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Probing Signal Phase in Direct Visualization of Short Transverse Relaxation Time Component (ViSTa)

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Abstract

Purpose—To demonstrate the phase evolutions of direct visualization of short transverse relaxation time component (ViSTa) matches with those of myelin water.

Method—Myelin water imaging (MWI) measures short transverse signals, and has been suggested as a biomarker for myelin. Recently, a new approach, ViSTa, has been proposed to acquire short T_2^* signals by suppressing long T_1 signals. This method does not require any ill-conditioned data processing and therefore, provides high quality images. In this work, the phase of the ViSTa signal is explored and compared with the phase of myelin water simulated by the magnetic susceptibility model of hollow cylinder.

Results—The phase evolutions of the ViSTa signal show great similarity to the simulated myelin water phase evolutions. When fiber orientation is perpendicular relative to the main magnetic field, both the ViSTa and the simulated myelin water phase show large positive frequency shifts, whereas the GRE phase shows a slightly negative frequency shift. Additionally, the myelin water phase map generated using DTI information shows a good match with the ViSTa phase image.

Conclusion—These results support the origin of ViSTa signal as myelin water. ViSTa phase may potentially provide sensitivity to demyelination.

Keywords

myelin water imaging; ViSTa phase imaging; frequency shift; microstructure in white matter; magnetic susceptibility of myelin; hollow cylinder model

Introduction

In the white matter of the brain, the decay of the transverse magnetization has been shown to be characterized by multiple exponential decays (1), with two or three distinct time constants (T_2 or T_2^*). These components have been associated with different water compartments in white matter. The short T_2 (~20 ms) or T_2^* (~10 ms) component has been suggested to originate from myelin water, whereas the long T_2 (~70 ms) or T_2^* (~50 ms) components have been associated with axonal and extracellular water signal (1–4). In several studies, longitudinal magnetization relaxation (T_1) has also been suggested to vary between the compartments with the shortest T_1 signal related to myelin water (5–11).

In addition to the relaxation property differences, myelin water has been demonstrated to experience different magnetic field perturbation from those experienced by axonal and extracellular water (12–16). In particular, when white matter fibers are oriented perpendicular relative to B_0 field, myelin water experiences a positive frequency shift, whereas axonal water experiences the opposite frequency shift (13,14). These observations have been explained by a model of hollow cylinder (13), which represents the myelin sheath as a hollow cylinder that has both isotropic and anisotropic magnetic susceptibilities (17–22). Based on these observations, Sati et al. (14) have visualized the frequency shift of myelin water in a multiple sclerosis patient, demonstrating its sensitivity to demyelination. This myelin water phase may potentially be more sensitive to demyelination than the GRE phase, which has shown to detect multiple sclerosis lesions earlier than contrast enhancing MRI (23).

Recently, we have developed a new approach to acquire a short T_2^* signal by taking advantage of the T_1 differences between water components with the assumption of a monotonic relationship between T_1 and T_2 in water components (24). This method, which is referred to as direct visualization of short transverse relaxation time component (ViSTa), suppresses long T_1 signals using a double inversion preparation, such that the short T_1 signal dominates the resulting image. The magnitude decay characteristics of ViSTa have demonstrated that the signal is primarily from short T_2^* (> 90%) in the range of myelin water (< 25 ms), suggesting the origin of the ViSTa signal as myelin water (24). Compared to conventional MWI, ViSTa does not require any ill-conditioned post-processing and, hence, provides superior image quality (24).

Here, we explored the frequency shift or phase characteristics of the ViSTa signal in order to support the attribution of the ViSTa signal to myelin water. The phase evolution of the ViSTa signal over multiple echo times was compared to the myelin water phase simulated using the hollow cylinder model (13). The results demonstrate that the phase evolution of ViSTa closely matches the simulated myelin water phase and is different from the phase of GRE signal, supporting the source of ViSTa signal as myelin water.

Methods

Data were acquired at two different slices that contained large regions of fibers parallel (corticospinal/corpus callosal tract) and perpendicular (splenium of the corpus callosum) to

B_0 field to determine phase evolutions of GRE and ViSTa at both fiber orientations. Note that the internal capsule in the lower slice also showed the fiber orientation parallel to B_0 field but was not chosen because of a potential complication of signal phase from a high iron concentration in the surrounding area. The experiments were performed over two separate sessions in order to limit the scan time of each session. A total of six subjects, who provided IRB-approved written consent, volunteered for the study. In the first session, five subjects (age: 33 ± 3 years) were scanned for a lower slice that contained splenium. In the second session, five subjects (age: 34 ± 4 years), four of whom participated in the previous session, were scanned for an upper slice that contained corticospinal/corpus callosal tract. A 3T MRI system (Trio, Siemens, Erlangen, Germany) with a phase arrayed 32-channel head coil was used.

Data Acquisition

In each session, the scan started with a 3-plane localizer followed by region-of-interest shimming. An RF-spoiled GRE sequence and a ViSTa sequence (24) were acquired multiple times in alternating order (GRE-ViSTa-GRE-ViSTa-GRE-ViSTa-GRE) in order to reduce background phase change from a quasi-linear magnetic field drift which results from temperature increase in the bore (25) (see Image Reconstruction and Processing for details). DTI was acquired in the upper slice session.

Common scan parameters for the GRE and ViSTa sequences were as follows: scan mode = 2D single slice acquisition, FOV = 220×220 mm², in-plane resolution = 1.72×1.72 mm², slice thickness = 5 mm, TR = 1160 ms, number of echoes = 32, TE = 3.00 ms to 78.64 ms with echo spacing of 2.44 ms, flip angle = 90° , matrix size = 128×128 , bandwidth = 490 Hz/pixel, and scan time = 2.6 min. Fat saturation was not applied. The double inversion timing for ViSTa was $TI_1 = 560$ ms, $TI_2 = 220$ ms and TD = 380 ms where TI_1 is the duration between the first inversion pulse to the second inversion pulse, TI_2 is the duration between the second inversion pulse to the excitation pulse, and TD is the duration between the excitation pulse to the following inversion pulse (24). Note that a common TR (=1160 ms) was used for both GRE and ViSTa in order to match the drift effects from each scan. DTI data were acquired at the same resolution and FOV while covering 16 slices with $b = 1000$ mm²/s in 30 diffusion directions.

Image Reconstruction and Processing

For all scans except for DTI, k-space data were processed to generate magnitude and phase images. Multichannel magnitude images were combined using a sum-of-squares method. For the phase images, complex images were combined using a phase-sensitive complex sum (26). Then, phase images were generated from the complex images. The resulting phase images from the 32 echoes were unwrapped voxel-wise along the echo time. The unwrapped phase images contained both local susceptibility information and non-local background phase. The nonlocal background phase was estimated from the unwrapped GRE phase using a method, RESHARP (27), with a regularization parameter of 0.001 and a convolution kernel size of 3 voxels. Then, the estimated background phase was removed from the unwrapped GRE phase images to generate the final GRE phase images. For ViSTa, the background phase that was estimated by the GRE phase images were subtracted from the

unwrapped ViSTa phase images. This approach of using a common background field is valid because the background field originates primarily from large-scale susceptibility differences in the brain (e.g. air/tissue) and an imperfect B_0 field of the scanner, and is independent of the sequences. Moreover, this approach is useful in estimating the ViSTa background phase since it has an overall low SNR with little signal in gray matter and CSF. One complication of using a common background field is the magnetic field drift, which adds a frequency shift in the background field (25). To minimize the drift effects, the scan alternated between GRE and ViSTa, and the mean of the two adjacent GRE background phases were averaged to remove the background field of the ViSTa unwrapped phase image. After completing the phase processing, multiple runs of GRE and ViSTa data were averaged separately. Multiple runs of magnitude images were also averaged. All of the phase images were masked by a thresholded first-echo ViSTa magnitude image to reveal only the white matter structure. The skull, which appeared bright in ViSTa due to unsuppressed fat, was manually removed. DTI images were processed using DTIFIT (28) to generate fractional anisotropy (FA), primary eigenvector (V_1) and FA-weighted V_1 maps.

ROI Analysis

After generating the magnitude and phase images, regions of interest (ROI) were drawn for perpendicular and parallel fibers to analyze the signal characteristics of the two sequences. For perpendicular fibers, an ROI was drawn at the splenium of the corpus callosum (Fig. 1M). DTI results confirmed that the primary fiber orientation of this ROI was approximately perpendicular ($85^\circ \pm 2^\circ$) relative to the B_0 field. For a parallel fiber ROI, upper slice regions that contained corticospinal and corpus callosal tracts were targeted. These parallel fibers did not have a clear anatomical landmark and were identified by a DTI fiber orientation map as follows: First, an FA map was registered to a ViSTa magnitude image manually. Then, voxels with fiber orientations less than 25° relative to the main magnetic field and with FA larger than 0.3, were selected as the parallel fiber ROI (Fig. 2M). Note that the perpendicular fiber ROI was determined by an anatomical landmark whereas the parallel fiber ROI was determined by the thresholds.

The mean magnitude decay and phase evolution over TE were calculated by taking the average over the voxels for each ROI in the ViSTa data and also in the GRE data. The magnitude decay was then fitted by a nonnegative least squares (NNLS) fitting of multiple exponential decay functions (29), given by:

$$S_i = \sum_{k=1}^M A_k \exp\left(-\frac{TE_i}{T_{2k}^*}\right), i=1, 2, \dots, 32$$

where S_i was the magnitude signal at i^{th} TE, M ($= 120$) was the number of T_2^* components, and A_k and T_{2k}^* are the amplitude and T_2^* of each k^{th} component, respectively. T_{2k}^* was spaced logarithmically from 2.77 ms to 300 ms (30). After estimating the T_2^* distribution, the short T_2^* fraction was calculated as the ratio of the sum of the short T_2^* signals (T_2^* 25 ms) to the sum of entire signal (Table 1). In each ROI, R^2 values were calculated to estimate the goodness of fit.

Comparison between ViSTa phase and myelin water phase from hollow cylinder model

The phase evolution of ViSTa was compared to that of the simulated myelin water from the hollow cylinder model (13) by 1) comparing the phase evolutions in the ROIs and 2) generating a myelin water phase image from a DTI fiber orientation map using the hollow cylinder model. The parameters for the hollow cylinder model were drawn from the anisotropy model in Table 2 of Wharton and Bowtell, 2013, which is as follows: isotropic susceptibility (χ_I) = -100 ppb, anisotropic susceptibility (χ_A) = -100 ppb, chemical exchange = 20 ppb, myelin water proton density = 0.7, axonal/extracellular water proton density = 1, fiber volume fraction = 0.5 and g-ratio = 0.8 (13). The field strength of the simulation was 3T. The T_2^* of myelin water and axonal/extracellular water were assumed to be 10 ms and 50 ms, respectively. For the ROI comparison, the angles for the hollow cylinder model were set to 90° for the perpendicular fibers and 18° for the parallel fibers. In the simulation of GRE phase using the hollow cylinder model, the total water pool was divided into axonal, myelin and extracellular water pools, and the volume fraction was calculated from the fiber volume fraction and g-ratio. The resulting volumes were scaled according to the proton density of each pool. In the myelin water phase simulation, the signal was assumed to originate solely from myelin water. To generate a myelin water phase image from a DTI fiber orientation map, the orientations of the fibers relative to B_0 field were calculated from the primary eigenvector (V_1) of DTI. The hollow cylinder model was used to calculate the myelin water frequency shifts. Then, the myelin water and the ViSTa phase images were compared at a TE of 10.32 ms (4th echo), which is approximately the T_2^* of myelin water. For comparison, GRE phase images at TEs of 10.32 ms and 49.36 ms were included. Note that DTI data was only acquired during the upper slice session and the registration of a DTI image to the lower slice was not precise.

Results

Figures 1, 2 and 4 are the results from a representative subject whereas Figure 3 and Table 1 are the averaged results from all subjects.

The magnitude and phase images at the 1st (= 3 ms), 3rd (= 7.88 ms) and 5th (= 12.76 ms) echoes are summarized in Figure 1A–L for the lower slice and in Figure 2A–L for the upper slice. The magnitude decay and phase evolution for the perpendicular and parallel fiber ROIs are plotted in Figure 1N and O, and Figure 2N and O, respectively. The display ranges of the magnitude images and plots are adjusted to account for the large signal intensity differences between the GRE and ViSTa signals. The phase images and plots are in the same ranges (images: -0.75 to +0.75 rad; plots: -1 to +1.5 rad) to allow for a direct comparison. The phase evolutions were plotted for the echoes that had a high magnitude SNR (> 20) for reliability (Figures 1O and 2O).

The ViSTa magnitude signal decays more rapidly than the GRE magnitude signals (Figures 1N and 2N). This can be explained by the NNLS fitting results (Table 1), which demonstrate that short T_2^* components (< 25ms) are the dominant signal in ViSTa ($98.1 \pm 1.9\%$ in the parallel fiber ROI; $92.0 \pm 5.1\%$ in the perpendicular fiber ROI). In contrast, the GRE signal is primarily from long T_2^* components ($98.0 \pm 1.1\%$ in the parallel fiber ROI; $92.6 \pm 2.2\%$ in the perpendicular fiber ROI).

The phase evolutions are also significantly different between GRE and ViSTa. The ViSTa phase images (Figures 1L and 2L) show large positive contrast in certain areas (e.g. the splenium and optic radiation). In the same regions, however, the GRE phase images show close to zero or slightly negative contrast (Figures 1I and 2I). The phase evolution in the perpendicular fiber ROI clearly demonstrate the opposite phase evolution between the GRE and ViSTa signals (Fig. 1O); the ViSTa phase shows a large positive phase evolution, whereas the GRE phase shows a relatively smaller negative phase evolution. Compared to the perpendicular fiber ROI ($85^\circ \pm 2^\circ$), the parallel fiber ROI ($18^\circ \pm 2^\circ$ relative to B_0) yields reduced phase contrasts in both ViSTa and GRE (Fig. 2O). These results are consistent with recent studies of multi-compartment frequency shifts that revealed the opposite frequency shifts between myelin water phase and GRE phase (13,14).

When the ViSTa phase evolutions are compared with the simulated myelin water phase from the hollow cylinder model, both the parallel and perpendicular fiber ROIs match well (Figure 3). The perpendicular fiber ROI (red lines) shows a substantially large positive frequency shift compared to the parallel fiber ROI (pink lines) in both ViSTa (solid lines) and the simulated myelin water phase (dashed lines) from the hollow cylinder model. The GRE phase evolutions (solid green line for the parallel fiber ROI and solid blue line for the perpendicular fiber ROI) show small negative frequency shifts in both ROIs that are similar to those from the hollow cylinder model (dashed green and blue lines).

In Figure 4, the myelin water phase maps (Figure 4B and G) were generated from the hollow cylinder model using DTI fiber orientation. The simulated myelin water phase maps show large positive frequency shifts in the perpendicular fibers (red arrows), but the contrast is close to zero in the parallel fibers (blue arrows). These results are in accordance with the ViSTa phase images (Figure 4C and H). Overall, the simulated myelin water phase maps (Figure 4B and G) and the ViSTa phase images (Figure 4C and H) are highly similar. In contrast, the GRE phase images were substantially different from the simulated myelin water phase maps or the ViSTa phase images at the same echo time (10.32 ms; Figure 4D and I) and at a TE of 49.36 ms (Figure 4E and J). The phase at the frontal lobe of the lower slice was masked out in order to avoid erroneous phase from large susceptibility variations at the brain-air interface.

The similarity between the simulated myelin water phase and the ViSTa phase supports the origin of the ViSTa signal as myelin water.

Discussion

In this study, we demonstrated that the phase characteristics of the ViSTa signal closely match that of the simulated myelin water signal from the hollow cylinder model. This result, in addition to the T_2^* characteristics, supports the origin of the ViSTa signal as myelin water.

Recently, a few studies have suggested that water exchanges between the compartments (e.g. between axonal water and myelin water or between extracellular water and myelin water) on a timescale that can affect MR measurement (31–37). The estimated water

residence time in myelin varied from 43 ms to 2064 ms assuming a single residence time for all of the myelin water. The exchange time has been suggested to depend on the thickness of myelin sheath (33) and may be affected by other conditions, such as in vivo vs. ex vivo, temperature, fixation, species (e.g. human, mouse...), etc. If the exchange time of all of the myelin water molecules is in the order of few hundred milliseconds, it may be difficult to observe an unmixed myelin water pool in ViSTa. Hence, the fast exchange may be inconsistent with the T_2^* and phase characteristics of ViSTa. One potential explanation for both the ViSTa results and the rapid water exchange results may be a more realistic myelin model with a relatively rapid exchange in the outer or inner layers of myelin sheath, and with a slower exchange in the middle layers. In this model, water molecules in the middle layers may remain as an unmixed pool for a TR of 1 sec or longer, producing ViSTa signals. Further research is necessary to validate this model.

In this experiment, a quasi-linear magnetic field drift was observed (data not shown), introducing additional phase offsets in the unprocessed phase images. In the GRE phase images, the effects were removed by the RESHARP filter. In the ViSTa phase image, the two neighboring GRE background phases were averaged and then subtracted from the unwrapped ViSTa phase image to minimize the effects of the drift. Therefore, the drift was expected to have limited effects. This was particularly true for the ViSTa phase images where only early echoes were used.

In the phase processing, nonlocal background field inhomogeneity was removed by the RESHAPE filter, but the effects of the large scale structures (i.e. distribution of gray matter, cerebral spinal fluid and white matter) were still present in the phase data. As a consequence, ViSTa and GRE data contained phase offsets from both the microstructures and large-scale structures whereas the hollow cylinder model was based only on microstructures. However, it was suggested that the phase contributions of the microstructures are much larger than those of the large-scale structures (39). Hence it may be valid to make inferences based on the comparison between the hollow cylinder model simulation of myelin water phase and the ViSTa phase data in both the perpendicular and parallel fiber ROIs.

In this study, the simulation parameters for the hollow cylinder model were taken from Table 2 in Wharton and Bowtell (13) except for the field strength dependent parameters. Similar results can be obtained using the parameters found in Table 3 of the same reference.

Our results are also in agreement with Sati et al.'s observation (14) of a large positive frequency shift in myelin water for perpendicular fibers. For parallel fibers, their results (14) suggest a slightly negative frequency shift, whereas the ViSTa phase signal shows a slightly positive frequency shift. This discrepancy may have originated from imperfect fiber orientations for the parallel fiber ROI ($18^\circ \pm 2^\circ$) in our experiment and/or the exclusion of exchange contrast in their model. Both of these effects would induce positive frequency shifts in myelin water phase.

The optimum TE for the ViSTa phase is when it is the T_2^* of myelin water (38). This is different from the optimum TE for the ViSTa magnitude, which is the shortest TE possible

for an appropriate data acquisition bandwidth. One approach to optimize a ViSTa sequence for both the magnitude and phase is to acquire two or more echoes and combine them. The magnitude images can be combined by the sum-of-squares of each echo of the magnitude images. For the phase images, each echo phase image can be scaled by TE and combined by a sum or weighted sum to increase the SNR. The first echo phase may be used to compensate for the transmit B_1 phase offset at high field.

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Figure 1.

The magnitude (A–F) and phase (G–L) images of the lower slice in GRE and ViSta at the 1st (= 3.00 ms), 3rd (= 7.88 ms), and 5th (= 12.76 ms) echoes. Magnitude decay (N) and phase evolution (O) measured in the perpendicular fiber ROI (splenium; M). The fibers were approximately perpendicular ($85^\circ \pm 2^\circ$) to B_0 . The GRE and ViSta curves show the opposite phase evolutions suggesting that the primary sources of their signals are different.

Figure 2.

The magnitude (A–F) and phase (G–L) images of the upper slice from GRE and ViSTa at the 1st (= 3.00 ms), 3rd (= 7.88 ms) and 5th (= 12.76 ms) echoes. Magnitude decay (N) and phase evolution (O) measured in the parallel fiber ROI (corticospinal/corpus callosal tract; M). The fibers were approximately parallel ($18^\circ \pm 2^\circ$) to B_0 . The frequency shifts are smaller than those of the perpendicular fiber ROI in both ViSTa and GRE.

Figure 3.

Comparison between the measured phase evolutions in ROIs (solid lines; all subjects) and the hollow cylinder model simulated phase evolutions (dashed lines) for perpendicular and parallel fibers. The ViSTA phase evolutions match the myelin water phase evolutions simulated from the hollow cylinder model.

Figure 4.

Myelin water phase maps vs. ViSTa and GRE phase images. DTI fiber orientation maps (A, F). Myelin water phase maps generated from the hollow cylinder model (B, G). ViSTa phase images (C, H). GRE phase images at TE of 10 ms (D, I), and 49 ms (E, J). The red arrows indicate perpendicular fibers and the blue arrows indicate parallel fibers. The ViSTa phase images show a good match with the myelin water phase maps.

Table

NNLS fitting results in ROIs (mean $\pm$ standard deviation). The mean and the standard deviation were computed over all subjects.

	Perpendicular fiber ROI		Parallel fiber ROI	
	Short T_2^* ($T_2^* \leq 25$ ms)	Long T_2^* ($T_2^* > 25$ ms)	Short T_2^* ($T_2^* \leq 25$ ms)	Long T_2^* ($T_2^* > 25$ ms)
GRE	$7.2 \pm 1.7\%$	$92.8 \pm 1.7\%$	$5.5 \pm 1.0\%$	$94.5 \pm 1.0\%$
	$1 - R^2 = 1.1 \times 10^{-3}$		$1 - R^2 = 1.1 \times 10^{-3}$	
ViSTa	$92.0 \pm 2.6\%$	$8.1 \pm 2.6\%$	$96.6 \pm 2.4\%$	$3.4 \pm 2.4\%$
	$1 - R^2 = 3.4 \times 10^{-4}$		$1 - R^2 = 4.2 \times 10^{-5}$	