ISMRM Weekend Educational Course

Imaging Microstructure:
Susceptibility Basics

Sunday, 31st May 2015

Karin Shmueli Ph.D.
Department of Medical Physics & Biomedical Engineering, University College London, UK
k.shmueli@ucl.ac.uk

Highlights

- Magnetic susceptibility is an intrinsic tissue property that determines tissue magnetisation in response to an applied magnetic field and depends on the tissue composition and microstructure
- Relative susceptibility maps can be calculated from T2*-weighted gradient-echo phase images
- There are several steps to the susceptibility mapping process including: accurate combination of phase images from multiple RF coil channels, phase unwrapping, removal of large-scale background fields, and susceptibility calculation by regularised inversion. There are many algorithms available for each stage of this processing pipeline.
- Susceptibility maps reveal information about tissue iron, myelin, and deoxyhaemoglobin content, venous oxygenation, calcifications and any other sources of sufficient concentration and susceptibility.
- Tissue susceptibility is also affected by tissue microstructure and compartmentalisation and the susceptibility in white matter has been found to be anisotropic.
- Models of complex microstructural effects need to be developed and incorporated into susceptibility mapping methods if they are to yield the maximum microstructural information.

Susceptibility Basics

TARGET AUDIENCE – Scientists and clinicians interested in understanding the basis of and methods for generating tissue magnetic susceptibility images and why they are useful for revealing microstructural information.

OBJECTIVES – Following this contribution, participants should be able to:

- understand what tissue magnetic susceptibility is
- implement susceptibility mapping techniques to create susceptibility images
- understand what susceptibility maps can tell us about tissue composition and microstructure

WHAT IS SUSCEPTIBILITY?

Susceptibility is an intrinsic bulk material or tissue property that determines how the material or tissue will interact with and behave in an applied magnetic field [1]. Tissues with positive susceptibility values are paramagnetic (i.e. their magnetisation increases with the applied magnetic field strength) and those with negative susceptibility values are diamagnetic. The reason we are interested in tissue magnetic susceptibility is that it is directly related to the tissue composition and microstructure. A simple way to understand how different tissue constituents contribute to the overall bulk magnetic susceptibility of the tissue is through Wiedemann's Additivity Law [2]. This law states that the overall susceptibility of a mixture of components is the sum of the susceptibility of each component weighted by its mass fraction or relative volume of occupation depending on whether we are calculating mass or dimensionless (volume) susceptibilities respectively. There are of

course complications to this law (such as chemical reactions or conformational changes in macromolecules) but it is a useful conceptual aid nonetheless.

HOW CAN WE MEASURE TISSUE MAGNETIC SUSCEPTIBILITY?

Now that we have established that susceptibility depends on tissue composition, how might we actually measure this tissue magnetic susceptibility? The key to this is that the phase of the complex MRI signal in simple T2*-weighted gradient-echo MRI sequences is directly determined by the underlying tissue magnetic susceptibility [3, 4]. Therefore we can exploit the rich contrast available in these phase images [5] to calculate maps of the underlying tissue magnetic susceptibility distribution.

This process of susceptibility mapping has developed rapidly over the last few years and has been described in a few recent review papers [6-8]. It is not as simple as it might first appear for several reasons: Phase images suffer from phase wrapping or aliasing and there are a large variety of unwrapping algorithms available, e.g. [9-11], each with their own advantages and drawbacks. The measured phase also depends upon imaging parameters such as the echo time (TE) and the voxel aspect ratio [12, 13]. It is important to be aware that the phase will also be affected by hardware differences in vendor systems such that there are two phase sign conventions [14]. Furthermore, when using multiple channel radio frequency coils, it is crucial to ensure that the phase images from each of the coil channels is combined correctly to reconstruct an accurate phase image [15-18] otherwise intractable artifacts known as open-ended fringe lines or phase singularities can occur.

For susceptibility mapping we need to take all of these effects into account. In addition to coil phase combination and phase unwrapping, the next step in calculating susceptibility maps is to remove large-scale background phase variations caused primarily by the relatively large susceptibility difference between tissue and air in cavities and outside the body. These background phase variations are often much larger than the susceptibility-induced phase differences of interest between different tissues and there are now a wide variety of techniques for removing them, e.g. [19, 20]. However, it is important to note that, as a result of removing these background phase variations, the contrast observed in susceptibility maps is relative rather than absolute.

The final step in calculating susceptibility images from these processed phase images is to solve the inverse problem i.e. calculate the susceptibility distribution from the measured phase images. Formulated in real space, the inverse problem is a deconvolution of the unit dipole function (the dipole kernel that describes the field distribution from a susceptibility point source) from the measured phase distribution. However, this becomes much simpler in the Fourier domain (k-space) as we can exploit the convolution theorem so that the inverse problem can be written as a simple division. Problems occur where the denominator (the Fourier transform of the dipole kernel) tends to zero as the result will then tend to infinity.

Several methods have been developed to overcome this ill-conditioned nature of the inverse problem. K-space based algorithms do this by removing, substituting or correcting the data inside ill-conditioned regions on and near two conical surfaces in k-space. Different methods can be classified according to whether they require acquisitions at multiple angles [21] or at a single orientation [22, 23] with respect to the main magnetic field. Some of these methods, based on thresholding the denominator (so-called Thresholded K-space Division or TKD methods [22, 23]), may be affected by streaking artifacts but these can be minimised by an appropriate choice of the threshold and a corresponding scaling of the resulting susceptibility map [24]. These k-space-based approaches are straightforward and computationally efficient relative to image-space-based methods. The latter e.g. [25-28] rely on a variety of techniques for regularizing the inverse problem e.g. by iterations and/or

by incorporating spatial prior information. These may result in a smoothed susceptibility map affected by the spatial prior information introduced. Newer hybrid methods exploit the advantages of both formulating the problem in k-space and solving it using image space information [29, 30].

The key message is that there are now a large variety of algorithms available, each one with its own relative merits and disadvantages. The tissue magnetic susceptibility maps produced using these methods have important advantages over the processed phase images from which they were calculated; they overcome the non-local and orientation-dependent nature of the contrast in phase images [31], allowing improvements in the visualisation of tissue structure and composition.

WHAT DOES SUSCEPTIBILITY TELL US ABOUT TISSUE COMPOSITION AND MICROSTRUCTURE?

IRON CONTENT

Tissues rich in ferritin (stored iron) are relatively paramagnetic and show strong contrast in susceptibility maps. Several investigators have found strong correlations between the measured tissue magnetic susceptibility in brain regions such as the red nucleus, substantia nigra and putamen and their iron content, often estimated from post-mortem studies [19, 22, 32, 33]. Tissue MRI susceptibility values have also been found to correlate with iron content measured in the same tissue using independent methods such as X-ray fluorescence imaging and inductively coupled plasma mass spectrometry [34, 35].

Phase contrast between cortical layers has also been shown to have a strong contribution from tissue iron as extracting the iron from fixed visual cortex has been shown to virtually eliminate the intra-cortical phase contrast [36]. In that study, the phase images showed a very small, (opposing) residual contrast that may be due to increased myelination in some cortical layers such as the stria of Gennari (see below). The dependence of susceptibility image contrast on iron content has been exploited for several clinical applications, for example to improve targeting of structures for deep-brain stimulation [37] and as a marker of increased iron content in the substantia nigra in patients with Parkinson's disease [38].

DEOXYHAEMOGLOBIN

It is well-established that deoxyhaemoglobin is paramagnetic with respect to most tissues and this is the basis of functional MRI and susceptibility-weighted imaging (SWI) [7, 39]. Despite being the dominant source of phase contrast in and near blood vessels, the contribution of endogenous deoxyhaemoglobin to the intrinsic phase contrast between grey and white matter in the brain has been shown to be negligible [40]. Because deoxyhaemoglobin is paramagnetic, susceptibility maps highlight the venous vasculature [41] and because the venous susceptibility depends linearly on the deoxyhaemoglobin concentration, susceptibility mapping allows quantification of venous oxygenation [42, 43]. The high paramagnetic susceptibility of deoxyhaemoglobin and other blood products (e.g. haemosiderin) has also enabled susceptibility maps to reveal and assess microbleeds [44-46]. A further and swiftly emerging application is the utilisation of endogenous oxygenation-dependent susceptibility contrast for functional imaging [47-49].

MYELIN

In addition to revealing paramagnetic contributions, susceptibility maps also show prominent diamagnetic sources including myelin which is thought to have a slightly more diamagnetic susceptibility than other tissues due to its high lipid content [5, 50]. Demyelination, induced by a cuprizone diet [50] or in shiverer mice [51], has been shown to almost completely remove the susceptibility-induced contrast between grey and white matter. Changes in the susceptibility contrast in and around Multiple Sclerosis lesions has been attributed to changes in both myelination

and iron content [18, 52-55] as well as microstructural alterations and this is an active and occasionally controversial area of research [56-60].

ETC

It follows from Wiedemann's Law and the examples above that any diamagnetic or paramagnetic tissue constituents can contribute to susceptibility contrast if they are present at sufficient concentrations and/or have a large enough (positive or negative) susceptibility. Thus, we can observe calcifications and distinguish them from haemorrhages in susceptibility images [61, 62] as calcium compounds are strongly diamagnetic. A recent study has also used susceptibility mapping to measure the effect of copper accumulation in the brain in Wilson disease [63].

MICROSTRUCTURE & SUSCEPTIBILITY ANISOTROPY

In addition to its composition, tissue's structure at several different scales affects the susceptibility contrast. Even if a tissue structure's overall macroscopic shape and geometry remain constant, if its microstructural orientation with respect to B_0 is altered, this changes the phase contrast and correspondingly the calculated magnetic susceptibility [64]. This phenomenon has been explained by susceptibility anisotropy [65]. Susceptibility anisotropy has been measured in white matter (whose fibres are found to be more diamagnetic when they run perpendicular to B_0) and seems to arise from the highly ordered macro-molecular structure of the lipid bilayers in the myelin sheath [66]. This effect has been exploited in Susceptibility Tensor Imaging [65, 67, 68] to reveal white matter structure via a mechanism complementary to that utilised in Diffusion Tensor Imaging.

Tissue cellular architecture, orientational ordering and compartmentalisation [69] play an important role in phase and susceptibility contrast [56-60, 68, 70, 71], with protons diffusing within, exchanging between and selectively sampling compartments with different susceptibilities and magnetic fields. Fibre-orientation-dependent phase contrast has been explained by a simple two-pool model in which the myelin sheath is modelled as a hollow cylinder of anisotropic susceptibility with water in the sheath having a reduced T2 and proton density than its surroundings [68]. All of these complex microstructural effects need to be modelled and these models need to be incorporated into susceptibility mapping methods to allow them to give us as much accurate information as possible on the underlying tissue composition and microstructure.

REFERENCES

[1] J. F. Schenck, "The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds," *Medical Physics,* vol. 23, pp. 815-850, 1996.

[2] P. W. Kuchel, B. E. Chapman, W. A. Bubb, P. E. Hansen, C. J. Durrant, and M. P. Hertzberg, "Magnetic susceptibility: Solutions, emulsions, and cells," *Concepts in Magnetic Resonance Part A: Bridging Education and Research,* vol. 18, pp. 56-71, 2003.

[3] J. P. Marques and R. Bowtell, "Application of a Fourier-based method for rapid calculation of field inhomogeneity due to spatial variation of magnetic susceptibility," *Concepts in Magnetic Resonance Part B: Magnetic Resonance Engineering,* vol. 25B, pp. 65-78, 2005.

[4] R. Salomir, B. D. De Senneville, and C. T. W. Moonen, "A fast calculation method for magnetic field inhomogeneity due to an arbitrary distribution of bulk susceptibility," *Concepts in Magnetic Resonance Part B-Magnetic Resonance Engineering,* vol. 19B, pp. 26-34, Oct 2003.

[5] J. H. Duyn, P. van Gelderen, T. Q. Li, J. A. de Zwart, A. P. Koretsky, and M. Fukunaga, "High-field MRI of brain cortical substructure based on signal phase," *Proc Natl Acad Sci U S A,* vol. 104, pp. 11796-801, Jul 10 2007.

[6] Y. Wang and T. Liu, "Quantitative susceptibility mapping (QSM): Decoding MRI data for a tissue magnetic biomarker," *Magn Reson Med,* Jul 17 2014.

[7] C. Liu, W. Li, K. A. Tong, K. W. Yeom, and S. Kuzminski, "Susceptibility-weighted imaging and quantitative susceptibility mapping in the brain," *J Magn Reson Imaging,* Oct 1 2014.
[8] E. M. Haacke, S. Liu, S. Buch, W. Zheng, D. Wu, and Y. Ye, "Quantitative susceptibility mapping: current status and future directions," *Magn Reson Imaging,* vol. 33, pp. 1-25, Jan 2015.
[9] M. Jenkinson, "Fast, automated, N-dimensional phase-unwrapping algorithm," *Magnetic Resonance in Medicine,* vol. 49, p. 193, 2003.
[10] S. Witoszynskyj, A. Rauscher, J. R. Reichenbach, and M. Barth, "Phase unwrapping of MR images using Phi UN - A fast and robust region growing algorithm," *Medical Image Analysis,* vol. 13, pp. 257-268, Apr 2009.
[11] M. A. Schofield and Y. M. Zhu, "Fast phase unwrapping algorithm for interferometric applications," *Optics Letters,* vol. 28, pp. 1194-1196, Jul 15 2003.
[12] Y. B. Xu and E. M. Haacke, "The role of voxel aspect ratio in determining apparent vascular phase behavior in susceptibility weighted imaging," *Magnetic Resonance Imaging,* vol. 24, pp. 155-160, Feb 2006.
[13] A. Deistung, A. Rauscher, J. Sedlacik, J. Stadler, S. Witoszynskyj, and J. R. Reichenbach, "Susceptibility weighted imaging at ultra high magnetic field strengths: theoretical considerations and experimental results," *Magn Reson Med,* vol. 60, pp. 1155-68, Nov 2008.
[14] G. E. Hagberg, E. B. Welch, and A. Greiser, "The sign convention for phase values on different vendor systems: definition and implications for susceptibility-weighted imaging," *Magnetic Resonance Imaging,* vol. 28, pp. 297-300, Feb 2010.
[15] S. Robinson, G. Grabner, S. Witoszynskyj, and S. Trattnig, "Combining Phase Images From Multi-Channel RF Coils Using 3D Phase Offset Maps Derived From a Dual-Echo Scan," *Magnetic Resonance in Medicine,* vol. 65, pp. 1638-1648, Jun 2011.
[16] S. Robinson and J. Jovicich, "B(0) Mapping With Multi-Channel RF Coils at High Field," *Magnetic Resonance in Medicine,* vol. 66, pp. 976-988, Oct 2011.
[17] D. L. Parker, A. Payne, N. Todd, and J. R. Hadley, "Phase Reconstruction from Multiple Coil Data Using a Virtual Reference Coil," *Magnetic Resonance in Medicine,* vol. 72, pp. 563-569, Aug 2014.
[18] K. E. Hammond, J. M. Lupo, D. Xu, M. Metcalf, D. A. Kelley, D. Pelletier*, et al.*, "Development of a robust method for generating 7.0 T multichannel phase images of the brain with application to normal volunteers and patients with neurological diseases," *Neuroimage,* vol. 39, pp. 1682-92, Feb 15 2008.
[19] F. Schweser, A. Deistung, B. W. Lehr, and J. R. Reichenbach, "Quantitative imaging of intrinsic magnetic tissue properties using MRI signal phase: an approach to in vivo brain iron metabolism?," *Neuroimage,* vol. 54, pp. 2789-807, Feb 14 2011.
[20] T. Liu, I. Khalidov, L. de Rochefort, P. Spincemaille, J. Liu, A. J. Tsiouris*, et al.*, "A novel background field removal method for MRI using projection onto dipole fields (PDF)," *Nmr in Biomedicine,* vol. 24, pp. 1129-1136, Nov 2011.
[21] T. Liu, P. Spincemaille, L. de Rochefort, B. Kressler, and Y. Wang, "Calculation of susceptibility through multiple orientation sampling (COSMOS): a method for conditioning the inverse problem from measured magnetic field map to susceptibility source image in MRI," *Magn Reson Med,* vol. 61, pp. 196-204, Jan 2009.
[22] K. Shmueli, J. A. de Zwart, P. van Gelderen, T. Q. Li, S. J. Dodd, and J. H. Duyn, "Magnetic susceptibility mapping of brain tissue in vivo using MRI phase data," *Magn Reson Med,* vol. 62, pp. 1510-22, Dec 2009.
[23] S. Wharton, A. Schafer, and R. Bowtell, "Susceptibility mapping in the human brain using threshold-based k-space division," *Magn Reson Med,* vol. 63, pp. 1292-304, May 2010.
[24] F. Schweser, A. Deistung, K. Sommer, and J. R. Reichenbach, "Toward online reconstruction of quantitative susceptibility maps: superfast dipole inversion," *Magn Reson Med,* vol. 69, pp. 1582-94, Jun 2013.

[25] L. de Rochefort, T. Liu, B. Kressler, J. Liu, P. Spincemaille, V. Lebon*, et al.*, "Quantitative susceptibility map reconstruction from MR phase data using bayesian regularization: validation and application to brain imaging," *Magn Reson Med,* vol. 63, pp. 194-206, Jan 2010.

[26] B. Kressler, L. de Rochefort, T. Liu, P. Spincemaille, Q. Jiang, and Y. Wang, "Nonlinear regularization for per voxel estimation of magnetic susceptibility distributions from MRI field maps," *IEEE Trans Med Imaging,* vol. 29, pp. 273-81, Feb 2010.

[27] T. Liu, J. Liu, L. de Rochefort, P. Spincemaille, I. Khalidov, J. R. Ledoux*, et al.*, "Morphology enabled dipole inversion (MEDI) from a single-angle acquisition: comparison with COSMOS in human brain imaging," *Magn Reson Med,* vol. 66, pp. 777-83, Sep 2011.

[28] B. Bilgic, A. P. Fan, J. R. Polimeni, S. F. Cauley, M. Bianciardi, E. Adalsteinsson*, et al.*, "Fast Quantitative Susceptibility Mapping with L1-Regularization and Automatic Parameter Selection," *Magnetic Resonance in Medicine,* vol. 72, pp. 1444-1459, Nov 2014.

[29] F. Schweser, K. Sommer, A. Deistung, and J. R. Reichenbach, "Quantitative susceptibility mapping for investigating subtle susceptibility variations in the human brain," *Neuroimage,* vol. 62, pp. 2083-2100, Sep 2012.

[30] J. Tang, S. Liu, J. Neelavalli, Y. C. Cheng, S. Buch, and E. M. Haacke, "Improving susceptibility mapping using a threshold-based K-space/image domain iterative reconstruction approach," *Magn Reson Med,* vol. 69, pp. 1396-407, May 2013.

[31] K. Shmueli, P. Van Gelderen, B. Yao, J. De Zwart, M. Fukunaga, and J. Duyn, "The Dependence of Tissue Phase Contrast on Orientation Can Be Overcome by Quantitative Susceptibility Mapping," *Proceedings 17th Scientific Meeting, International Society for Magnetic Resonance in Medicine,* p. 466, 2009.

[32] F. Schweser, A. Deistung, B. W. Lehr, K. Sommer, and J. R. Reichenbach, "SEMI-TWInS: Simultaneous Extraction of Myelin and Iron using a T2*-Weighted Imaging Sequence," *Proceedings 19th Scientific Meeting, International Society for Magnetic Resonance in Medicine,* p. 120, 2011.

[33] S. Wharton and R. Bowtell, "Whole-brain susceptibility mapping at high field: a comparison of multiple- and single-orientation methods," *Neuroimage,* vol. 53, pp. 515-25, Nov 1 2010.

[34] C. Langkammer, F. Schweser, N. Krebs, A. Deistung, W. Goessler, E. Scheurer*, et al.*, "Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study," *Neuroimage,* vol. 62, pp. 1593-1599, Sep 2012.

[35] W. L. Zheng, H. Nichol, S. F. Liu, Y. C. N. Cheng, and E. M. Haacke, "Measuring iron in the brain using quantitative susceptibility mapping and X-ray fluorescence imaging," *Neuroimage,* vol. 78, pp. 68-74, Sep 2013.

[36] M. Fukunaga, T. Q. Li, P. van Gelderen, J. A. de Zwart, K. Shmueli, B. Yao*, et al.*, "Layer-specific variation of iron content in cerebral cortex as a source of MRI contrast," *Proc Natl Acad Sci U S A,* vol. 107, pp. 3834-9, Feb 23 2010.

[37] R. L. O'Gorman, K. Shmueli, K. Ashkan, M. Samuel, D. J. Lythgoe, A. Shahidiani*, et al.*, "Optimal MRI methods for direct stereotactic targeting of the subthalamic nucleus and globus pallidus," *Eur Radiol,* vol. 21, pp. 130-6, Jan 2011.

[38] A. K. Lotfipour, S. Wharton, S. T. Schwarz, V. Gontu, A. Schafer, A. M. Peters*, et al.*, "High resolution magnetic susceptibility mapping of the substantia nigra in Parkinson's disease," *J Magn Reson Imaging,* vol. 35, pp. 48-55, Jan 2012.

[39] E. M. Haacke, Y. Xu, Y. C. Cheng, and J. R. Reichenbach, "Susceptibility weighted imaging (SWI)," *Magn Reson Med,* vol. 52, pp. 612-8, Sep 2004.

[40] J. Lee, Y. Hirano, M. Fukunaga, A. C. Silva, and J. H. Duyn, "On the contribution of deoxy-hemoglobin to MRI gray-white matter phase contrast at high field," *Neuroimage,* vol. 49, pp. 193-8, Jan 1 2010.

[41] S. F. Liu, K. Mok, J. Neelavalli, Y. C. N. Cheng, J. Tang, Y. Q. Ye*, et al.*, "Improved MR Venography Using Quantitative Susceptibility-Weighted Imaging," *Journal of Magnetic Resonance Imaging,* vol. 40, pp. 698-708, Sep 2014.

[42] B. Xu, T. Liu, P. Spincemaille, M. Prince, and Y. Wang, "Flow Compensated Quantitative Susceptibility Mapping for Venous Oxygenation Imaging," *Magnetic Resonance in Medicine,* vol. 72, pp. 438-445, Aug 2014.

[43] A. P. Fan, B. Bilgic, L. Gagnon, T. Witzel, H. Bhat, B. R. Rosen*, et al.*, "Quantitative oxygenation venography from MRI phase," *Magn Reson Med,* vol. 72, pp. 149-59, Jul 2014.

[44] J. Klohs, I. W. Politano, A. Deistung, J. Grandjean, A. Drewek, M. Dominietto*, et al.*, "Longitudinal Assessment of Amyloid Pathology in Transgenic ArcA beta Mice Using Multi-Parametric Magnetic Resonance Imaging," *Plos One,* vol. 8, Jun 19 2013.

[45] J. Klohs, A. Deistung, F. Schweser, J. Grandjean, M. Dominietto, C. Waschkies*, et al.*, "Detection of cerebral microbleeds with quantitative susceptibility mapping in the ArcAbeta mouse model of cerebral amyloidosis," *Journal of Cerebral Blood Flow and Metabolism,* vol. 31, pp. 2282-2292, Dec 2011.

[46] T. Liu, K. Surapaneni, M. Lou, L. Q. Cheng, P. Spincemaille, and Y. Wang, "Cerebral Microbleeds: Burden Assessment by Using Quantitative Susceptibility Mapping," *Radiology,* vol. 262, pp. 269-278, Jan 2012.

[47] D. Z. Balla, R. M. Sanchez-Panchuelo, S. J. Wharton, G. E. Hagberg, K. Scheffler, S. T. Francis*, et al.*, "Functional quantitative susceptibility mapping (fQSM)," *Neuroimage,* vol. 100, pp. 112-124, Oct 15 2014.

[48] M. Bianciardi, P. van Gelderen, and J. H. Duyn, "Investigation of BOLD fMRI resonance frequency shifts and quantitative susceptibility changes at 7 T," *Human Brain Mapping,* vol. 35, pp. 2191-2205, May 2014.

[49] J. R. Reichenbach, "The future of susceptibility contrast for assessment of anatomy and function," *Neuroimage,* vol. 62, pp. 1311-5, Aug 15 2012.

[50] J. Lee, K. Shmueli, B. T. Kang, B. Yao, M. Fukunaga, P. van Gelderen*, et al.*, "The contribution of myelin to magnetic susceptibility-weighted contrasts in high-field MRI of the brain," *Neuroimage,* vol. 59, pp. 3967-75, Feb 15 2012.

[51] C. L. Liu, W. Li, G. A. Johnson, and B. Wu, "High-field (9.4 T) MRI of brain dysmyelination by quantitative mapping of magnetic susceptibility," *Neuroimage,* vol. 56, pp. 930-938, Jun 1 2011.

[52] D. A. Yablonskiy, J. Luo, A. L. Sukstanskii, A. Iyer, and A. H. Cross, "Biophysical mechanisms of MRI signal frequency contrast in multiple sclerosis," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 109, pp. 14212-14217, Aug 28 2012.

[53] B. Yao, F. Bagnato, E. Matsuura, H. Merkle, P. van Gelderen, F. K. Cantor*, et al.*, "Chronic Multiple Sclerosis Lesions: Characterization with High-Field-Strength MR Imaging," *Radiology,* vol. 262, pp. 206-215, Jan 2012.

[54] W. Chen, S. A. Gauthier, A. Gupta, J. Comunale, T. Liu, S. Wang*, et al.*, "Quantitative Susceptibility Mapping of Multiple Sclerosis Lesions at Various Ages," *Radiology,* vol. 0, p. 130353.

[55] C. Wisnieff, S. Ramanan, J. Olesik, S. Gauthier, Y. Wang, and D. Pitt, "Quantitative susceptibility mapping (QSM) of white matter multiple sclerosis lesions: Interpreting positive susceptibility and the presence of iron," *Magnetic Resonance in Medicine,* pp. n/a-n/a, 2014.

[56] D. A. Yablonskiy, X. He, J. Luo, and A. L. Sukstanskii, "Lorentz Sphere Versus Generalized Lorentzian Approach: What Would Lorentz Say About It?," *Magnetic Resonance in Medicine,* vol. 72, pp. 4-7, Jul 2014.

[57] D. A. Yablonskiy and A. L. Sukstanskii, "Biophysical Mechanisms of Myelin-Induced Water Frequency Shifts," *Magnetic Resonance in Medicine,* vol. 71, pp. 1956-1958, Jun 2014.

[58] A. L. Sukstanskii and D. A. Yablonskiy, "On the Role of Neuronal Magnetic Susceptibility and Structure Symmetry on Gradient Echo MR Signal Formation," *Magnetic Resonance in Medicine,* vol. 71, pp. 345-353, Jan 2014.
[59] J. H. Duyn and T. M. Barbara, "Sphere of Lorentz and Demagnetization Factors in White Matter," *Magnetic Resonance in Medicine,* vol. 72, pp. 1-3, Jul 2014.
[60] J. H. Duyn, "Frequency Shifts in the Myelin Water Compartment," *Magnetic Resonance in Medicine,* vol. 71, pp. 1953-1955, Jun 2014.
[61] F. Schweser, A. Deistung, B. W. Lehr, and J. R. Reichenbach, "Differentiation between diamagnetic and paramagnetic cerebral lesions based on magnetic susceptibility mapping," *Med Phys,* vol. 37, pp. 5165-78, Oct 2010.
[62] F. Schweser, K.-H. Herrmann, A. Deistung, M. Atterbury, P. A. Baltzer, H. P. Burmeister*, et al.*, "Quantitative magnetic susceptibility mapping (QSM) in breast disease reveals additional information for MR-based characterization of carcinoma and calcification," *Proceedings 19th Scientific Meeting, International Society for Magnetic Resonance in Medicine,* p. 1014, 2011.
[63] D. Fritzsch, M. Reiss-Zimmermann, R. Trampel, R. Turner, K. T. Hoffmann, and A. Schafer, "Seven-Tesla Magnetic Resonance Imaging in Wilson Disease Using Quantitative Susceptibility Mapping for Measurement of Copper Accumulation," *Invest Radiol,* Nov 11 2013.
[64] J. Lee, K. Shmueli, M. Fukunaga, P. van Gelderen, H. Merkle, A. C. Silva*, et al.*, "Sensitivity of MRI resonance frequency to the orientation of brain tissue microstructure," *Proc Natl Acad Sci U S A,* vol. 107, pp. 5130-5, Mar 16 2010.
[65] C. Liu, "Susceptibility tensor imaging," *Magn Reson Med,* vol. 63, pp. 1471-7, Jun 2010.
[66] W. Li, B. Wu, A. V. Avram, and C. Liu, "Magnetic susceptibility anisotropy of human brain in vivo and its molecular underpinnings," *NeuroImage,* vol. 59, pp. 2088-2097, 2/1/ 2012.
[67] C. Liu, W. Li, B. Wu, Y. Jiang, and G. A. Johnson, "3D fiber tractography with susceptibility tensor imaging," *NeuroImage,* vol. 59, pp. 1290-1298, 1/16/ 2012.
[68] S. Wharton and R. Bowtell, "Fiber orientation-dependent white matter contrast in gradient echo MRI," *Proceedings of the National Academy of Sciences,* vol. 109, pp. 18559-18564, November 6, 2012 2012.
[69] W. C. Chen, S. Foxley, and K. L. Miller, "Detecting microstructural properties of white matter based on compartmentalization of magnetic susceptibility," *Neuroimage,* vol. 70, pp. 1-9, Apr 15 2013.
[70] X. He and D. A. Yablonskiy, "Biophysical mechanisms of phase contrast in gradient echo MRI," *Proc Natl Acad Sci U S A,* vol. 106, pp. 13558-63, Aug 11 2009.
[71] P. Sati, P. van Gelderen, A. C. Silva, D. S. Reich, H. Merkle, J. A. de Zwart*, et al.*, "Micro-compartment specific T2* relaxation in the brain," *Neuroimage,* vol. 77, pp. 268-78, Aug 15 2013.