Clin Neuroradiol (2015) (Suppl) 25:225–230
DOI 10.1007/s00062-015-0432-9

REVIEW ARTICLE

Quantitative Susceptibility Mapping: Concepts and Applications

J. R. Reichenbach · F. Schweser · B. Serres · A. Deistung

Received: 9 April 2015 / Accepted: 30 June 2015 / Published online: 22 July 2015

Abstract
Purpose To review the fundamental principles of susceptibility-weighted imaging (SWI) and quantitative susceptibility mapping (QSM), and to discuss recent clinical developments.
Methods SWI is a magnetic resonance imaging method that takes advantage of magnitude signal loss and phase information to reveal anatomic and physiologic information about tissue and venous vasculature. The method enhances image contrast qualitatively, relying on phase shifts due to differences in magnetic susceptibility between tissues. QSM, extending SWI in an elegant way, is a new sophisticated postprocessing technique that numerically solves the inverse *source-effect* problem to derive local tissue magnetic susceptibility (*source*) from the measured magnetic field distribution (*effect*) as it is reflected in the phase images of gradient-echo sequences.
Results SWI has meanwhile been established in numerous clinical as well as basic biomedical applications due to its ability to highlight tissue structures and compounds that are difficult to detect by conventional magnetic resonance imaging (MRI), including iron, calcifications, small veins, blood, and bones. The field of QSM has also progressed rapidly, both in terms of optimizing the post-processing strategies and algorithms as well as in gaining ground for new clinical applications that take advantage of its quantitative nature and improved specificity to identify the magnetic signature of lesions.
Conclusions Though magnetic susceptibility may be a major nuisance producing image artifacts in MRI, recent work has transformed it into a useful source of image contrast. Both SWI and QSM are gaining increasing acceptance in clinical practice. In particular, QSM provides new insights into tissue composition and organization due to its more direct relation to the actual physical tissue magnetic properties.

Keywords Magnetic resonance imaging · Magnetic susceptibility · Susceptibility-weighted imaging · Quantitative susceptibility mapping

J. R. Reichenbach (✉) · B. Serres · A. Deistung
Medical Physics Group, Institute for Diagnostic and Interventional Radiology, University Hospital Jena, Friedrich-Schiller University,
Philosophenweg 3,
07743 Jena, Germany
e-mail: juergen.reichenbach@med.uni-jena.de

J. R. Reichenbach
Michael Stifel Center for Data-driven and Simulation Science Jena, Friedrich Schiller University,
Jena, Germany

F. Schweser
Buffalo Neuroimaging Analysis Center,
Deptartment of Neurology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo,
Buffalo, NY, USA

F. Schweser
MRI Clinical and Translational Research Center,
School of Medicine and Biomedical Sciences,
State University of New York at Buffalo,
Buffalo, NY, USA

Introduction

Contrast generation in magnetic resonance (MR) imaging conventionally relies on the exploitation of several basic physical tissue properties. These basic properties typically include the spin density of the various biological tissues or fluids being analyzed and the longitudinal and transverse

relaxation time constants of these tissues or fluids. There also exists a plethora of other physical phenomena, like diffusion, perfusion, flow, chemical shift, or spin exchange, that have been taken advantage of to impart characteristic contrast in MRI.

Magnetic susceptibility, a basic material property that measures the ability of a substance to become magnetized, has only relatively lately been transformed into a useful source of intrinsic tissue image contrast. Susceptibility-weighted imaging (SWI) is one particular type of susceptibility-based MR imaging that uses phase information derived from gradient-echo imaging with relatively long echo times to *enhance* image contrast. SWI has meanwhile become established in the neuroimaging toolbox as it allows highlighting tissue structures and compounds that may be difficult to detect by conventional MRI. Since the first description in 1997 [1], SWI has been proven useful in a multitude of clinical applications including high-resolution MR venography, imaging of traumatic intracranial hemorrhage, visualizing blood products and vascularization of tumors or assessing iron deposits in the brain [2–6].

One limitation of SWI, however, is related to the fact that the phase, despite reflecting the actual magnetic field locally, is affected by tissue geometry and orientation relative to the static main magnetic field (B_0), and that phase changes extend beyond areas from which they are originating. Consequently, efforts have more recently concentrated on overcoming this nonlocal phase problem and deriving tissue susceptibility in vivo directly by solving the inverse problem. The developed postprocessing technique, commonly referred to as quantitative susceptibility mapping (QSM), recovers the susceptibility distribution of the human brain and body from the measured local field (i.e. phase) distribution [7–14]. The new field of QSM is growing rapidly and initial clinical susceptibility mapping studies have already been carried out with larger studies underway [15–19]. The purpose of this brief report is to review the principle and the current status of susceptibility-weighted imaging and its quantitative extension.

Table 1 Magnetic susceptibility, χ, of biological tissues and substances

Tissue/substance	Volume magnetic susceptibility (χ)	References
Pure water (T = 37 °C)	-9.05×10^{-6}	[20]
Human tissue	$\sim(-11$ to $-7) \times 10^{-6}$	[20]
Myelin	-10×10^{-6}	[20]
Red blood cell (deoxygenated)	-6.52×10^{-6}	[20]
Red blood cell (oxygenated)	-9.19×10^{-6}	[35]
Red blood cell (methemoglobin)	-7.2×10^{-6}	[35]
Bovine rib bone powder	-11.3×10^{-6}	[36]
Ferritin (fully loaded with 4500 Fe^{3+} ions)	$+520 \times 10^{-6}$	[20]

Basic Concepts

Magnetic susceptibility is a fundamental physical property ([20], Table 1) that can significantly affect MR image contrast. Using T_2*-weighted gradient-echo imaging, variations of tissue magnetic susceptibility typically lead to local signal cancellations in magnitude images and nonlocal changes in phase images due to the induced frequency shifts (Fig. 1, left and middle). SWI dramatically enhances image contrast qualitatively between tissues of different magnetic susceptibility by combining the magnitude and the phase into a single image, the so-called susceptibility-weighted image. To this end, the phase images are filtered to remove phase wraps and unwanted background fields, and afterwards combined with the corresponding magnitude via multiplication. This process is usually followed by a minimum intensity projection [1, 2, 4].

QSM obtains quantitative maps of bulk tissue magnetic susceptibility, employing the very same phase signal as conventional, dual- or multi-echo, gradient-echo (GRE) magnetic resonance (MR) sequences [7]. Hence, susceptibility maps come, in principle, at no additional cost from examinations including the well-established SWI technique. QSM is achieved by, first, estimating the magnetic field distribution from raw MRI phase data, second,

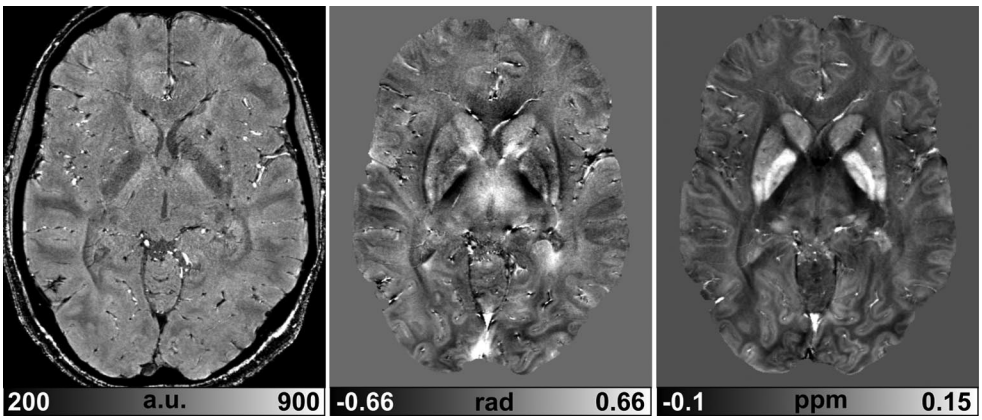

Fig. 1 *Left*: Magnitude image of a 3D T2*-weighted gradient-echo scan acquired at 3 T. *Middle*: Corresponding phase image in which phase wraps and unwanted background fields have been removed [13]. *Right*: Reconstructed susceptibility map, showing the magnetic susceptibility distribution of brain tissue. The displayed susceptibility values are referenced to frontal *white matter* (0 ppm)

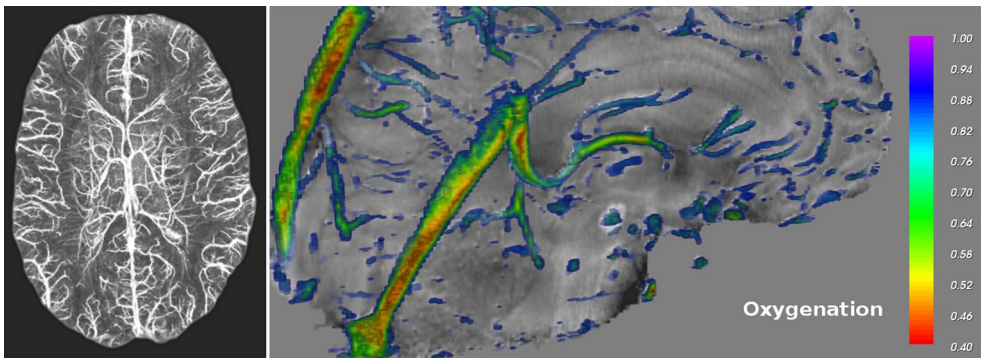

Fig. 2 *Left*: Magnetic resonance venography of a healthy subject acquired at 7 T. Inverted minimum intensity projection over 20 mm of median-filtered susceptibility-weighted images (SWI). Cortical, central, and medullary veins are clearly visible as bright tubular structures, illustrating the complexity of the cerebral venous vascular system. *Right*: Visualization of the blood oxygenation in venous vessels. Quantitative susceptibility mapping (QSM) allows analysis of the local oxygenation level within veins in vivo by converting the susceptibility values in the veins to the underlying oxygen saturation. (*Serres B, Deistung A, Schäfer A, Kocinski M, Materka A, Reichenbach JR. Automatic segmentation of the venous vessel network based on quantitative susceptibility maps and its application to investigate blood oxygenation. Proceedings ISMRM 2015, #169*)

eliminating background field contributions that result from susceptibility sources outside of the area of interest (e.g., brain) and, third, solving the inverse problem from field perturbation to magnetic susceptibility. However, each of these post-processing steps needs to be carried out very carefully and tailoring algorithms for QSM still represents an active area of research [12–14, 21–23]. Paramagnetic substances, such as deoxyheme and ferritin, appear bright on susceptibility maps (Fig. 1, right) and diamagnetic substances, such as calcium and myelin, appear dark [12], thus allowing for, e.g., specific differentiation of calcified from hemorrhagic lesions [15, 24], which has been difficult so far with MRI.

Applications of Quantitative Susceptibility Mapping

In this section, several areas of recent research are briefly discussed with a focus on applications related to neuroradiology and neuroimaging.

MR Venography and Oxygen Saturation

One of the first hallmarks of SWI has been the visualization of the venous vascular network of the human brain in unprecedented detail ([1, 2, 4], Fig. 2, left). With the development of QSM, it has now even become possible to estimate oxygen saturation directly in the venous blood vessels ([9, 25], Fig. 2, right), opening the door for a characterization of the subject-specific vasculature, which may have implications for, e.g., presurgical planning procedures or identifying venous anomalies such as telangiectasia (Fig. 3d).

Traumatic Brain Injury

One key application of SWI and QSM with great potential is imaging of traumatic brain injury (TBI) or mild TBI, due to the great sensitivity towards depicting (micro-)hemorrhages that result from blood–brain barrier permeability changes and injuries of small vessels, particularly in settings of diffuse axonal injury ([26], Fig. 3a). In addition, first experimental reports have further indicated that QSM may reveal distinctly greater differences in mild TBI compared with fractional anisotropy derived from diffusion tensor imaging indicating damage to myelin and not just the axonal membranes [27].

Cerebral Microbleeds and Vascular Malformations

Concerning detection of cerebral microbleeds (CMB), T_2*-weighted GRE imaging and SWI are currently considered the methods of choice due to their sensitivity in delineating the paramagnetic effects of intraparenchymal hemosiderin deposits. However, the appearance of hypointense lesions associated with CMB on these images is highly sequence parameter dependent, limiting, for example, longitudinal comparisons. QSM, on the other hand, elegantly removes these blooming artifacts, reduces the geometric dependence, and can be used as a universal quantitative measure of lesion burden [13, 14]. QSM has recently also been applied to evaluate iron deposition in these lesions in human cerebral cavernous malformations (CCM) [17], providing a potential biomarker for monitoring CCM disease activity and treatment response.

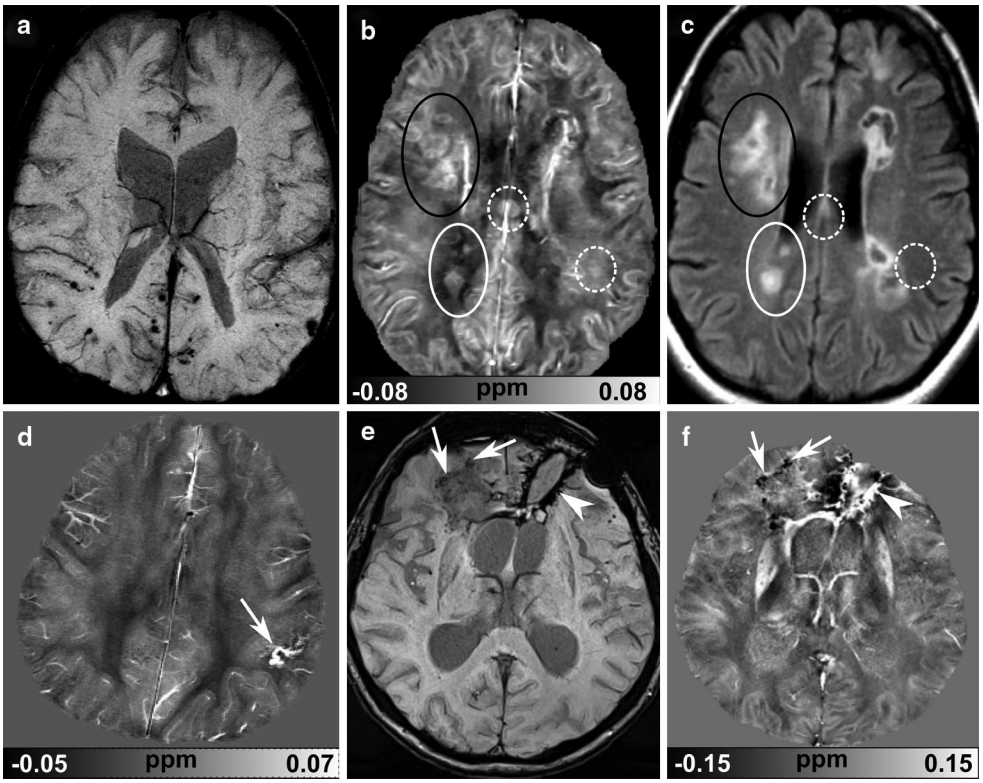

Fig. 3 Collection of clinical cases acquired at 1.5 and 3 T, respectively. **a** Susceptibility-weighted imaging (SWI) of a 3-year-old patient with diffuse axonal injury showing multiple hemorrhages in the occipital part of the brain. **b** Quantitative susceptibility mapping (QSM) and **c** corresponding FLAIR image of a patient with multiple sclerosis (MS). QSM displays the lesions not only similarly to the ones on the fluid-attenuated inversion recovery (FLAIR) image (*white circle*) but also shows additional lesions (dashed white circle) as well as additional information about MS lesion structure (*black circle*). **d** Susceptibility map of a patient (5 years) with cortical telangiectasia. **e** SWI and **f** QSM of a 46-year-old patient with glioblastoma in the frontal lobe, who was treated with bevacizumab. Several bleedings (*arrow head*, more paramagnetic lesions) and calcifications (*arrows*, more diamagnetic lesions) are seen in the tumor area that are discriminable with QSM but not with SWI. (Figure parts **e** and **f** adapted from [15])

Multiple Sclerosis

SWI and QSM have both been successfully applied to patients with multiple sclerosis for detecting MS lesions (Fig. 3b, c) and visualizing their anatomical relationship with penetrating veins [4]. It has, however, been argued that combining QSM with further quantitative MRI contrasts (e.g., relaxation rate maps, magnetization transfer images) may turn out beneficial for disentangling the main contributors of brain tissue contrast, namely iron concentration and non-iron contributions (e.g. myelin), particularly in white matter. The rationale for this relates to the fact that QSM provides information on an intrinsic biophysical tissue property which is complementary to, for example, relaxation rate mapping. Results have demonstrated that QSM is indeed more sensitive to disease induced tissue changes (e.g., neurodegeneration with brain iron accumulation) than other quantitative MRI methods [13, 14, 16] and allows assessment of tissue changes even in patients at early stages of MS [18].

Brain Tumors

In the study of primary brain neoplasms, especially malignant glioma, SWI has demonstrated its advantages in depicting the intratumoral architecture encompassing venous vasculature, blood products, calcification, and edema [28]. With QSM, however, it has become possible to unequivocally differentiate between paramagnetic blood deposits and diamagnetic calcifications in brain tumors [15]. Furthermore, it was also demonstrated with QSM that calcifications occur in recurrent glioblastoma (Figs. 3e, f). Providing a promising biomarker to evaluate patient response and therapeutic outcome, it is anticipated that QSM will influence differential diagnosis of enhancing brain lesions, assessment of their progression as well as understanding the underlying pathophysiology.

Discussion

Magnetic susceptibility is a constitutive tissue property that changes with tissue or organ function, disease state, and intervention. Since SWI data can be acquired with any generic 2D or 3D gradient echo sequence, the technique can be used with all common clinical MRI scanners, making it highly convenient and robust for routine clinical work. Since the contrast is based on small susceptibility differences and the method uses gradient echo imaging with rather small SAR limitations, it is particularly suited for high and ultra-high field applications. Clinical applications of SWI have been continuously growing over the years with increasing indications for neuroradiology.

QSM—representing the quantitative extension of SWI—provides quantitative information about magnetic susceptibility distributions in various brain regions, thereby offering unique and specific insight into disease development and progression in patients. Being the result of an ill-posed inverse reconstruction approach that maps the phase, that is, the magnetic field, into a source image means, however, that there are multiple mathematical susceptibility distributions corresponding to the same measured field. To find a reasonable solution usually requires additional prior information, a process that is commonly referred to as regularization. The simplest regularization is to construct a regularized inverse filter kernel in *k*-space and to perform a kernel division in Fourier space. Although being usually computationally efficient and easy to implement [29, 30], these methods usually produce results with streaking artifacts as they provide erroneous susceptibility energy in the zero-cone region of the dipole kernel. Alternate and more sophisticated regularization methods impose priors like morphological consistency of the susceptibility map [31, 32], piecewise constant susceptibilities [24, 33] or weighted *k*-space derivatives [11]. Further approaches include solving the inverse problem by oversampling the data based on multiple orientations [8] or improving the information in the cone of singularity by using efficient *k*-space/image-domain iterative algorithms where in each iteration, the data points in the cone of singularities are updated with geometry-dependent information [34]. Despite impressive progress that has been made in recent years with respect to the development of QSM algorithms, there is still ongoing research to identify the best approach in solving the intricate source-effect problem.

Independent of these challenges, QSM is an emerging and currently fast growing area in the field of medical imaging. Besides the clinical applications outlined before, it enables also biophysical studies in neuroimaging, providing an important tool for neuroscience. Applying QSM to investigate white matter tracts and iron deposition holds great promise in better understanding, diagnosing, and treating neurodegenerative brain disorders. Although QSM is only able to quantify magnetic susceptibility in relation to a (mostly internally chosen) reference value rather than in absolute terms, it nevertheless offers a unique opportunity to correlate susceptibility values with clinical conditions and treatment outcomes. Lastly, physical and technical extensions to QSM have already been undertaken to explore the anisotropic nature of magnetic susceptibility by applying so-called magnetic susceptibility tensor imaging (STI) [6] that provides information about the structure of white matter complementary to DTI and also helps in disentangling the complex microstructures of the human brain and their contributions to magnetic susceptibilities.

Conclusion

Quantitative susceptibility mapping provides a novel, quantitative contrast of an intrinsic physical tissue quantity that reflects the response of tissue to the presence of a static magnetic field. QSM represents an important step towards more specific imaging of tissue properties and a major addition to the neuroimaging armamentarium with important implications for routine applications due to its high specificity, in particular with regard to differentiating between the magnetic signatures of lesions.

Sources of Funding This work was supported by grants from the German Research Foundation (DFG, RE 1123/9-2) and the Interdisciplinary Center of Clinical Research (IZKF) Jena (J37).

Ethical Standards The work has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Reichenbach JR, Venkatesan R, Schillinger DJ, Kido D, Haacke EM. Small vessels in the human brain: MR venography with deoxyhemoglobin as an intrinsic contrast agent. Radiology. 1997;204(1):272–7.
2. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). Magn Reson Med. 2004;52(3):612–8.
3. Deistung A, Rauscher A, Sedlacik J, Stadler J, Witoszynskyj S, Reichenbach JR. Susceptibility weighted imaging at ultrahigh magnetic field strengths: theoretical considerations and experimental results. Magn Reson Med. 2008;60(5):1155–68.
4. Haacke EM, Reichenbach JR, editors. Susceptibility weighted imaging in MRI: basic concepts and clinical applications. 1st ed. Hoboken: Wiley-Blackwell; 2011. 776 pp.
5. Reichenbach JR. The future of susceptibility contrast for assessment of anatomy and function. Neuroimage. 2012;62(2):1311–5.
6. Liu C, Li W, Tong KA, Yeom KW, Kuzminski S. Susceptibility-weighted imaging and quantitative susceptibility mapping in the brain. J Magn Reson Imaging. 2015;42(1):23–41.

7. Li L, Leigh JS. Quantifying arbitrary magnetic susceptibility distributions with MR. Magn Reson Med. 2004;51(5):1077–82.
8. Liu T, Spincemaille P, de Rochefort L, Kressler B, Wang Y. 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. 2009;61(1):196–204.
9. Haacke EM, Tang J, Neelavalli J, Cheng YC. Susceptibility mapping as a means to visualize veins and quantify oxygen saturation. J Magn Reson Imaging. 2010;32(3):663–76. (Erratum in: J Magn Reson Imaging. 2011;33(6):1527–9.)
10. Wharton S, Bowtell R. Whole-brain susceptibility mapping at high field: a comparison of multiple- and single-orientation methods. Neuroimage. 2010;53(2):515–25.
11. Li W, Wu B, Liu C. Quantitative susceptibility mapping of human brain reflects spatial variation in tissue composition. Neuroimage. 2011;55(4):1645–56.
12. Schweser F, Deistung A, Lehr BW, Reichenbach JR. Quantitative imaging of intrinsic magnetic tissue properties using MRI signal phase: an approach to in vivo brain iron metabolism? Neuroimage. 2011;54(4):2789–807.
13. Haacke EM, Liu S, Buch S, Zheng W, Wu D, Ye Y. Quantitative susceptibility mapping: current status and future directions. Magn Reson Imaging. 2015;33(1):1–25.
14. Wang Y, Liu T. Quantitative Susceptibility Mapping (QSM): decoding MRI data for a tissue magnetic biomarker. Magn Reson Med. 2015;73(1):82–101.
15. Deistung A, Schweser F, Wiestler B, Abello M, Roethke M, Sahm F, Wick W, Nagel AM, Heiland S, Schlemmer HP, Bendszus M, Reichenbach JR, Radbruch A. Quantitative susceptibility mapping differentiates between blood depositions and calcifications in patients with glioblastoma. PLoS One. 2013;8(3):e57924.
16. Langkammer C, Liu T, Khalil M, Enzinger C, Jehna M, Fuchs S, Fazekas F, Wang Y, Ropele S. Quantitative susceptibility mapping in multiple sclerosis. Radiology. 2013;267(2):551–9.
17. Tan H, Liu T, Wu Y, Thacker J, Shenkar R, Mikati AG, Shi C, Dykstra C, Wang Y, Prasad PV, Edelman RR, Awad IA. Evaluation of iron content in human cerebral cavernous malformation using quantitative susceptibility mapping. Invest Radiol. 2014;49(7):498–504.
18. Blazejewska AI, Al-Radaideh AM, Wharton S, Lim SY, Bowtell RW, Constantinescu CS, Gowland PA. Increase in the iron content of the substantia nigra and red nucleus in multiple sclerosis and clinically isolated syndrome: a 7 T MRI study. J Magn Reson Imaging. 2015;41(4):1065–70.
19. Barbosa JH, Santos AC, Tumas V, Liu M, Zheng W, Haacke EM, Salmon CE. Quantifying brain iron deposition in patients with Parkinson's disease using quantitative susceptibility mapping, R_2 and R_2*. Magn Reson Imaging. 2015;33(5):559–65.
20. Schenck JF. The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds. Med Phys. 1996;23(6):815–50.
21. Li W, Wang N, Yu F, Han H, Cao W, Romero R, Tantiwongkosi B, Duong TQ, Liu C. A method for estimating and removing streaking artifacts in quantitative susceptibility mapping. Neuroimage. 2015;108:111–22.
22. Langkammer C, Bredies K, Poser BA, Barth M, Reishofer G, Fan AP, Bilgic B, Fazekas F, Mainero C, Ropele S. Fast quantitative susceptibility mapping using 3D EPI and total generalized variation. Neuroimage. 2015;111:622–30.
23. Wen Y, Wang Y, Liu T. Enhancing k-space quantitative susceptibility mapping by enforcing consistency on the cone data (CCD) with structural priors. Magn Reson Med. 2015. [Epub ahead of print].
24. Schweser F, Deistung A, Lehr BW, Reichenbach JR. Differentiation between diamagnetic and paramagnetic cerebral lesions based on magnetic susceptibility mapping. Med Phys. 2010;37(10):5165–78.
25. Fan AP, Bilgic B, Gagnon L, Witzel T, Bhat H, Rosen BR, Adalsteinsson E. Quantitative oxygenation venography from MRI phase. Magn Reson Med. 2014;72(1):149–59.
26. Liu J, Xia S, Hanks RA, Wiseman NM, Peng C, Zhou S, Haacke EM, Kou Z. Susceptibility weighted imaging and mapping of micro-hemorrhages and major deep veins after traumatic brain injury. J Neurotrauma. 2015. [Epub ahead of print].
27. Li W, Long J, Watts LT, Shen Q, Duong TQ. Altered magnetic susceptibility in white matter after mild traumatic brain injury. Proc Intl Soc Mag Reson Med. 2014;22:900.
28. Sehgal V, Delproposto Z, Haddar D, Haacke EM, Sloan AE, Zamorano LJ, Barger G, Hu J, Xu Y, Prabhakaran KP, Elangovan IR, Neelavalli J, Reichenbach JR. Susceptibility-weighted imaging to visualize blood products and improve tumor contrast in the study of brain masses. J Magn Reson Imaging. 2006;24(1):41–51.
29. Shmueli K, de Zwart JA, van Gelderen P, Li TQ, Dodd SJ, Duyn JH. Magnetic susceptibility mapping of brain tissue in vivo using MRI phase data. Magn Reson Med. 2009;62(6):1510–22.
30. Wharton S, Schäfer A, Bowtell R. Susceptibility mapping in the human brain using threshold-based k-space division. Magn Reson Med. 2010;63(5):1292–304.
31. Liu T, Liu J, de Rochefort L, Spincemaille P, Khalidov I, Ledoux JR, Wang Y. Morphology enabled dipole inversion (MEDI) from a single-angle acquisition: comparison with COSMOS in human brain imaging. Magn Reson Med. 2011;66(3):777–83.
32. Schweser F, Sommer K, Deistung A, Reichenbach JR. Quantitative susceptibility mapping for investigating subtle susceptibility variations in the human brain. Neuroimage. 2012;62(3):2083–100.
33. de Rochefort L, Brown R, Prince MR, Wang Y. Quantitative MR susceptibility mapping using piece-wise constant regularized inversion of the magnetic field. Magn Reson Med. 2008;60(4):1003–9.
34. Tang J, Liu S, Neelavalli J, Cheng YCN, Buch S, Haacke EM. Improving susceptibility mapping using a threshold-based k-space/image domain iterative reconstruction approach. Magn Reson Med. 2013;69(5):1396–407.
35. Plyavin YA, Blum EY. Magnetic parameters of blood cells and high-gradient paramagnetic and diamagnetic phoresis. Magnetohydrodynamics. 1983;19:349–59.
36. Hopkins JA, Wehrli FW. Magnetic susceptibility measurement of insoluble solids by NMR: magnetic susceptibility of bone. Magn Reson Med. 1997;37(4):494–500.