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Enhanced Positive-Contrast Visualization of Paramagnetic Contrast Agents Using Phase Images

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Abstract

Iron oxide–based MRI contrast agents are increasingly being used to noninvasively track cells, target molecular epitopes, and monitor gene expression in vivo. Detecting regions of contrast agent accumulation can be challenging if resulting contrast is subtle relative to endogenous tissue hypointensities. A postprocessing method is presented that yields enhanced positive-contrast images from the phase map associated with T_2^* -weighted MRI data. As examples, the method was applied to an agarose gel phantom doped with superparamagnetic iron-oxide nanoparticles and in vivo and ex vivo mouse brains inoculated with recombinant viruses delivering transgenes that induce overexpression of paramagnetic ferritin. Overall, this approach generates images that exhibit a 1- to 8-fold improvement in contrast-to-noise ratio in regions where paramagnetic agents are present compared to conventional magnitude images. This approach can be used in conjunction with conventional T_2^* pulse sequences, requires no prescans or increased scan time, and can be applied retrospectively to previously acquired data.

Keywords

positive contrast; MRI; SPIO; paramagnetic; contrast agents

Paramagnetic contrast agents (CAs) are widely used for a multitude of emerging cellular-molecular applications (1). Commonly used superparamagnetic iron-oxide (SPIO) particles, with iron-oxide core diameters ranging between 5 nm and 1 μ m, create microscopic static magnetic field perturbations that extend 10-100 times the particle's diameter, thereby reducing the effective T_2 and T_2^* of nearby water protons. The resulting T_2 - and T_2^* -weighted images often exhibit regions of hypointensity in magnitude images where agent has accumulated. Clinical-grade SPIO agents such as Resovist[®], Feridex[®], and Combidex[®] are used to enhance various pathologies. SPIO particles have been used to detect molecular epitopes by conjugating their surfaces to a variety of target entities, such as peptides or antibodies (1,2). Intracellular labeling with SPIO, either ex vivo or in situ, is a rapidly evolving approach for preclinical cell trafficking and inflammation studies (3). Clinical translation of cell tracking has been demonstrated in pilot studies (4). In addition, paramagnetic CAs also encompass intracellular labeling approaches that image gene expression by utilizing genetically encoded metalloproteins (1,5-9). In these approaches, metalloproteins, particularly from the ferritin family, are selectively overexpressed in specific host tissues. These iron storage proteins become paramagnetic by sequestering and aggregating iron from the organism, thereby imparting exogenous MRI contrast to transduced tissues.

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Across all of these important iron-based paramagnetic CA applications, a common challenge is distinguishing the image intensity dropout generated by the agents from other sources of endogenous image hypointensity. For example, endogenous T_2 - and T_2^* -weighted hypointensity may originate from disparate tissue relaxation times, magnetic susceptibility interface gradients, blood vessels, and low proton density in tissues. To address this challenge, previous studies have generated positive contrast images highlighting the presence of SPIOs by changing how images are acquired. Exemplary studies utilize differential imaging before and after agent delivery, specialized weighted contrast methods (10,11), spectrally selective excitation (12,13), gradient dephasing (14), quantum coherence imaging (15), and ultrashort echo time image subtraction (16). These techniques often complement magnitude images but may also carry limitations. For example, several methods require foreknowledge of the magnitude of the field disturbances caused by the iron oxides, and this information is used to configure critical MRI scan parameters such as excitation (carrier) frequency, bandwidth, and selective radiofrequency pulse shape (12), rephasing gradient amplitude (13) or echo times, and slice thickness (14). Additionally, some of these techniques demand high-end hardware (16) or additional anatomic scans that result in longer acquisition times (12-14).

An alternative approach for addressing this common challenge is to highlight SPIO by generating positive-contrast images from MRI phase images (17,18). Because phase image pixel values correlate with local magnetic field, applying high-pass filters to phase images has been shown to accentuate spatial magnetic field variations (i.e., paramagnetic CA deposits). Postprocessing of phase images does not require altering image acquisition procedures, as is required for many of the prior art methods, as discussed above. In one study, a smoothing high-pass filter was applied to phase images of an air-water phantom and in vivo brain tissue (18). The filter used in this study, however, results in images with an effective resolution roughly two times lower than the original image (18). In a second study, a high-pass filter that does not reduce effective resolution was applied to phase images of bovine muscle tissue (17). More recently, the linear component of phase spatial variation was visualized by performing quadratic fits to k -space phase shifts (19). This method uses a variable-size sliding-window approach that avoids potential phase-unwrapping errors but sacrifices image resolution as a result of partial-voluming.

These studies (17-19) provide strong visual evidence for enhanced sensitivity to magnetic susceptibility disturbances among tissues when using filtered phase maps. However, these studies either do not quantify sensitivity gains or sacrifice spatial resolution during the image generation process. This study aims to simultaneously preserve image resolution while quantifying sensitivity improvements that result from high-pass filtering phase images. Our resulting phase slope magnitude (PSM) images emphasize spatial magnetic field variations. The PSM image contrast-to-noise ratio (CNR) was calculated in regions surrounding paramagnetic CA distributions and compared against CNR values from conventional magnitude images. Initially, using PSM we analyzed an agarose gel phantom doped with SPIO particles. PSM analysis was also performed on a fixed mouse brain that had been stereotactically inoculated in one hemisegment of the striatum with a replication-defective adenovirus (AdV). The AdV contained transferrin receptor (TfR-1) transgenes; overexpression of TfR in transduced cells upregulates ferritin, a paramagnetic cellular iron storage protein that produces a weak contrasting effect in T_2 and T_2^* -weighted MRI scans (5,20). Last, PSM analysis was performed using in vivo data acquired in a mouse brain that had been inoculated with AdV containing transgenes for ferritin subunits. These transgenes cause the formation of paramagnetic holoferritin as brain cells sequester endogenous iron from the organism (5). The paramagnetic disturbance from ferritin is weaker compared to SPIO, and PSM images may make the difference between seeing and not seeing a targeted CA. Overall, PSM images exhibit a significant 1- to 8-fold CNR improvement in regions where paramagnetic agent is present compared to conventional magnitude images. A method for thresholding PSM images to

eliminate noise from phase measurements is also described. The PSM method does not require extra MRI scans because it relies on phase images that are a by-product of conventional MRI scans; it can be used retrospectively on previously acquired data. PSM image generation requires no prior knowledge about the magnitude of the field disturbance created by arbitrary CA distributions and can be used in conjunction with any T_2^* -weighted MRI pulse sequence.

Theory

Phase Map Preparation

MR images are typically reconstructed from a series of echoes acquired in k -space using a multidimensional Fourier transform. Every voxel in the reconstruction has both a real and imaginary component (i.e., $I = a + bi, i^2 = -1$). The magnitude image is normally displayed, given by $|I| = \sqrt{a^2 + b^2}$ for each voxel. The phase angle information, given by $\phi = \arctan(b/a)$, is typically discarded. This quantity is proportional to the magnetic field in a given voxel and thus contains valuable information about the local magnetic field distortions due to the presence of high magnetic susceptibility CA. The phase angle in each voxel of a phase map can be expressed as

$$\phi = \phi_{\text{low-}f} + \phi_{\text{CA}} + \phi_{\text{high-}f} \quad [-\pi \leq \phi < \pi] \quad [1]$$

where ϕ is the measured phase angle, $\phi_{\text{low-}f}$ is the low-spatial-frequency contribution to the phase angle (e.g., applied gradients, large-scale inhomogeneity), ϕ_{CA} is the contribution from nearby CA, and $\phi_{\text{high-}f}$ is the non-CA high-spatial-frequency contribution. When working with a single-echo gradient-echo image, one must first ‘unwrap’ the phase image before one can distinguish the desired ϕ_{CA} component from the other phase angle contributions (21). Specifically, phase images often display discontinuities (i.e., wraps) when crossing from $-\pi$ to $+\pi$ over the image field of view (22). The $-\pi/+\pi$ boundaries can be eliminated using unwrapping algorithms, previously described (21-25), that determine the multiple of 2π that must be added or subtracted from the phase angle to obtain a discontinuity-free phase map. When unwrapping is applied, Eq. [1] becomes

$$\phi_{\text{Unwrapped}} = \phi_{\text{low-}f} + \phi_{\text{IOX}} + \phi_{\text{high-}f} + 2\pi n \quad [2]$$

where $n \in \{\dots, -2, -1, 0, 1, 2, \dots\}$. We eliminate $\phi_{\text{low-}f}$ by applying a high-pass filter to the unwrapped phase map in Eq. [2], resulting in a phase-offset image, where each voxel is represented by

$$\phi_{\text{Offset}} = \phi_{\text{IOX}} + \phi_{\text{high-}f} \quad [3]$$

The resulting phase-offset image (Eq. [3]) now contains only paramagnetic CA susceptibility effects and other high-spatial-frequency phase contributions (e.g., material/tissue interfaces) and can be used to highlight and analyze the commensurate magnetic field disturbances.

PSM Image Generation

To accentuate perturbations in phase due to paramagnetic agent deposits, we first calculate the mathematical gradient of the phase-offset image (Eq. [3]), which results in a vector field:

$$\nabla\varphi_{\text{Offset}} = \sum_{i=1}^n \frac{d\varphi_{\text{Offset}}}{dx_i} \hat{x}_i \quad [4]$$

In Eq. [4], n indicates the number of dimensions for comparison (e.g., $n = 3$ for three-dimensional [3D] volumes). Using the vector field from Eq. [4], we set the magnitude of each vector as a pixel value in our final PSM image product:

$$I(x, y, z) = \|\nabla\varphi_{\text{Offset}}(x, y, z)\| \quad [5]$$

where x, y, z represent image grid coordinates, and I represents PSM image pixel intensity. Additional computational details used in generating PSM images are described in the Materials and Methods section.

PSM Image Regional Noise Thresholding

Pixel intensity values in PSM images are generated from phase maps as described by Eqs. [3-5]. Phase maps also contain an underlying probabilistic noise intensity that is inversely proportional to their corresponding magnitude image's signal-to-noise ratio (26,27). One can eliminate likely noise pixels in PSM images by applying the following statistical criterion. First, we assume that the phase-offset images from which PSM images are generated (Eq. [3]) have corresponding magnitude images with regional signal-to-noise ratio >3 (27). This allows the phase image noise distribution to be approximated as gaussian (27), and one can calculate the standard deviation (SD) of noise values (σ_φ) in the phase-offset images using the relation:

$$\sigma_\varphi = \sigma / \sqrt{\bar{M}^2 - \sigma^2} \quad [6]$$

where $\bar{M}$ is the magnitude image's average intensity in this region of interest and σ is the SD of the real or imaginary gaussian noise in this same region (27). Alternatively, σ can be estimated by:

$$\sigma^2 = \sigma_N^2 / (2 - \pi/2) \quad [7]$$

where σ_N is the noise SD in a region devoid of proton signal (27). Combining Eqs. [6] and [7] gives the relation:

$$\sigma_\varphi = 1.5264 \cdot \sigma_N / \sqrt{\bar{M}^2 - 2.33 \cdot \sigma_N^2} \quad [8]$$

Since Eq. [8] provides the noise level in phase-offset images (Eq. [3]), we can use this to calculate noise in PSM-images by considering Eq. [5]. Specifically, along *each* spatial dimension, (i.e., dx , dy , or dz) noise values in the PSM image will also follow a gaussian distribution, with a new SD of

$$\sigma_{\varphi dx} = \sigma_{\varphi dy} = \sigma_{\varphi dz} = \sqrt{\sigma_{\varphi A}^2 + \sigma_{\varphi B}^2} = \sqrt{2} \cdot \sigma_{\varphi} \quad [9]$$

where $\sigma_{\varphi A}$ and $\sigma_{\varphi B}$ represent SD in two adjacent voxels, and σ_{φ} is found using Eq. [8]. Since this distribution is gaussian, 95% of its values are expected to fall within the range

$[-2\sqrt{2}\sigma_{\varphi}, 2\sqrt{2}\sigma_{\varphi}]$. Thus, when generating two-dimensional or 3D PSM images using Eqs. [4-5], one can optionally threshold out values of dx , dy , or dz that are within this range, thereby removing a significant number of ‘false-positive’ pixels from our final PSM image product that likely represent random phase-angle noise variations.

Materials and Methods

Gel Phantom Studies

A gel phantom was constructed using a 3-mL syringe filled with 2% agarose that was lightly doped with 1.6- μ m-diameter micron-sized paramagnetic iron oxide particles (Bangs Laboratories, Fishers, IN). The phantom was imaged using an 11.7-T, 89-mm, vertical-bore, Bruker AVANCE microimaging system (Bruker BioSpin, Billerica, MA). We used a 25-mm diameter birdcage coil and a standard 3D gradient-echo pulse sequence with parameters echo time/pulse repetition time = 7/1500 ms, $\theta \approx 90^\circ$, and 40- μ m isotropic resolution. Raw echo data were reconstructed to create phase images, as described below.

Mouse Brains Expressing Transferrin and Ferritin Transgenes

Adult 20-g female C57BL/6J mice (Harlan Laboratories, Indianapolis, IN) were anesthetized using an intraperitoneal cocktail of ketamine and xylazine and placed in a head stereotaxic device. Animals were injected with a recombinant AdV carrying either the TfR-1 gene or a 1:1 mixture of the light and heavy subunits of ferritin, as described in Genove et al. (5). Inoculations were made into the right striatum with a 32-gauge needle (total of 1.6×10^9 plaque-forming units). A control AdV containing the β -galactosidase reporter (LacZ) was injected into the contralateral hemisphere. Animals were monitored until recovered and housed with a normal diet and water ad libitum. In the AdV-TfR-1-transduced brain, at day 5 postinjection, the mouse was perfused and fixed in 4% paraformaldehyde and the brain removed. The brain was suspended in 1% agarose in a plastic tube prior to imaging. Samples were imaged at 11.7 T using acquisition parameters echo time/pulse repetition time = 6.4/50 ms, $\theta \approx 30^\circ$, 51- μ m isotropic voxels, $512 \times 256 \times 256$ image points, and 16 averages. The light subunit of ferritin– and heavy subunit of ferritin–AdV inoculated mouse was imaged in vivo. At day 5 after injection, the mouse was anesthetized using isoflurane in air and imaged as above except using a motion-gated gradient-echo pulse sequence with acquisition parameters echo time/pulse repetition time = 7.7/175 ms, 98- μ m isotropic voxels, 256×256 image points, and four averages. Additional experimental details about these procedures and materials are described elsewhere (5). All animal experiments were performed in accordance with the Carnegie Mellon Institutional Animal Care and Use Committee guidelines and the US National Institutes of Health Guide for the Care and Use of Laboratory Animals.

PSM Image Construction

For all MRI data sets, raw echo data were reconstructed into two-dimensional and 3D phase images. A cost minimization–based phase-unwrapping algorithm was applied to each image or 3D image stack (23). Phase-unwrapped data were then imported into MATLAB (The Mathworks Inc., Natick, MA) and filtered with a high-pass filtering kernel designed to exclude the lowest 10% of frequencies. These operations resulted in a series of two-dimensional phase-offset images, as described by Eq. [3]. The phase gradient vector field from Eq. [4] was

constructed by calculating $d\phi/dx$, $d\phi/dy$, and $d\phi/dz$ in each voxel of the phase-offset image and then expressing these three components as a single vector. PSM images were visually rendered in grayscale to show the magnitude of each vector in the phase gradient vector field, as described by Eq. [5].

PSM Image CNR Analysis

To evaluate the efficacy of PSM image enhancement compared to conventional magnitude images, we measured the mean CNR surrounding each region of interest containing presumed CA deposits in both image types. Image CNR was calculated using the formula:

$$\text{CNR} = |I_A - I_B| / \sigma \quad [10]$$

where I_A represents the average image intensity around the presumed CA deposit, I_B represents the average image intensity of the background substance surrounding the region of interest (e.g., agarose gel or tissue), and σ represents the background substance's pixel-wise SD. PSM image thresholding was not performed before CNR analysis. Specifically, using Eq. [10], the CNR was calculated for the following samples as described below:

Agarose Gel Phantom Doped With Micron-sized Paramagnetic Iron Oxide—For the gel phantom, an arbitrary two-dimensional slice through the volume was selected for CNR analysis. A small area containing four apparent dipolar perturbations was selected from the slice. Each dipole's average intensity (i.e., I_A in Eq. [10]) was calculated from a 6×6 voxel cluster, of $240 \times 240 \times 40\text{-}\mu\text{m}$ total size, centered on each dipole. A 32×32 voxel background region, devoid of apparent dipoles, was used to measure the average background intensity (i.e., I_B in Eq. [10]) and background noise (σ). In addition, we also calculated the maximum, single-pixel CNR for each region of interest by substituting I'_A for I_A in Eq. [10], where I'_A represents the single voxel in the 6×6 voxel cluster exhibiting the largest deviation from the background I_B value.

Ex Vivo Mouse Brain—For the mouse brain, a region centered on the site of AdV inoculation was segmented manually from the 3D mouse brain volume. Slice by slice, this region's average intensity (I_A in Eq. [10]) was calculated from a 20×20 voxel region of total volume $1 \times 1 \times 0.25\text{ mm}^3$. A comparable 32×32 voxel region on the contralateral side was also segmented, where AdV-LacZ control vector was injected; this region was used to measure average background intensity, I_B , via Eq. [10]. Background noise (σ) was measured using a 32×32 voxel region from the homogeneous agarose gel embedding the brain. Image CNR was calculated using Eq. [10] on a slice-by-slice basis, five slices total, for both PSM and magnitude image types. In addition to analysis of the average regional CNR, we also calculated the maximum, single-pixel CNR slice-by-slice for this region by substituting I'_A for I_A in Eq. [10], where I'_A represents the single pixel in the 20×20 pixel transduced brain region exhibiting the largest deviation from the average background I_B value. The 3D PSM result was volume rendered and made semitransparent using the software package Amira (Mercury Computer Systems, Chelmsford, MA).

In Vivo Mouse Brain—A region centered on the site of AdV inoculation was segmented manually from the mouse brain slice. This region's average intensity (I_A in Eq. [10]) was calculated from a 9×15 voxel region of total volume $0.9 \times 1.5\text{ mm}^2$. A comparable 16×16 voxel region on the contralateral (AdV-LacZ) side was also segmented to measure average background intensity, I_B , via Eq. [10]. Background noise (σ) was measured using the same 16×16 voxel homogeneous background region. Image CNR was calculated using Eq. [10] for

both PSM and magnitude image types. In addition to analysis of the average regional CNR, we also calculated the maximum single-pixel CNR for this region by substituting I'_A for I_A in Eq. [10], where I'_A represents the single pixel in the 9×15 pixel transduced brain region exhibiting the largest deviation from the average background I_B value.

Results

PSM images were generated from three diverse data sets to assess efficacy at highlighting CA deposits. None of the presented PSM images underwent the regional noise thresholding procedure, but we found that applying the procedure results in nearly noise-free PSM images suitable for effective visualization of CA distribution. To compare PSM images to conventional magnitude images, the CNR was measured in both images in regions encompassing the CA deposits. Table 1 summarizes the numerical CNR analysis for the micron-sized paramagnetic iron oxide–doped agarose gel phantom; Fig. 1 shows the PSM and magnitude images used to obtain the results in Table 1. In the gel phantom, PSM images were found to exhibit a 2- to 8-fold CNR improvement over magnitude images in regions containing the micron-sized paramagnetic iron oxide deposits.

The analysis results for the AdV-TfR inoculated mouse brain are shown in Table 2, where Fig. 2 shows the associated PSM and magnitude images. Figure 3 shows several views of a 3D volumetric rendering of this entire mouse brain using 3D PSM data. Results for the light subunit of ferritin/heavy subunit of ferritin–AdV inoculated mouse brain are displayed as PSM and magnitude images in Fig. 4. PSM images exhibited a 1- to 5-fold CNR improvement at sites of AdV injection (Table 2). Inspection of Figs. 2 and 4 supports this finding, where transduced cells are significantly more apparent in the PSM images (Figs. 2a, 4a) compared to the magnitude images (Figs. 2b, 4b). Figure 3 shows that full-brain visualization of the transgene distribution is feasible and efficacious, despite the presence of several regions of endogenous PSM contrast throughout the volume.

Discussion and Conclusions

In this paper, we describe how paramagnetic CA distributions can be highlighted using PSM images. Visualizing phase slope with PSM images provides a sensitive picture of magnetic field disturbances. In our pilot experiments, the PSM images exhibit a 1- to 8-fold CNR improvement in CA-containing regions compared to conventional magnitude images. No loss in CNR was found in any images studied. We show that PSM images can be generated in 3D to visualize arbitrary agent distributions and that these images help differentiate hypointense image regions due to CA, leading to improved detectability. Indeed, we find that when analyzing samples that show a weak paramagnetic effect, PSM images can make the difference between detecting and not detecting magnetic disturbances (Fig. 2, panels 1 and 3). We also show that PSM is effective for in vivo applications. However, acquired images should be relatively free from motion artifacts. By superimposing PSM images onto magnitude images, one can reap the benefits of increased sensitivity to magnetic susceptibility effects while retaining the critical anatomic backdrop.

However, there are several limitations to the PSM method. First, an inherent limitation is its potential inability to distinguish between some tissue interfaces and regions containing CA. Both the agarose gel phantom and mouse brains had relatively homogeneous backgrounds for testing PSM image generation and resulting CNR measurements. PSM image methods applied to tissues or interfaces of high magnetic susceptibility heterogeneity may not be as effective at distinguishing paramagnetic CA deposits from background. Furthermore, PSM-image generation may introduce computational artifacts if highly relaxative CAs generate rapid spatial changes in phase angle (25). If image resolution is too low to sample these rapid phase

changes, undersampling occurs, which can potentially cause phase unwrapping algorithms to choose an incorrect multiple of 2π to add to each phase image pixel. Any incorrect choice will propagate through the PSM image-generation process, generating false-positive or -negative pixel results. To mitigate this effect, one might acquire phase maps using multiecho gradient-echo pulse sequences that employ ‘temporal unwrapping’ in order to determine phase angle values with greater certainty (28,29). The detection limit of PSM images is primarily determined by phase image signal-to-noise ratio. The outlined PSM image regional thresholding method can be used to identify all PSM image pixels that have a ~95% certainty of representing a true susceptibility disturbance.

Emerging cellular-molecular MRI applications can benefit from improved sensitivity to paramagnetic CA distributions. The PSM approach generates positive contrast images that help to differentiate CAs from endogenous sources of tissue hypointensity. Unlike many other positive-contrast imaging methods, PSM-image generation requires no prior knowledge of magnetic agent strength or distribution, no special pulse or gradient sequences, and no extra scan time, and it can be applied retrospectively to already acquired data. Finally, these image-generation methods can be made into an automated routine with few or no input parameters.

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FIG. 1.

Three different image types formed from the same region of SPIO-doped agarose gel phantom. Images include (a) conventional magnitude image, (b) inverted magnitude image, and (c) positive-contrast PSM image. **a:** The four paramagnetic dipoles are labeled “1” through “4,” corresponding to the same four dipoles enumerated in the gel dipole CNR improvement analysis (Table 1). In regions where SPIO is present, the PSM image exhibits CNR values 2-8 $\times$ greater than the conventional magnitude image. The inverted magnitude image in (b) is provided for comparison with the PSM result in (c). This comparison demonstrates that the PSM method does not just create simple positive contrast visuals but also generates additional contrast that spatially extends around and accentuates CA.

FIG. 2.

Mouse brain transduced with TfR-1 transgenes via an AdV-vector injected into the striatum. The TfR-1 upregulates paramagnetic ferritin, leading to iron accumulation in transduced cells and enhanced paramagnetism. Three image slices are shown comparing **(a)** positive-contrast PSM images generated using our described approach and **(b)** conventional magnitude images. These three sections correspond to the slices analyzed in Table 2. Arrows indicate where AdV/TfR-1 was injected, while the contralateral side was injected with an AdV/LacZ control and shows no contrast. In regions where ferritin is present, PSM images exhibit CNR values $1-5 \times$ greater than the conventional magnitude images **(b)**.

FIG. 3. PSM 3D volume rendering of the mouse brain inoculated with AdV/TfR-1 into the striatum. The panels show (a) dorsal, (b) lateral, (c) cranial, and (d) oblique views. The arrows indicate the site of AdV-TfR-1 injection, while the contralateral side was injected with AdV-LacZ control. These 3D PSM images are easily able to distinguish the paramagnetic deposits induced by the TfR-1 transgene. This is the same brain shown in Table 2 and Fig. 2.

FIG. 4.

In vivo MRI of mouse brain transduced with heavy subunit of ferritin and light subunit of ferritin transgenes via an AdV-vector injected into the striatum. The coronal section shown compares (a) positive-contrast PSM image and (b) conventional magnitude image. Arrows indicate the light subunit of ferritin/heavy subunit of ferritin-AdV mix injection site, while the contralateral side injected with the AdV-LacZ control shows no contrast. In the ferritin-transduced region, the PSM image exhibits CNR values $1.6\text{--}1.8 \times$ greater than the conventional magnitude image.

Table 1

PSM Analysis Results for the Gel Phantom Doped With Micron-Sized Paramagnetic Iron Oxide

Measurement	Dipole1	2	3	4
Average PSM CNR	11.6	5.3	12.0	28.5
Average MAG CNR	1.6	1.3	2.1	3.4
PSM improvement	7.1×	4.0×	5.7×	8.3×
Maximum PSM CNR	57.5	31.4	66.0	143.4
Maximum MAG CNR	3.1	2.8	3.3	3.5
PSM improvement	2.9×	2.1×	2.9×	5.5×

Shown is a comparison between the CNR present in PSM and conventional magnitude (MAG) images.

PSM Analysis Results for the Mouse Brain Transduced With TfR-1 Transgenes

Measurement	Section 1	2	3	4	5
Average PSM CNR	1.9	3.0	3.9	4.2	4.5
Average MAG CNR	2.2	1.9	2.5	3.2	3.3
PSM improvement	0.9×	1.6×	1.6×	1.3×	1.4×
Maximum PSM CNR	28.0	56.7	50.7	72.0	127.4
Maximum MAG CNR	10.2	11.0	13.1	23.2	24.6
PSM improvement	2.7×	5.2×	3.9×	3.1×	5.2×

Shown is a comparison between the CNR present in the PSM and conventional magnitude (MAG) images.