exchange experiments that I had done as a graduate student. So it was a big step forward from the slice selective experiments Don and I were doing and John came back to Pittsburgh for these new experiments. We already had the theory and it was straightforward for Don to saturate the flowing blood in the neck using a series of 90 degree pulses at the neck. The change from slice selective perturbation of tissue water in the brain to continuous saturation of water in the neck while monitoring the decrease in brain tissue water caused by perfusion made the experiments work much better. Of course, the short transit time it takes blood to get from the neck to the brain of a rat helped to make sure magnetization was not recovered after saturation at the neck..

An intense weekend of work convinced us that the continuous labeling strategy worked because the calculated perfusion numbers were about right and death, as well as varying inhaled CO₂, modulated the calculated blood flow as expected. The results were first presented as a Works in Progress Abstract at the Ninth Annual Meeting of the Society of Magnetic Resonance Research in Medicine in New York in 1990. The first paper was submitted to Magnetic Resonance in Medicine in mid-1990 and, after many back and forth discussions with skeptical reviewers, was finally published in early 1992 (Detre et al, 1992). Don Williams suggested we should use Dixon's adiabatic fast passage to invert the flowing water magnetization rather than saturate at the neck to double the dynamic range,. This approach enabled Dixon to produce fantastic angiograms (Dixon et al., 1986). This further increased the sensitivity by a factor of two and the measurement was now robust (Williams et al, 1992). By 1992 we had a much easier time convincing reviewers of the validity of the spin labeling approach to measure regional blood flow. It was in this second paper, published in Proc Natl. Acad. Sci. that Don and John began to coin the terminology of arterial spin labeling to describe the experiment.

A Call From Ken Kwong

In 1991, I received a call from Ken Kwong from MGH. Ken was very excited about some results observing signal changes in MRI signals of the brain due to visual stimulation. He had performed two classes of experiments. One measured changes in signal on T₂* weighted MRI that Ken was interpreting to be due to Ogawa's BOLD effect. The other set of experiments were changes in signal on T₁ weighted images that he was interpreting in our ASL framework to be due to changes in regional blood flow. He gave me the great honor of seeing an early draft of his work in order to have me comment on the theory he used for the blood flow experiments. I still have a copy of the draft he sent and the fax is dated Oct. 25, 1991. The title at the time was, "Magnetic Resonance Movies of Brain Function", a title that got modified by the time of publication. Indeed, he nulled the tissue water at rest with T₁ weighting and detected the intensity changes caused by increased blood flow altering the apparent T₁. An idea that should have been obvious to Don and I when we were trying to quantitate slice selective T₁ measurements in our first experiments! Thus, Kwong, Rosen and colleagues verified their initial BOLD results using an ASL based experiment giving them an independent measure of functional brain activity (Kwong et al. 1992). The fact that functional activation could have an oxygenation and a perfusion component (or an in-flow component as it was referred to as well) led to studies trying to gauge the contribution of each to fMRI signals (Duyn et al, 1994). Having had early knowledge of the birth of fMRI, I sometimes regret not having dropped everything and joined my colleagues in Pittsburgh, Doug Noll, Jonathan Cohen and Walt Schneider on the fMRI express. Jonathan invited me on a number of occasions to join in. Lalith Talagala did try some early ASL in humans with us and this got him interested in translating ASL to humans (Talagala and Noll, 1998, Talagala et al, 2004). Indeed, we still argue whether the results he obtained from my future wife's brain in 1992 at 1.5T were real or an artifact (Fig. 1). Fortunately, the rodent brain and new types of MRI contrast have kept us busy.

Flushing Out the Complexities and Extension to Other Tissues

We knew there were interesting complexities to the ASL measurements. The control labeling had to be carefully selected to make sure potential MTC effects induced by the water labeling strategies were properly accounted. Furthermore, we liked to think that all the water had transferred to the tissue; we treated the water as a freely diffusible tracer and neglected contributions of labeled water in vessels. Finally, there was a transit delay of water from the label plane to the tissue that we had neglected. Wei-Guo Zhang and Afonso Silva took on these challenging problems. We extended the theory to account for MTC effects (Zhang et al, 1992) and Afonso developed a two coil strategy to use a small coil at the neck for the arterial spin labeling. This enabled three dimensional perfusion images to be readily obtained as well as to modulate MTC effects (Silva et al., 1995, Zhang et al., 1995). This in turn enabled us to quantitate how much of the labeled water remained in vessels and how much had exchanged to tissue by measuring the amount of MTC on the label and the diffusion coefficient of the label (Silva et al, 1997a, Silva et al, 1997b).

Don Williams was particularly interested in extending ASL techniques from brain to other organs, most notably kidney and heart (Williams et al, 1993, Williams et al, 1994). The perfused heart enabled Don to experimentally verify the relation between T_1 and perfusion that was predicted by theory and used in early fMRI studies by Ken Kwong (Williams et al, 1993). Considering the small signal changes that had to be detected, successful measurement in these moving tissues is a real testament to his remarkable experimental skills. In Philadelphia, John and Jack demonstrated human and kidney perfusion images with arterial spin labeling (Roberts et al, 1994, Roberts et al, 1995). They also noticed the value of doing angiography with a continuous labeling strategy (Roberts et al, 1993).

An Alphabet of ASL Techniques

Fig. 1 shows as ASL image from twenty years ago and recent ASL MRI results from my colleague S. Lalith Talagala. The improvements are incredible thanks to higher fields, better detectors, and optimized arterial spin labeling strategies. (Talagala et al, 2004). Indeed, ASL MRI of regional blood flow remains a robust area for development of novel MRI techniques and applications to human disease. Ken Kwong's use of background nulled T_1 measurements to measure changes in regional blood flow and his idea of using selective minus non-selective inversion as a quantitative perfusion labeling strategy (Kwong et al, 1992, Kwong et al, 1994, Kwong et al 1995) along with Dave Roberts early brain images (Roberts et al, 1994) clearly indicated that it would be possible to implement ASL on humans. Indeed, that there were a large number of techniques for ASL that could be developed was anticipated by early presentations at the Society for Magnetic Resonance (Williams et al, 1994, Kwong et al, 1994). Important early contributions were the development of EPISTAR by Robert Edelman and coworkers (Edelman et al, 1994) and the elaboration of selective-non-selective labeling strategies such as FAIR by Seong-Gi Kim (Kim, 1995). QUIPSS and its derivatives from Eric Wong also helped overcome problems with translating ASL to humans (Wong et al., 1996). John Detre continues to be very active developing ASL for a variety of neurological disorders in human. John and David Alsop have also helped to solve many of the issues associated with MTC and vessel contributions

that affect perfusion quantification (Alsop and Detre, 1996, Alsop and Detre, 1998, Alsop et al 2010). An important result was achieved when McLaughlin and co-workers at NIH verified ASL in humans with PET (Ye et al. 2000). Indeed, the NIH group was very active in the early development of ASL (Duyn et al, 1994, Ye et al, 1996).

The major changes in the different ASL techniques is the manner in which spins are labeled. A variety of complex labeling paradigms have been developed and there continues to be advancements (Barbier et al, 1999, Norris and Schwartzbauer, 1999, Wong, 2007, Dai et al, 2008, Chuang et al 2008). These labeling strategies have been used to optimize ASL. A recent study shows that proper labeling strategies can unambiguously separate BOLD artifacts from perfusion measurements enabling perfusion based resting state measurements (Chuang et al, 2008). A growing area is using ASL to map perfusion territories from specific vessels. Early on John Detre and Don Williams showed that one could label specific vessels in the rat to do perfusion territory mapping using ASL techniques (Detre et al., 1994). This was extended to humans and efficient techniques to map the perfusion territories from major arteries to the brain have now been developed (Talagala and Noll, 1998, Zaharchuk et al, 1999, Wong, 2007, Paiva et al 2008, Chappell et al, 2010). Another area of continued progress has been to address the problem of quantitating how much label is in the vessels. This in turn has led to techniques that emphasize detection of water in vessels to measure blood volume (Silva et al 1997a, Silva et al, 1997b, Lu. et al. 2003, Hua et al 2011, Kim and Kim 2005). Indeed, there are clear indications that in one set of experiments it should be possible to generate angiograms, cerebral blood volume and cerebral blood flow images (Barbier et al, 2001). The range of clinical problems being addressed with ASL techniques continues to grow and the move to very high fields should lead to increases in resolution and sensitivity (Duyn et al, 2005). In general perfusion techniques for the human brain are still at resolutions lower than the size of relevant brain structures leading to measurements that are affected by partial volume from very low perfusion in white matter. Recent high resolution results (Fig. 1) indicate that with the optimization of high field scanners whole brain ASL perfusion measurements will approach 1 mm³ resolution. My prediction is that at this high resolution the relatively small changes in perfusion detected with neurological and psychiatric disorders at present with ASL MRI techniques will increase and begin to have a large impact on the neuro-radiological sciences and in the development of pharmaceuticals. I look forward to the Neuroimage issue celebrating 40 years of fMRI to see what whether we've succeeded in translating functional MRI techniques to widespread and robust radiological applications!

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References

- Ackerman JJ, Ewy CS, Kim SG, Shalwitz RA. Deuterium magnetic resonance in vivo: the measurement of blood flow and tissue perfusion. *Ann NY Acad Sci.* 1987; 508:89–98. [PubMed: 3439714]
- Alsop D, Detre JA. Reduced transit time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J Cereb Blood Flow Metab.* 1996; 16:1236–1249. [PubMed: 8898697]
- Alsop D, Detre JA. Multisection cerebral blood flow MR imaging with continuous arterial spin labeling. *Radiology.* 1998; 208:410–416. [PubMed: 9680569]
- Alsop DC, Dai W, Grossman M, Detre JA. Arterial spin labeling blood flow MRI: its role in the early characterization of Alzheimer's disease. *J Alzheimers Dis.* 2010; 20:871–880. [PubMed: 20413865]
- Balaban RS, Koretsky AP. Interpretation of ³¹P NMR saturation transfer experiments: what you can't see might confuse you. *Am J Physiol Cell Physiol.* 2011; C12–C15. [PubMed: 21490314]
- Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain function during task activation. *Magn Reson Med.* 1992; 25:390–397. [PubMed: 1614324]
- Barbier E, Silva AC, Kim HJ, Williams DS, Koretsky AP. Perfusion analysis using dynamic arterial spin labeling (DASL). *Magn Reson Med.* 1999; 41:299–308. [PubMed: 10080277]
- Barbier E, Silva AC, Kim SG, Koretsky AP. Perfusion imaging using dynamic arterial spin labeling. *Magn Reson Med.* 2001; 45:1021–1029. [PubMed: 11378880]
- Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science.* 1991; 254:716–719. [PubMed: 1948051]
- Bothnerby AA, Stephens RL, Lee JM, Warren CD, Jeanloz RW. Structure determination of a tetrasaccharide-transient nuclear overhauser effects in the rotating frame. *J Am Chem Soc.* 1984; 106:811–813.
- Bradley WG, Waluch V. Blood flow: magnetic resonance imaging. *Radiology.* 1985; 154:443–450. [PubMed: 3966131]
- Brown TR, Kincaid BM, Ugurbil K. NMR Chemical shift imaging in three dimensions. *Proc Natl Acad Sci USA.* 1982; 79:3523–3526. [PubMed: 6954498]
- Chappell MA, Okell TW, Jezzard P, Woolrich MW. *Magn Reson, Med.* 2010; 64:1529–1539. [PubMed: 20677231]
- Chuang KH, van Gelderen P, Merkle H, Bodurka J, Ikonomidou VN, Koretsky AP, Duyn JH, Talagala SL. Mapping resting-state functional connectivity using perfusion MRI. *Neuroimage.* 2008; 40:1595–1605. [PubMed: 18314354]
- Clow H, Young IR. Britain's brains produce first NMR scans. *New Scientist.* 1978; 80:588.
- Crooks LE, Mills CM, Davis PL, Brant-Zawadzki M, Hoenninger J, Arakawa M, Watts J, Kaufman L. Visualization of cerebral and vascular abnormalities by NMR imaging. The effects of imaging parameters on contrast. *Radiology.* 1982; 144:843–852. [PubMed: 7111736]
- Dadok J, Sprecher RF. Correlation NMR spectroscopy. *J Magn Reson.* 1974; 13:243–248.
- Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-drive inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med.* 2008; 60:1488–1497. [PubMed: 19025913]
- Deuel RK, Yue GM, Sherman WR, Schickner DJ, Ackerman JJ. *Science.* 1985; 228:1329–1330. [PubMed: 4001946]
- Detre JA, Eskey CJ, Koretsky AP. Measurement of cerebral blood flow in rat brain by ¹⁹F-detection of trifluoromethane washout. *Magn Reson Med.* 1990a; 15:45–57. [PubMed: 2374499]
- Detre JA, Williams DS, Koretsky AP. Nuclear magnetic resonance determination of flow, lactate, and phosphate metabolites during amphetamine stimulation of the rat brain. *NMR Biomed.* 1990b; 3:272–278. [PubMed: 2092743]
- Detre JA, Subramanian VH, Mitchell MD, Smith DS, Kobayashi A, Zaman A, Leigh JS Jr. Measurement of regional cerebral blood flow in cat brain using intracarotid ²H₂O and ²H imaging. *Magn Reson Med.* 1990c; 14:389–395. [PubMed: 2345518]

- Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion Imaging. *Magn Reson Med*. 1992; 23:37–45. [PubMed: 1734182]
- Detre JA, Zhang W, Roberts DA, Silva AS, Williams DS, Grandis DJ, Koretsky AP, Leigh JS. Tissue specific perfusion imaging using arterial spin labeling. *NMR Biomed*. 1994; 7:75–82. [PubMed: 8068529]
- Dixon WT, Du LN, Faul DD, Gado M, Rossnick S. Projection angiograms of blood labeled by adiabatic fast passage. *Magn Reson Med*. 1986; 3:454–462. [PubMed: 3724425]
- Doyle FH, Pennock JM, Orr JS, Gore JC, Bydder GM, Steiner RE, Young IR, Clow H, Bailes DR, Burl M, Gilderdale DJ, Walters PE. Images of the brain by nuclear magnetic resonance. *Lancet*. 1981; 11:53–57. [PubMed: 6113437]
- Du F, Zhu XH, Zhang Y, Friedman M, Zhang N, Ugurbil K, Chen W. Tightly coupled brain activity and cerebral ATP metabolic rate. *Proc Natl Acad Sci USA*. 2008; 105:6409–6414. [PubMed: 18443293]
- Dumoulin CL, Hart HR. Magnetic Resonance Angiography. *Radiology*. 1986; 161:717–720. [PubMed: 3786721]
- Duyn JH, Moonen CT, van Yperen GH, de Boer RW, Luyten PR. Inflow versus deoxyhemoglobin in BOLD functional MRI using gradient echoes at 1.5T. *NMR Biomed*. 7:83–88. [PubMed: 8068530]
- Duyn JH, van Gelderen P, Talagala L, Koretsky A, de Zwart JA. Technological advances in MRI measurement of brain perfusion. *J Magn Reson Imag*. 2005; 22:751–753.
- Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. *Radiology*. 1994; 192:513–520. [PubMed: 8029425]
- Eleff SM, Schnall MD, Ligetti L, Osbakken M, Subramanian VH, Chance B, Leigh JS Jr. Concurrent measurements of cerebral blood flow, sodium, lactate, and high-energy phosphate metabolism using ¹⁹F, ²³Na, ¹H, and ³¹P nuclear magnetic resonance spectroscopy. *Magn Reson Med*. 1988; 7:412–424. [PubMed: 3173056]
- Eskey CJ, Koretsky AP, Domach MM, Jain RK. 2H-nuclear magnetic resonance imaging of tumor blood flow: spatial and temporal heterogeneity on a tissue-isolated mammary adenocarcinoma. *Cancer Res*. 1992; 52:6010–6019. [PubMed: 1394226]
- Fish DR, Brooks DJ, Young IR, Bydder GM. Use of magnetic resonance imaging to identify changes in cerebral blood flow in epilepsy partialis continua. *Magn Reson Med*. 1988; 8:238–240. [PubMed: 3145383]
- Ho C, Perussi JR. Proton nuclear-magnetic resonance studies of hemoglobin. *Meth Enzymol*. 1994; 232:97–139. [PubMed: 8057888]
- Holland GN, Moore WS, Hawkes RC. NMR Neuroradiography. *British J Radiology*. 1980; 53:253–255.
- Hua J, Qin Q, Donahue MJ, Zhou J, Pekar JJ, van Zijl PC. Inflow based vascular-space-occupancy (iVASO) MRI. *Magn Reson Med*. 2011; 66:40–56. [PubMed: 21695719]
- Kim SG, Ackerman JJ. Quantitative determination of tumor blood flow and perfusion via deuterium nuclear magnetic resonance spectroscopy in mice. *Cancer Res*. 1988; 48:3449–3453. [PubMed: 2836055]
- Kim SG. Quantification of relative cerebral blood flow change by flow-sensitive alternative inversion recovery (FAIR) technique: application to functional mapping. *Magn Reson Med*. 1995; 34:293–301. [PubMed: 7500865]
- Kim T, Kim SG. Quantification of cerebral arterial blood volume and cerebral blood flow using MRI with modulation of tissue and vessel (MOTIVE) signals. *Magn Reson Med*. 2005; 54:333–342. [PubMed: 16032688]
- Koretsky AP, Basus VJ, James TL, Klein MP, Weiner MW. Detection of exchange reactions involving small metabolite pools using NMR magnetization transfer techniques: relevance to subcellular compartmentation of creatine kinase. *Magn Reson Med*. 1985; 2:586–594. [PubMed: 3880100]

- Koretsky AP, Wang S, Klein MP, James TL, Weiner MW. ³¹P NMR saturation transfer measurements of phosphorus exchange reactions in rat heart and kidney in situ. *Biochemistry*. 1986; 25:77–84. [PubMed: 3954995]
- Kramer DM, Schneider JS, Rudin AM, Lauterbur PC. True three-dimensional nuclear magnetic zeugmatographic images of a human brain. *Neuroradiology*. 1981; 21:239–244. [PubMed: 7266858]
- Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng HM, Brady TJ, Rosen BR. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA*. 1992; 89:5675–5679. [PubMed: 1608978]
- Kwong KK, Chesler DA, Weisskoff RM, Rosen BR. Perfusion MR Imaging. *Proceedings of the Society of Magnetic Resonance*. 1994; 2:1005.
- Kwong KK, Chesler DA, Weisskoff RM, Donahue KM, Davis TL, Ostergaard L, Campbell TA, Rosen BR. MR perfusion studies with T1-weighted echo planar imaging. *Magn Reson Med*. 1995; 34:878–887. [PubMed: 8598815]
- Lauterbur P. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature*. 1973; 242:190–191.
- Le Bihan D, Breton E, Lallemond D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions : application to diffusion and perfusion in neurologic disorders. *Radiology*. 1986; 161:401–407. [PubMed: 3763909]
- Llinas M, Klein MP, Neilands JB. Solution conformation of ferrichrome, a microbial iron transport cyclohexapeptide as deduced by high resolution proton magnetic resonance. *J Mol Biol*. 1970; 52:399–405. [PubMed: 5492288]
- Lowe IJ. Free Induction Decays of Rotating Solids. *Phys Rev Lett*. 1959; 2:285–287.
- Lowe IJ, Norberg RE. Free Induction Decays in Solids. *Phys Rev*. 1957; 107:46–61.
- Lu H, Golay X, Pekar JJ, Van Zijl PC. Functional magnetic resonance imaging based on changes in vascular space occupancy. *Magn Reson Med*. 2003; 50:263–274. [PubMed: 12876702]
- Maudsley AA, Hilal SK, PErman WH, Simon HE. Spatially resolved high resolution spectroscopy by “four dimensional” NMR. *J Magn Reson*. 1983; 51:147–152.
- Moran PR. A flow velocity zeugmatographic interlace for NMR imaging in humans. *Magn Reson Imag*. 1982; 1:197–203.
- Norris DG, Schwartzbauer C. Velocity selective radiofrequency pulse trains. *J Magn Reson Med*. 1999; 137:231–236.
- Moseley ME, Cohen Y, Mintorovich J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR. Early detection of regional ischemia in cats: comparison of diffusion-and T2-weighted MRI and spectroscopy. *Magn Reson Med*. 1990a; 14:330–346. [PubMed: 2345513]
- Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, Tsuruda J, Norman D. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology*. 1990b; 176:439–445. [PubMed: 2367658]
- Murphy-Boesch J, Koretsky AP. An in vivo NMR circuit for improved sensitivity. *J Magn Reson*. 1983; 54:526–532.
- Ogawa S, Lee TM, Nayak A, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*. 1990a; 14:68–78. [PubMed: 2161986]
- Ogawa S, Lee TM. Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. *Magn Reson Med*. 1990; 16:9–18. [PubMed: 2255240]
- Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA*. 1990b; 87:9868–9872. [PubMed: 2124706]
- Ogawa S, Tank DW, Menon R, Ellerman JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA*. 1992; 89:5951–5955. [PubMed: 1631079]
- Paiva FF, Tannus A, Talagala SL, Silva AC. Arterial spin labeling of cerebral perfusion territories using a separate labeling coil. *J Magn Reson Imag*. 2008; 27:970–977.

- Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. 1990; 14:249–265.
- Roberts DA, Bolinger L, Detre JA, Insko EK, Bergey P, Leigh JS. Continuous inversion angiography. *Magn Reson Med*. 1993; 29:631–636. [PubMed: 8505899]
- Roberts DA, Detre JA, Bolinger L, Insko EK, Leigh JS. Quantitative magnetic resonance imaging of human brain perfusion at 1.5T using steady-state inversion of arterial water. *Proc Natl Acad Sci USA*. 1994; 91:33–37. [PubMed: 8278387]
- Roberts DA, Detre JA, Bolinger L, Insko EK, Lenkinski RE, Pentecost MJ, Leigh JS. Renal perfusion in humans: MR imaging with spin tagging of arterial water. *Radiology*. 1995; 196:281–286. [PubMed: 7784582]
- Silva AC, Zhang W, Williams DS, Koretsky AP. Multi-slice MRI of rat brain perfusion during amphetamine stimulation using arterial spin labeling. *Magn Reson Med*. 1995; 33:209–214. [PubMed: 7707911]
- Silva AC, Zhang W, Williams DS, Koretsky AP. Estimation of water extraction fractions in rat brain using magnetic measurement of perfusion with arterial spin labeling. *Magn Reson Med*. 1997a; 37:58–68. [PubMed: 8978633]
- Silva AC, Zhang W, Williams DS, Koretsky AP. Evidence for the exchange of arterial spin-labeled water with tissue water in rat brain from diffusion sensitized measurements of perfusion. *Magn Reson Med*. 1997b; 38:232–237. [PubMed: 9256102]
- Singer JR. Blood flow rates by nuclear magnetic resonance measurements. *Science*. 1959; 130:1652–1653. [PubMed: 17781388]
- Talagala SL, Noll DC. Functional MRI using steady-state arterial water labeling. *Magn Reson Med*. 1998; 39:179–183. [PubMed: 9469699]
- Talagala SL, Ye FQ, Ledden PJ, Chesnick S. Whole brain 3D perfusion MRI at 3.0T using CASL with a separate labeling coil. *Magn Reson Med*. 2004; 52:131–140. [PubMed: 15236376]
- Villringer A, Rosen BR, Belliveau JW, Ackerman JL, Lauffer RB, Buxton RB, Chao YS, Wedeen VJ, Brady TJ. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. *Magn Reson Med*. 1988; 6:164–174. [PubMed: 3367774]
- Yeh TC, Zhang W, Ildstad ST, Ho C. Intracellular labeling of T-cells with superparamagnetic contrast agents. *Magn Reson Med*. 1993; 30:617–625. [PubMed: 8259062]
- Young IR, Hall AS, Pallis CA, Bydder GM, Legg NJ, Steiner RG. Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet*. 1981; 14:1063–1066. [PubMed: 6118521]
- Walsh TR, Detre JA, Koretsky AP, Simplaceanu E, Halow JM, Rao P, Makowka L, Ho C. Response of normal and reperfused liver to glucagon stimulation: NMR detection of blood flow and high-energy phosphates. *Biochim Biophys Acta*. 1993; 1181:7–14. [PubMed: 8457608]
- Ward KM, Aletras AH, Balaban RS. A new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST). *J Magn Reson*. 2000; 143:79–87. [PubMed: 10698648]
- Wedeen VJ, Meuli RA, Edelman RR, Geller SC, Frank LR, Brady TJ, Rosen BR. Projective imaging of pulsatile flow with magnetic resonance. *Science*. 1985; 230:946–948. [PubMed: 4059917]
- Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci USA*. 1992; 89:212–216. [PubMed: 1729691]
- Williams DS, Grandis DJ, Zhang W, Koretsky AP. Magnetic resonance imaging of perfusion in the isolated rat heart using spin inversion of arterial water. *Magn Reson Med*. 1993; 30:361–365. [PubMed: 8412609]
- Williams DS, Zhang W, Koretsky AP, Adler S. Perfusion imaging of the rat kidney with MR. *Radiology*. 1994; 190:813–818. [PubMed: 8115632]
- Williams DS, Detre JD, Zhang W, Silva AC, Koretsky AP. A survey of labeling strategies for perfusion imaging by arterial spin labeling. *Proceeding of Society of Magnetic Resonance*. 1994; 2:1004.
- Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Magn Reson Med*. 1989; 10:135–144. [PubMed: 2547135]
- Wong EC, Buxton RB, Frank LR. Quantitative imaging of perfusion using a single subtraction (QUIPSS). *Neuroimage*. 1996; 3:S5.

- Wong EC. Vessel-encoded arterial spin-labeling using pseudocontinuous tagging. *Magn Reson Med*. 2007; 58:1086–1091. [PubMed: 17969084]
- Wood, JH. Cerebral Blood Flow. In: Wood, JH., editor. *Physiologic and Clinical Aspects*. McGraw-Hill; NY: 1987.
- Xu S, Shen J. Studying Enzymes by In Vivo C Magnetic Resonance Spectroscopy. *Prog Nucl Magn Reson Spectrosc*. 2009; 55:266–283. [PubMed: 20161496]
- Ye F, Pekar JJ, Jezzard P, Duyn J, Frank JA, McLaughlin AC. Perfusion Imaging of the human brain at 1.5T using a single-shot EPI spin tagging approach. 1996
- Ye F, Berman KF, Ellmore T, Esposito G, van Horn JD, Yang Y, Duyn J, Smith AM, Frank JA, Weinberger DR, McLaughlin AC. H(2)(15)O PET validation of steady-state arterial spin tagging cerebral blood flow measurements in humans. *Magn Reson Med*. 2000; 44:450–456. [PubMed: 10975898]
- Zaharchuk G, Ledden PJ, Kwong KK, Reese TG, Rosen BR, Wald LL. Multislice perfusion and perfusion territory imaging in humans with separate label and image coils. *Magn Reson Med*. 1999; 41:1093–1098. [PubMed: 10371440]
- Zhang W, Williams DS, Detre JA, Koretsky AP. Measurement of brain perfusion by volume localized NMR spectroscopy using inversion of arterial water spins: accounting for transit time and cross-relaxation. *Magn Reson Med*. 1992; 25:362–371. [PubMed: 1614321]
- Zhang W, Silva AC, Williams DS, Koretsky AP. NMR measurement of perfusion using arterial spin labeling without saturation of macromolecular spins. *Magn Reson Med*. 1995; 33:370–376. [PubMed: 7760704]

Figure 1.

ASL MRI of regional cerebral blood flow of the human brain twenty years ago (left) and now (right) obtained by S.L. Talagala. The left panel was taken in 1992 at the Pittsburgh NMR Institute from a brain near and dear to the author's heart. This difference image between control and steady-state labeling achieved with multiple inversions was taken at 1.5T with a spin echo sequence. Resolution was $2\text{ mm} \times 2\text{ mm} \times 10\text{ mm}$ and it took about 30 min to obtain. Motion artifacts, scanner instability, and potential MTC artifacts plagued measurements at the time. The right panel shows cerebral regional blood flow at $1\text{ mm} \times 1\text{ mm} \times 3\text{ mm}$ resolution taken on a 3T MRI at NIH using array detectors, a separate arterial labeling coil and EPI (Talagala et al, 2004). This image took about 15 min to acquire. Increases in sensitivity expected at 7T and higher magnetic fields point to the potential for very high resolution perfusion images of the human brain.