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Unambiguous identification of superparamagnetic iron oxide (SPIO) particles through quantitative susceptibility mapping of the nonlinear response to magnetic fields

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Abstract

Superparamagnetic iron oxide (SPIO) particles generate signal void regions on gradient echo images due to their strong magnetization. In practice, the signal void region might be indistinguishable from that generated by air. However, the response of SPIO to an externally applied magnetic field is non-linear. Magnetization of SPIO saturates at around 1 Tesla while magnetization of water and air increase linearly with field strength. Phantom experiment and mice experiments demonstrated the feasibility of a non-ambiguous identification of superparamagnetic contrast agents.

Keywords

MRI; SPIO; air; non-linear magnetization response; quantitative susceptibility mapping; COSMOS

Introduction

Superparamagnetic iron oxide (SPIO) nanoparticles have been widely used as an MRI contrast agent (1–3). The strong magnetization of SPIO particles generates a local disturbance to the uniformly applied B_0 field. This field disturbance leads to spin dephasing, resulting in signal void regions on MRI images (3). Therefore, $T2^*$ weighted pulse sequences have been used to image SPIO and have been considered to be the most sensitive. Recently, many efforts have been put into the detection and the estimation of SPIO (4–12). However, in general, it may prove difficult for gradient echo imaging to distinguish signal voids created by SPIO clusters from other sources of signal void such as the ones created by air. This becomes particularly problematic in molecular MRI when SPIO labeled cells are frequently embedded in porous gel phantoms for validation experiment (13) or when various air cavities obscure the presence of nearby SPIO in animal experiments. In such procedures, an additional optical histological examination may be needed after MRI to validate the presence and location of SPIO particles (14).

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Air bubbles create signal void regions because of both their lack of spins and the strong positive magnetization difference with the surrounding tissue ($\chi_{\text{air-water}} = 9.41\text{ppm}$) (12). The magnetization of a SPIO cluster at practical concentrations may be very similar to that of air (relative to water), leading to similar dephasing and T2* effects. Therefore, the ambiguity may not be reliably solved.

In this study, we aim to improve the specificity of gradient echo based SPIO imaging. We hypothesize that by quantifying the magnetic moment of the signal void regions at two different field strengths, air and SPIO are distinguishable because the magnetization of SPIO saturates at around 1 Tesla while magnetization of air, water and tissue increase linearly with field strength. As part of the work, we introduce an improved quantitative susceptibility mapping (QSM) technique: improved Calculation Of Susceptibility through Multiple Orientation Sampling (iCOSMOS), and applied it to confirm the presence of SPIO by imaging at two different field strengths and exploiting the nonlinear response of SPIO. Phantom experiment and *ex vivo* mice experiments were conducted to demonstrate the feasibility of a non-ambiguous identification of SPIO particles.

Theory

A major magnetic characteristic of SPIO is its nonlinear response to the applied polarization magnetic field. SPIO in contrast agent Feridex (ferumoxides) saturates at around 1T (2). For instance, the magnetization of ferumoxides at a concentration of 4mM Fe is 17.3A/m at 1.5T and 18.7A/m at 3T (2). However, magnetizations of air, water and tissue increase linearly with field strength. Fig. 1 illustrates the magnetization and volume susceptibility curves of SPIO and air, where susceptibility is defined as (15):

$$\chi = \mathbf{M} \times \mu_0 / B_0 \quad (1)$$

We hypothesize that the difference in magnetizations obtained from two different fields can be used to distinguish non-linear SPIOs from other linear materials such as air and water. One way to demonstrate this difference is through quantitative susceptibility mapping. Here, we use an improved COSMOS method for reconstructing QSMs.

Improved COSMOS using regularization

Previously, we have demonstrated that by oversampling from multiple orientations, susceptibility is accurately quantifiable from the measured field map by eliminating the non-trivial null space in the dipole kernel (11). Nevertheless, oversampling cannot create new signal in signal void regions, including regions occupied by materials of high susceptibility, such as Feridex, and regions of little or no spins, such as air. In such situation, we make an assumption that susceptibility in a signal void region should be homogeneous because the materials in the void exhibit similar signal decay. Therefore, a smooth solution is favored in an isolated signal void region to eliminate solutions with sharp discontinuities.

To mathematically model this assumption, a Bayesian regularized quantitative susceptibility mapping technique that utilizes the gradient information from magnitude image was proposed in (16). This image gradient regularization is adopted with COSMOS, and the minimization problem is formulated as:

$$\chi^* = \arg \min_{\chi} \left\{ \sum_{i=1}^N \|W_i \cdot (d_i \otimes \chi - \delta_{B_{0,i}})\|^2 + \alpha^2 \|EG\chi\|^2 \right\} \quad (3)$$

Where G denotes a gradient operator and E is the weighting matrix derived from the magnitude image acquired at the first orientation. The detailed derivation of G and E was elaborated in (16). α is the regularization parameter. The regularization term provides a high penalty to the cost function if an edge on the reconstructed QSM does not have a corresponding edge on the magnitude image. It has been shown in (16) that the quantity of the solution is fairly independent of the choice of α over two orders of magnitude. Here, α is fixed at 0.1 throughout the following experiments. After the QSM is derived, magnetization can be calculated from Eq. [1].

Methods and Materials

Numerical simulation

A numerical 3D phantom was designed to evaluate the influence of the regularization term to COSMOS. The phantom (Fig. 2) consisted of a large sphere mimicking a water phantom, and multiple internal small spheres mimicking signal voids with radii ranging from 1 to 6 voxels. A uniform intensity of 20 was assigned to the “water” region. Susceptibility of the large sphere was set to 0 because water was usually chosen as reference. Then the background susceptibility and the susceptibility of the small spheres were set to 9.4ppm to simulate air. The field map was generated 3 times by using a forward calculation (15,17–18) and changing the direction of B_0 to 0° , 120° and 240° to simulate the reorientation process. A phase map was calculated from the field map assuming a TE of 1ms and B_0 of 1.5T. Zero-mean Gaussian white noise with a standard deviation of 1 was added to both the real and imaginary parts of the intensity image independently.

QSMs were subsequently reconstructed from the simulated MR data using original COSMOS and iCOSMOS by setting α to 0 and 0.1, respectively. Means and standard deviations of the relative susceptibility values inside each small sphere were measured and compared.

Phantom and ex vivo validations

Two virtually identical cylindrical water containers were filled with tap water. The diameter of the containers was 70mm and the height was 25mm. Five vertical straws (diameter = 2.5mm, height = 25cm) were glued to the bottom of one of the container. One straw was left open to the outside air, while the four other straws were filled with 1.5, 3.0, 4.5 and 6.0% concentration of a Feridex solution (Advanced Magnetics, Inc., Cambridge, MA, USA) respectively.

A euthanized wild type adult mouse was imaged. The use of the mouse was approved by Institutional Animal Care and Use Committee (IACUC). 5 μ L of Feridex at a dilution factor of 10 was injected to the left thigh using a 100 μ L micro syringe immediately after the mouse was sacrificed. The mouse was subsequently immersed in a 50mL Falcon tube (Becton-Dickinson, Franklin Lake, N.J.) containing a saline solution. A second Falcon tube was filled with the same volume of saline solution to be used as a reference.

Data acquisition

The samples were scanned at both 1.5T and at 3T using clinical scanners. (General Electric Excite HDx; GE Healthcare, Waukesha, WI, USA). A dedicated 3D gradient-echo sequence was designed to sample at different TEs in an interleaved manner.

For the phantom scan, eight channel wrist coils with identical geometries (Invivo Corporation, Gainesville, FL) were used at both field strengths. Imaging parameters were identical at both field strengths. Field of view and matrix size were adjusted to achieve an isotropic resolution of 500 μ m. Bandwidth, TR, flip angle and number of excitations were $\pm 125\text{kHz}/20\text{ms}/30^\circ/1$. Four TEs were chosen to achieve a balance between the precision of the field map estimation and the total scan time: 2.3, 2.8, 4.8, and 14.84 ms. In order to use iCOSMOS as described in

(11) for image analysis, the phantom was scanned from three orientations. After the first scan was finished, the phantom was rotated in the coronal plane by 120° for the second and by -120° for the third scan. The water phantom without the straws was also scanned as a reference scan to remove background inhomogeneity and the susceptibility effect caused by the air-phantom interface.

For the mouse scan, the tube containing the animal was placed vertically in a home-built birdcage mouse coil. Field of view and matrix size were adjusted to achieve an isotropic resolution of $500\mu\text{m}$. At 1.5T, bandwidth, TR, flip angle and the number of excitations were $\pm 31.25\text{kHz}/25\text{ms}/30^\circ/2$. Three TEs were acquired (2.8, 7.34, and 20.98ms). Note that TE spacing was an integer multiple of $4545\mu\text{s}$, a period in which water and fat have consistent phase difference at 1.5T. Therefore, water fat separation (19) is not required to obtain the field map necessary for the iCOSMOS processing. At 3T, to achieve similar SNR and dephasing effects, the TR and the number of excitations were set to 15.6ms and 1. Three TEs were acquired (2.8, 5.07, and 11.89ms). The tube was also rotated in the coronal plane by 120° and -120° for the second and third scan, respectively. The tube filled with only water was also scanned as a reference to remove background field inhomogeneity and susceptibility effect from air-phantom interface.

Qualitative and Quantitative Distinction

Because the susceptibility of SPIO varies with field strength, while the susceptibilities of other materials are field-strength independent, we subtract the QSMs reconstructed at 3T from the QSM reconstructions at 1.5T to obtain SPIO-specific images for qualitative distinctions.

Magnetization maps for 1.5T and 3T were directly calculated by scaling the QSMs with field strengths to determine the quantitative distinctions, as described in Eq. [1]. As magnetization is the density of magnetic moment, it is subject to volume measurement errors, such as those caused by blooming artifacts (20). On the contrary, the magnetic moment is a physical quantity less sensitive to volume measurement errors. Therefore, on the reconstructed images, regions of interest (ROIs) were drawn over the signal void regions and magnetic moments in each ROI were calculated. Specifically, on the phantom data, five circles were drawn to cover the straws on the middle slice. Magnetic moment inside each circle was calculated by summing the magnetization of all the voxels, and multiplying the voxel size. On the mouse data, ellipses were drawn to cover the lungs and SPIO injection regions. Magnetic moments were calculated in a similar manner. Magnetic moment were subsequently converted to iron mass by the conversion factor $M = 77.3 \times 10^{-3} \text{A} \cdot \text{m}^2/\text{g}$ at 1.5T and $M = 83.65 \times 10^{-3} \text{A} \cdot \text{m}^2/\text{g}$ at 3T (2). Because the selected volume of each of the straws is $2.45 \mu\text{L}$ and iron concentration of pure Feridex is 11.2mg/mL , expected iron mass inside the straws with the different Feridex concentrations (see above) is 0.41, 0.82, 1.24 and $1.65 \mu\text{g}$, respectively. For the mouse injection, expected iron mass was $5.6 \mu\text{g}$. For both experiments, the ratio between the magnetic moments at 3T and 1.5T was calculated.

Results

For the numerically simulated experiment, QSM results are shown in Fig. 2, and the means and standard deviations of measured susceptibilities in the signal voids are listed in Table 1. The regularization did not change the average susceptibility value (mean in Table 1), but it drastically reduced the susceptibility variations in the signal void (standard deviation in Table 1 and Fig.2c vs Fig.2d).

For the phantom experiment, Figs.3a&3b show the magnitude of the gradient echo image. The straw containing air as well as the straws with high Feridex concentrations (above 3%) appeared as signal void regions. On the QSMs, both air and Feridex solution demonstrated positive

susceptibility relatively to water. For qualitative distinction, straw containing air was almost cancelled out on the difference image due to the constant susceptibility difference between air and water, while Feridex-containing straws remained clearly visible because the susceptibility of SPIO varies with field strength (Fig. 3e). For quantitative distinction, estimated magnetic moments and converted iron mass are listed in Table 2 and Table 3, respectively. The ratio of magnetic moments at 3T and 1.5T for air is approximately 2, indicating air's linear response to the applied field. The ratio of magnetic moments at 3T and 1.5T for Feridex is approximately 1, demonstrating SPIO's saturated response to applied field.

In the mouse experiment, similar effects were observed. Air in the lung demonstrated an almost constant susceptibility, while susceptibility of SPIO varied with field strength. Magnetic moments and converted iron mass are listed in Table 2 and Table 3, respectively. The magnetic moment ratio between 3T and 1.5T was approximately 2 for air and approximately 1 for Feridex.

Discussion

Our preliminary data demonstrate that nonlinear SPIO can be distinguished from linear air by reconstructing the QSMs at two field strengths. Both air and highly concentrated SPIO regions appear as simple signal voids in standard magnitude gradient echo images. The susceptibility of air is independent of magnetic field strength, but the susceptibility of SPIO is approximately inversely proportional to the field strength. Using QSMs at 1.5T and 3T, SPIO can be differentiated from air, and the mass of the SPIO can be obtained.

In the phantom experiment, the measured iron mass were in fair agreement with expected iron mass. In the mouse experiment, the measured iron mass was lower than the expected value by 37%. This discrepancy was consistent across two different field strengths, and was likely due to the injection protocol. Some Feridex solution may have diffused into the channel created by needle, or was displaced when the needle was withdrawn as commonly observed in such procedures.

QSM in regions of no observable spins is intrinsically difficult, because only the total magnetic moment may be uniquely determined for a signal void region. For instance, two concentric spheres or long cylinders with different radii generate almost indistinguishable outside fields as long as they have identical magnetic moments (11,21). In this study, we introduced a regularization that preferred a smooth distribution in the signal void region for the COSMOS reconstruction method. The gradient of the traditional magnitude image is used to identify the signal void region for smooth susceptibility assignment. A small regularization parameter that weighed heavily on data fidelity was chosen for the iCOSMOS. It has been shown in (16) that in this gradient regularization, the quantitative outcome is fairly insensitive to the choice of regularization parameter. The smallest regularization parameter tested in (16) was chosen and fixed throughout the experiment ($\alpha = 0.1$).

Although the experiments were conducted at two specific field strengths 1.5T and 3T, in principle any two sufficiently different field strengths above 1T can be used, a condition satisfied by most current commercial scanners. A larger field difference would make the magnetic moment ratio greater for air, thus making it easier to distinguish SPIO from air. Currently, 1.5T and 3T scanners are widely available in all major medical centers, rendering applicability to general preclinical and clinical investigations.

The experimental results confirmed our hypothesis that air and SPIO are distinguishable in MRI by exploiting their different magnetization properties. Further improvement on the magnetization quantification is achievable to make the concept more practical. Several background field removal techniques that do not require reference scans have been proposed

recently (22–24). Additionally, quantitative susceptibility mapping (QSM) is currently a research area progressing rapidly (25–27). Especially with advanced regularization techniques (16,27–29), only one scan at each field strength is required for susceptibility quantification, reducing the total scan time by 75%.

The idea of exploiting the nonlinear response of magnetic particles was inspired by the recent development of magnetic particle imaging (MPI). In MPI, the magnetic field oscillates and the electromagnetic response from a certain point in the space is received (30). Only magnetic particles with nonlinear response will cause higher harmonics to be recorded. The image space is sequentially scanned in a point-by-point manner. This MPI device provides a high scanning speed to verify SPIO with sensitivity and resolution warranting further investigation. The lack of background reference in MPI may require additional MRI or CT scans, while QSM through MRI conveniently provide relative susceptibility distribution to the background and anatomical structure. (Perhaps you can reiterate what QSM is in the discussion, so that the readers will not forget)

Conclusion

In this study, we demonstrated that using quantitative susceptibility mapping in MRI at two field strengths, the non-linear response of SPIO particles allows distinction of SPIO from linear materials such as air, water and tissue. Quantifying susceptibility at two different field strengths allows SPIO-specific imaging.

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Figure 1.

a) Illustration of magnetizations curves of SPIO and air. The magnetization of SPIO is calculated for ferumoxides at a concentration of 4mM Fe (2). The magnetization of air is proportional to the field strength with a constant susceptibility of 9.4ppm (12) b) Susceptibility curves of SPIO and air. Susceptibility values were calculated from Eq. [1]

Figure 2.

Numerical simulation of a susceptibility mapping experiment a) is the magnitude image. b) is the phase image). c) is the susceptibility map reconstructed from original COSMOS. d) is the susceptibility map reconstructed from regularized COSMOS. Note that regularized COSMOS has smoother distributions in signal voids.

Figure 3.

Phantom experimental results a) and b) are gradient echo images from 1.5T and 3T, respectively. The rightmost signal void region is the air straw, while other signal void regions contain Feridex solutions 1.5%, 3.0%, 4.5% and 6.0% in clockwise order. Air is indistinguishable from high concentrated Feridex solution on gradient echo images. Figures c) and d) show the quantitative susceptibility maps from 1.5T and 3T. The difference between 1.5T and 3T is shown on Fig e).

Figure 4.

a) gradient echo image of a mouse at 3T. Both lung and the SPIO injection region appear to be signal void regions. b), c) susceptibility reconstructions at the cross section that contains the SPIO injection region from 1.5T and 3T, respectively. d) the difference between b) and c). e), f) susceptibility reconstructions at the cross section that contains lung. g) the difference between e) and f).

Magnetic Moment Ratios

Figure 5.

Magnetic moment ratios between 3T and 1.5T. The left five columns are data from the phantom experiment. The right two columns are data from the *ex vivo* mouse experiment. Error bars, which correspond to the estimated noise level in the quantification, are smaller than the error of graphical display.

Table 1

Measured susceptibilities in different signal void spheres (mean±standard deviation)

Mean±std Unit ppm	Radius = 1	Radius = 2	Radius = 3	Radius = 4	Radius = 5	Radius = 6
Original COSMOS	9.66	9.48±0.76	9.37±8.48	9.39±5.09	9.42±4.59	9.40±6.81
Improved COSMOS	9.63	9.45±0.46	9.41±0.50	9.40±0.50	9.42±0.52	9.40±0.67

Table 2

Calculated magnetic moments

Unit 1×10^{-9} $A \cdot m^2$	1.5% Feridex	3.0% Feridex	4.5% Feridex	6.0% Feridex	Air straw	Feridex injection	Lung (air)
1.5T	35.1	67.8	93.2	124.6	27.0	273.8	101.0
3T	36.9	70.9	105.7	136.4	52.2	278.9	198.1

Table 3

MRI measured iron mass through quantitative susceptibility mapping

Unit μg	1.5% Feridex	3% Feridex	4.5% Feridex	6% Feridex	Air straw	Feridex injection	Lung (air)
1.5T	0.45	0.88	1.21	1.61	N/A	3.54	N/A
3T	0.44	0.85	1.26	1.63	N/A	3.33	N/A