Published in final edited form as:

J Magn Reson. 2015 March ; 252: 20–28. doi:10.1016/j.jmr.2014.12.005.

Phase imaging in brain using SWIFT

Lauri Juhani Lehto^{a,b}, Michael Garwood^b, Olli Gröhn^a, and Curtis Andrew Corum^b

^aDepartment of Neurobiology, A. I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland ^bCenter for Magnetic Resonance Research, University of Minnesota, 2021 6th Street SE, Minneapolis, MN 55455, USA

Abstract

The majority of MRI phase imaging is based on gradient recalled echo (GRE) sequences. This work studies phase contrast behavior due to small off-resonance frequency offsets in brain using SWIFT, a FID-based sequence with nearly zero acquisition delay.

1D simulations and a phantom study were conducted to describe the behavior of phase accumulation in SWIFT. Imaging experiments of known brain phase contrast properties were conducted in a perfused rat brain comparing GRE and SWIFT. Additionally, a human brain sample was imaged.

It is demonstrated how SWIFT phase is orientation dependent and correlates well with GRE, linking SWIFT phase to similar off-resonance sources as GRE. The acquisition time is shown to be analogous to TE for phase accumulation time. Using experiments with and without a magnetization transfer preparation, the likely effect of myelin water pool contribution is seen as a phase increase for all acquisition times.

Due to the phase accumulation during acquisition, SWIFT phase contrast can be sensitized to small frequency differences between white and gray matter using low acquisition bandwidths.

Keywords

SWIFT; FID; phase; brain; orientation; magnetization transfer; white matter; gray matter

Introduction

Phase contrast, frequency and susceptibility mapping in brain has become increasingly utilized in recent years due to possibilities for excellent and unique contrast (1). These methods measure phase accumulation due to slight resonance frequency differences between brain structures using mainly gradient recalled echo (GRE) sequences. Interestingly, SWIFT (sweep imaging with Fourier transformation) (2), with acquisition delays in the microsecond range, has also been shown to display phase contrast due to off-resonance effects of nanoparticles (3) and calcifications in brain (4). However, the field perturbations created by

these nano- and micro-scale objects are considerably larger than the WM-GM frequency differences that are in the order of <10 Hz depending on the field strength (1, 5). In this manuscript, we investigate SWIFT phase contrast due to brain structures.

Phase contrast in GRE is based on off-resonance phase accumulation during TE so that phase in the final image is largely determined by timing of acquisition at the center of k-space. SWIFT on the other hand is an FID-based sequence with no echo formation and hence nearly zero TE. The excitation is followed by an acquisition delay that is dependent on hardware, e.g. T/R switching and RF coil ringdown. This delay is usually between 2-16 μ s, thus leading to essentially zero phase accumulation before acquisition begins. However, due to off-resonance evolution, phase will still accumulate during the acquisition time interval of the FID. Phase contrast in meniscus has also been reported with ultra-short echo time imaging (6) that also tries to minimize the acquisition delay using fast ramping of the readout gradient after excitation. The meniscus likely contains much higher off-resonance frequencies than the brain.

The properties and exact origins of MRI phase contrast in brain are still under investigation. The GM-WM phase difference has been attributed mainly to myelin (7-9). The contrast is known to be dependent on the orientation of the white matter fibers (10-13) with respect to B_0 possibly because of anisotropic susceptibility of myelin sheets (11, 14, 15) and microstructure (16). Also T_2^* (17-21) and hence GRE magnitude contrast has been shown to be orientation dependent. Recently, phase contrast has also been linked to more than one compartments, where one pool is linked to so-called myelin water trapped between myelin sheets and has a shorter T_2^* , and another water pool with longer T_2^* residing inside axons and outside of the whole myelinated fiber (15, 22). Also a three compartment model has been proposed (13), so that the water inside and outside the axon are treated separately. These pools have different frequencies that vary with orientation (13). Another contribution to frequency contrast has been found to be chemical exchange of water in contact with myelin bilayer (23-25).

The main contribution to phase contrast in brain is from long T_2^* components, although short T_2^* components also have an effect. The aim of this study is to characterize this contrast using SWIFT by investigating different aspects of the phase contrast and comparing it to GRE-based phase and frequency mapping. Most of the experiments used perfused rat brains, although *in vivo* imaging is demonstrated in rat. Additionally, a human brain sample was imaged at high resolution.

Methods

SWIFT phase behavior in Phantom and Simulation

To study the SWIFT phase behavior with different T_2^* s, 5 mm NMR tubes with 0.25 mM, 1.00 mM and 4.00 mM $MnCl_2$ solutions were imaged with SWIFT using a horizontal Agilent 9.4 T magnet (Agilent, CA, USA) equipped with an Agilent DirectDrive console and using a 20 mm quadrature volume coil providing a very homogeneous transmit field. The center frequency was shifted by 0, -30, -60, -90 and -120 Hz. The relaxation times were

measured to be 18.8 ms, 5.2 ms and 1.8 ms, respectively, at the center slice of the sample using multi GRE 3D (MGRE3D, TE = 0.8 / 1.8 / 2.8 / 3.8 / 4.8 / 5.8 / 6.8 / 7.8 ms). The phantom was imaged with different SWIFT bandwidths (sw), to achieve varying acquisition times, and with different FOVs to have different relative object sizes. SWIFT parameters were: sw/pixel = 325, 217, 162, 130, 114, 93 and 81 Hz/pixel, TR $\approx$ acquisition time, flip angle = 10°, 64k spokes and matrix size = 192³. The data was acquired using a gapped hyperbolic secant (HS) pulse (n = 2, R = 128) (2, 26) so that the first half of the TR alternates between RF pulsing and acquisition, and in the second half acquisition is continued without RF pulsing (27). A total of 128 points were collected, reducing to 96 points after correlating with the HS pulse, since the post-correlation FID effectively begins at the center of the RF pulse (2, 28). Data was acquired and reconstructed using CMRRpack v0.45a software (www.cmrr.umn.edu/swift/). True off-resonances and drift were approximated with linear interpolation between B₀ maps before and after SWIFT acquisitions. To reduce Gibbs ringing, all simulations (below) and data were multiplied with a cosine lobe filter going from 1 to 0 starting at 12.5% points before the edge of k-space.

Given that an object is globally off-resonance, the object's original k -space $s(\mathbf{k})$ is multiplied with a radial off-resonance term so that

$$s(\mathbf{k}) = |s(\mathbf{k})| \exp(-i2\pi\phi(\mathbf{k})) \exp(-i2\pi\Delta f t) \exp(-t/T_2^*), \quad [1]$$

Where f is the off-resonance and $t \in [0, T_{acq}]$. Solving time t from the known relations for $|\mathbf{k}|$ and readout bandwidth (sw), the amount of off-resonance can be written in pixels n_{shift} and T_2^* can be set in terms of the acquisition time T_{acq} :

$$\begin{aligned} s(\mathbf{k}) &= |s(\mathbf{k})| \exp(-i2\pi\phi(\mathbf{k})) \exp(-i2\pi|\mathbf{k}|\Delta f / \text{sw } 2N) \exp(-2|\mathbf{k}|T_{acq}T_2^*) \\ &= |s(\mathbf{k})| \exp(-i2\pi\phi(\mathbf{k})) \exp(-i2\pi|\mathbf{k}|n_{shift}) \exp(-2|\mathbf{k}|T_{acq}/T_2^*), \end{aligned} \quad [2]$$

Where N is the number of readout points and now $|\mathbf{k}| \in [0, 0.5]$

To verify Eq. [1] and [2], simulations of a cylindrical object with parameters equal to the phantom were made and compared to average phases of regions of interest (ROI) drawn in Matlab (Mathworks, MA, USA) using Aedes (aedes.uef.fi) at the center of the phantoms and simulated cylinders. Pixels close to the phantom edge were excluded to avoid partial voluming effects.

Additional simulations with varying magnitude ratios of GM and WM, and varying WM T_2^* were conducted in a 1D “WM stripe” (see Fig 1 (g)) to demonstrate phase behavior in a structure with a different geometry.

Orientation dependence

Rat brains were transcardially perfused and fixed with 4% PFA and washed in saline for 24 h before scanning as described earlier (4). *Ex vivo* animal procedures were approved by the Animal Ethics Committee of the Provincial Government of Southern Finland, and conducted in accordance with the guidelines of the European Community Council Directives 86/609/

EEC. The brains were scanned on a horizontal 9.4 T magnet using a linear single loop coil. The brains were put inside the coil in a 20 mm NMR tube immersed in perfluoroether (Galden, Solvay, TX, USA). To study the orientation dependence of SWIFT phase contrast, the brains were scanned in different orientations so that the rostro-caudal axis of the brain was at angles 0°, 18°, 36°, 54°, 72° and 90° to B₀. The angle was checked based on pilot images. SWIFT parameters were: sw/pixel = 81 Hz/pixel, TR = 8.6 ms, flip angle = 7°, 500k spokes, six averages, resolution = 78³ μm³ and scan time = 8 h. The data were acquired using a gapped HS pulse (n = 2, R = 256) (2, 26) similarly as above but with 192 post-correlation acquisition points.

For comparison, the brains were scanned in the same orientations using a MGRE3D sequence. The MGRE3D parameters were: TE = 3.4 / 9.5 / 15.6 / 21.7 / 27.8 ms, sw = 62.5 kHz, TR = 34.5 ms, flip angle = 14°, resolution = 78³ μm³ and scan time = 8 h. Flip angle and TR were set according to the Ernst equation so that the contrast was approximately the same as with SWIFT. For frequency and phase map calculation, the data were high-pass filtered using complex division (Gaussian kernel, FWHM = 10 pixels) (29). The frequency maps were calculated using a simple linear fit. Different ROIs of the brain were analyzed using Aedes.

Length of acquisition

To change the amount of accumulated phase in SWIFT, the acquisition time needs to be changed. Hence, rat brains were scanned in a horizontal 9.4 T magnet using a 20 mm quadrature volume coil. Different spectral widths were used so that sw/pixel = 41, 54 and 81 Hz/pixel leading to effective acquisition times of 12.3 / 9.2 / 6.1 ms. TR was set to equal 34.5 ms by adding the corresponding delay after the acquisition. Other parameters were: flip angle = 14°, 500k spokes, resolution 96³ μm³ and scan time = 5 h 50 min for each sw/pixel.

To compare the phase accumulation mechanisms the brains were also scanned with MGRE3D so that TE = 2.7 / 7.6 / 12.5 / 17.3 / 22.2 ms, sw = 62.5 kHz, TR = 34.5 ms, flip angle = 14°, resolution 96³ μm³ and scan time 8 h 5 min.

MT preparation

To study if short T_2 species seen by SWIFT affect the phase contrast, scans with the parameters stated above were conducted with and without a magnetization preparation with the purpose of suppressing short T_2 components assuming that they also have a long T_1 . A Gaussian pulse of 24.4 ms at -1.4 kHz off-resonance with amplitude of 0.6 kHz was applied every 4th TR in both SWIFT and MGRE3D. As a reference, the scans were repeated with a 24.4 ms delay every 4th TR. To avoid amplitude ghosting, MGRE3D was acquired with a centric acquisition order. Different regions of the brain were analyzed using Aedes.

Additionally, to interpret the phase with and without an MT preparation, two WM compartments were modeled according to Eq. [1] so that $f_1 = -5$ Hz, $f_2 = 30$ Hz and $T_{2,1}^* = 20$ ms, $T_{2,2}^* = 5$ ms based on Wharton et al (15), Sati et al. (13) and our own T_2^* measurements of fixed rat brains (data not shown). Based on the acquired rat brain data, the

simulated ratio of the magnitudes for GM and WM were set to GM:WM 1.15:1 without the MT preparation and 1.45:1 with it.

Human brain sample

To demonstrate SWIFT phase contrast in human brain at high resolution and in high magnetic field, an approximately 1 cm thick formalin fixed human temporal lobe sample was imaged on the horizontal Agilent 16.4 T using a TEM coil. SWIFT parameters were $sw/pixel = 81$ Hz/pixel, $TR = 8.6$ ms, flip angle = 7° , 1049k spokes, resolution = $130^3 \mu m^3$ and scan time 2 h 30 min. MGRE3D parameters were: $TE = 2.0 / 5.4 / 8.8 / 12.1$ ms, $sw = 62.5$ kHz, $TR = 20.0$ ms, flip angle = 11° and scan time 2 h 3 min.

In vivo imaging

To demonstrate the feasibility of in vivo imaging, a rat was imaged in a horizontal 16.4 T magnet equipped with an Agilent DirectDrive console using a quadrature surface coil. The SWIFT parameters were $sw/pixel = 122$ Hz/pixel, $TR = 8.6$ ms, flip angle = 5° , 393k spokes, resolution of $156^3 \mu m^3$ and scan time = 1 h 7 min. Fat suppression (Gaussian, 120° , 1 ms) was applied every 16 acquisitions. All *in vivo* imaging was conducted with the approval of the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota.

Results

SWIFT phase behavior in Phantom and Simulation

Simulations and the phantom study match well as shown in Figure 1 (a-f). In this scenario shorter T_2^* leads to slightly higher phase accumulation both with varying accumulation time and relative object size. The biggest discrepancy is seen in (d) with a FOV of 18 cm. This may be related to partial voluming that is difficult to avoid using large FOVs, but needed here to show the effect. Additionally, it is nearly impossible to shim the phantom to have perfectly homogenous B_0 , thus leading to a further difference between the phantom and simulation.

Fig 1. (g-i) further demonstrates the phase behavior in a simulation mimicking a narrow WM structure. Interestingly, as shown in Fig 1. (g,h), the ratio of the image intensities and T_2^*/T_{acq} both influence the phase sensitivity of SWIFT.

Orientation dependence

Comparisons of the phase maps of SWIFT and frequency maps of MGRE3D while rotating the brain in B_0 are presented in Fig 2. On qualitative inspection, the contrast changes are highly similar (a-l), which is further confirmed by the results of the ROI analysis in Fig. 3 (a-c). There is a strong linear correlation between SWIFT phase and MGRE3D frequency pooled from different ROI's (Fig. 3 c, $R^2 = 0.95$, $P < 0.001$). There was also a linear correlation between SWIFT and separate echoes of MGRE3D (from TE1 to TE5: $R^2 = 0.95$, 0.93, 0.92, 0.91 and 0.90, $P < 0.001$). Also, individual ROI's had linear correlation, although with different slopes (data not shown). Both sequences have reasonable standard deviation (SD) of phase or frequency in all the ROI's in all of the orientations (Fig 3). The largest SD

is seen in the lateral ventricle likely due to partial voluming. All the analyzed structures respond to the change in orientation, although the strongest response is seen in the lateral ventricle. The effect of the rotation is also seen in other regions not analyzed (Fig 2). It should also be noted how SWIFT differs in response to larger scale field variations, as can be seen, for example, close to the dorsal third ventricle and close to the rostral brain (Fig 2, areas designated with asterisks in a). MGRE3D displays effects of wrapping after high-pass filtering, even without post-processing, whereas SWIFT does not.

Length of acquisition

In SWIFT, since the acquisition delay is essentially zero, the time of phase accumulation is defined by the acquisition time. Hence, decreasing sw/pixel increases the amount of phase as shown by the ROI (Fig 4. d) analysis results in Fig 5a, b. For MGRE3D, the same effect is gained with increasing TE (Fig 5d, e). SWIFT phase approximately doubles with double acquisition time.

The noise standard deviation of the ROIs is not displayed since it would increase with more phase accumulation time not only due to noise, but also due to intra-ROI frequency variability. Phase noise is known to be inversely proportional to the magnitude SNR values (30), which are displayed for the ROIs in Table 1. The SNR was calculated as the mean signal/background SD. Increased magnitude SNR with a longer acquisition time is expected for SWIFT, and decreased magnitude SNR with a longer TE is expected for MGRE3D due to T_2^* decay. The lower SNR without an MT preparation with SWIFT sw/pixel = 41 Hz/pixel may be due to folding signal from chemical shift blurred coil structures visible to SWIFT, limiting the lowest usable sw/pixel and FOV. With an MT preparation, the coil element signal is spoiled. MGRE3D SNR values are clearly lower overall due to the shorter acquisition times per echo.

MT preparation

The effect of applying an MT magnetization preparation for the phase images can be seen in Fig 4 and 5. With the exception of the mammillothalamic tract (mt), there is a decrease in SWIFT phase due to the MT preparation in every analyzed region with all the three acquisition times (Fig 4a-c, Fig 5a-c). There is also an apparent increase in non-linearity (Fig 5a, b) in all ROIs so that there is less relative phase accumulation with increasing acquisition time when the MT preparation is used. The optic tract (opt) has the greatest decrease in phase due to the preparation.

MGRE3D also shows a response to the MT preparation, although less clearly (Fig 4d-h, Fig 5e-g). There is no similar plateau for phase accumulation as for SWIFT due to the MT preparation. There seems to be a decrease in the phase accumulation of mt and fim, no change in opt, and an increase in sg and dhc. The frequencies calculated from MGRE3D data are presented in Table 2. Fim and mt have an apparent decrease in frequencies.

Results of a 1D SWIFT simulation based on Eq. [1] with two WM compartments and corresponding plots for GRE with and without the shorter T_2^* pool are shown in the Supplementary material. The absence of the shorter T_2^* pool leads to a seemingly global

decrease in SWIFT phase and a slight decline in the speed of phase accumulation with higher acquisition times. A similar but relatively smaller effect is seen for GRE phase.

Magnitude images and MTR maps are shown in Fig 6. MTR values are listed in Table 3. MTR is smaller in all MGRE3D ROIs in comparison to SWIFT. There is also a clear MTR difference with 54 Hz/pixel SWIFT bandwidth in comparison to 81 Hz/pixel and 41 Hz/pixel. The difference between SWIFT and MGRE3D MTR is not a just baseline difference; largest MTR difference is seen in fim and opt.

Human brain sample

A comparison of SWIFT phase and MGRE3D phase map is shown in Fig 7. Again, similar features can be seen in both images. SWIFT phase seems to be more blurred, whereas the MGRE3D frequency map appears sharp. There is an orientation-dependent phase at the WM/GM interfaces from the U-fibers. Also the line of Gennari can be seen inside the gray matter with both sequences.

In vivo imaging

SWIFT phase imaging *in vivo* in rat is demonstrated in Fig 8 imaged at 16.4 T. Most of the main WM structures are delineated, along with the separation of singulum, corpus callosum and dhc.

Discussion

The goal of this work was to study how SWIFT phase contrast behaves with small off-resonance frequencies seen in brain. Unlike GRE, SWIFT has no time (TE) for phase accumulation at the center of k-space. A key element of phase images is the structure orientation dependence which SWIFT phase exhibited with a good correlation with GRE measured frequencies. The time for SWIFT phase accumulation was clearly shown to be the acquisition time in contrast to TE in GRE. Additionally, a possible phase contribution from a short T_2^* compartment was demonstrated by using an MT preparation. We have demonstrated that SWIFT is sensitive to small off-resonances in brain mainly in a perfused rat brain but also in a human brain sample.

Phase evolution of SWIFT and GRE

SWIFT is effectively a radial FID-based pulse sequence meaning that the acquisition starts at the center of k-space. This also implies that the captured phase evolution starts from zero at the center and increases towards the edges of k-space. This is different from GRE where phase evolution starts before the acquisition window, depending on the TE and spectral width.

In GRE, phase increases while traversing through k-space. The effect of the phase accumulation can be divided into two parts: a linear shift in the read-out direction due to the linear phase evolution in k-space and a constant phase defined at time TE at the center of k-space leading to the phase contrast. In SWIFT, the phase at the center of k-space is zero, meaning that the phase contrast is not defined at the center of k-space. This is similar to a

single spin-echo acquisition where the phase due to static field deviations is nulled at the center of k-space. This implies only a shift in the read-out direction. However, the difference to a full spin-echo acquisition in SWIFT is that the phase evolves in the same direction – positive or negative, depending on the sign of the off-resonance – in opposite k-space lines. This leads the image spaces of the opposite spokes to shift into opposite directions causing imaginary components and thus phase in image space.

The center-out phase evolution means that the higher the spatial frequency, the more there is the potential for phase evolution. Hence, structures that are, for example, narrow, point-like, or close to a sharp edge will have stronger phase than large, flat objects. This means that SWIFT phase is intrinsically high-pass filtered so that phase wrapping due to large scale field variations is automatically removed, but it also means that the amount of phase not only depends on the field but also on the structure geometry.

In comparison to other similar sequences as SWIFT, i.e. UTE (6) and ZTE (31, 32), the phase behavior is likely very similar. UTE may still suffer from some wrapping, since there is a finite time between raising the readout gradient and excitation. Currently, unlike with SWIFT, it is possible to collect multiple echoes with UTE. As for ZTE, which is based on a pure FID during the readout gradient, the phase contrast is assumed to be equal, given that the same imaging parameters can be used and there are no additional error sources.

It should also be noted that the type of phase behavior described here is not completely unique to SWIFT, UTE or ZTE; it is also possible to achieve similar contrast with SE by using radial acquisition and only the first or the second half of the echo. Naturally, short T_2 components would be filtered out depending on the TE. Radial GRE could also be used in the same manner, but the phase at the center of k-space is never nulled.

SWIFT phase behavior in Phantom and Simulation

The simulations show that for a given off-resonance frequency of a homogeneous structure, SWIFT phase decreases as the structure size increases since the structure is defined by lower spatial frequencies as the structure widens. Brain structures will never be completely homogenous in magnitude or frequency, and hence will diverge from this result. A linear increase in WM off-resonance frequency was also shown to give an approximately linear increase in SWIFT phase in a structure with constant dimensions, which is reasonable, since each spatial frequency has the same relative increase in phase.

The effect of T_2^* decay on the phase of a structure was also demonstrated to happen into two directions with the same sign of the frequency shift: increase in the cylindrical phantoms, increase and decrease in the “WM stripe”. Since T_2^* decay decreases the weight of the high spatial frequencies, it will also decrease their phase contribution. However, blur due to short T_2^* shifts higher phase at the cylinder and “WM stripe” edges towards the center. This leads to higher average phase inside the cylinder ROI and initially at the center of the “WM stripe”. Hence, the effect of T_2^* on SWIFT phase is also dependent on the structure geometry.

Large scale field variations can add to the frequency of the WM structure, but they will also add to the frequency of the surrounding tissue through an imaginary tail, with an opposite sign, outside the structure. The structure surrounding can then in reverse affect the phase of the structure. Hence, the overall phase contrast behavior depends on the magnitude contrast, since this defines the amplitudes of the imaginary tails.

Orientation dependence

SWIFT phase and GRE phase or frequency show a strong linear correlation. This shows how SWIFT is sensitive to small off-resonance frequencies and also to equally small frequency changes in those same structures. It also ties SWIFT phase mainly to the same off-resonance sources as GRE.

There was also a good linear correlation between SWIFT phase and the phases of different MGRE3D echoes, but with a decreasing correlation coefficient towards longer echo times possibly due to the decreasing SNR of MGRE3D for later echoes or already decayed T_2^* components (15, 22)

The linear correlation between GRE phase and SWIFT phase was not obvious. As shown in the results, the amount of phase in SWIFT depends on the acquisition time. Hence, with a different acquisition time the slope of the linear fit would change, but it would still be linear, since the change of the acquisition time just acts as a scaling factor for the amount of phase.

Length of acquisition

The results demonstrate how the amount of accumulated phase in SWIFT phase images depends on the acquisition time.

A longer acquisition time equates with using a smaller sw/pixel. This provides an SNR benefit for SWIFT in the magnitude image, since the more phase contrast is needed, the higher is the SNR. On the other hand, in GRE, more phase accumulation necessitates using a longer TE, leading to less signal. However, it should be noted that the optimal phase contrast-to-noise ratio for GRE is achieved at $TE \approx T_2^*$ (1). When lower sw/pixel is needed for SWIFT to improve phase contrast, SWIFT will still be able to detect short T_2^* signal, whereas lowering sw/pixel of GRE will increase the minimum TE. There are limits to lowering SWIFT sw/pixel, namely blur due to stronger off-resonances and short T_2^* components, blur due to T_2^* When $T_{acq} \geq T_2^*$ (33), and finally scan time.

SWIFT phase contrast of WM structures were first seen with an effective acquisition time of 3 ms giving a relatively weak WM-GM contrast (4). In this work, we used effective acquisition times up to 12.3 ms at sw/pixel of 41 Hz/pixel giving much better phase contrast. This is likely close to the practical lower limit taking into consideration shimming and water linewidth.

Looking at single WM areas, opt, fim and dhc had the strongest phase in SWIFT whereas MGRE3D showed highest frequency shifts in opt, fim and sg. Why sg does not exhibit

strong phase in SWIFT may be related to its' relatively large width so that it possesses less signal at higher spatial frequencies.

MT preparation

There is evidence of a shorter T_2^* compartment with a relatively high, opposite sign frequency in WM (e.g. Sati et al. (13)). This compartment has been related to the so-called myelin water (13, 15, 19, 20). The results of our brain rotation experiment support a short T_2^* contribution to SWIFT phase in the sense of decreasing linear correlation between SWIFT phase and MGRE3D phase at increasing TE.

MT preparation will saturate part of the signal of water in close relation to the macromolecules in WM. Myelin water is known to be affected more strongly (13, 34, 35), and hence, with short repetition interval of the MT preparation, myelin water pool is largely saturated. By removing this component with large opposite signed frequency shift in comparison to the free water pool, there is effectively an increased amount of phase accumulation in WM and more so with lower acquisition times where fast decay of the signal has smaller relative effect. This would imply a smaller phase difference between signal without and with MT preparation using higher acquisition times as shown by our data and simulation. Part of the phase increase due to the MT preparation may be explained by a spatially large scale B_0 variation and magnitude contrast increase as shown by the simulations.

Human brain sample

The human brain sample was studied to demonstrate how SWIFT phase behaves when the overall width of structures is clearly several pixels. However, at high resolution, small details of the WM structures become visible so that SWIFT phase is included also in higher spatial frequencies giving clear contrast. This implies an intermediate resolution range where a structure does not give phase contrast since it is mainly composed of low spatial frequencies. When resolution is increased and fine structure is revealed, also phase contrast is gained.

In vivo imaging

Our *in vivo* data acts as a proof of principle for *in vivo* SWIFT phase imaging. The current *in vivo* images were of lesser quality in comparison to *ex vivo*. Since SWIFT phase contrast is mostly defined at higher spatial frequencies of k-space, the contrast is inherently weaker than in GRE and needs a relatively high SNR to become visible. The *in vivo* data was also acquired with lower resolution, meaning that the acquisition time is relatively short (4.1 ms) for phase evolution and that there is less high spatial frequencies to provide phase contrast. The *in vivo* image also showed large signal voids close to the air cavities of the skull. These are due to bulk susceptibility difference induced frequency shifts, where the majority of the signal is retained but “piled up” into a bright rim as demonstrated before in phantoms (3). These signal voids may become too large when a stronger phase contrast sought by increasing the acquisition time through decreased sw/pixel. An additional factor may be flow induced phase: since SWIFT is a 3D radial sequence, all flow directions will contribute to the phase of the final image.

Conclusion

We have shown the feasibility of near zero acquisition delay phase imaging in *ex vivo* and *in vivo* rat brains, and in a human brain sample. By using an MT magnetization preparation, a decrease in phase accumulation was seen which implies suppression of short T_2^* myelin water previously also detected by GRE. SWIFT may prove to be useful in revealing new information about the short T_2^* component phase contribution in brain and in other applications.

Even though SWIFT phase does not have a linear relationship to the field inhomogeneities, it had a good linear correlation to frequency maps measured with GRE in different WM regions in different orientations to B_0 . SWIFT also has a self-high-pass filtering property, which reduces the amount of required post-processing and may give a chance for phase images of small off-resonances in the presence of strong susceptibility fields. This work further describes the phase behavior of SWIFT and is likely applicable to other radial FID-based sequences such as UTE and ZTE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank our funders ASLA-Fulbright, North Savo Regional Fund, Finnish Foundation for Technology Promotion, Emil Aaltonen Foundation, Academy of Finland, UEF-Brain, NIH KL2TR000113, R21CA139688 and P41EB015894. The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°602102 (EPITARGET).

References

1. Duyn JH, Van Gelderen P, Li TQ, De Zwart JA, Koretsky AP, Fukunaga M. High-field MRI of brain cortical substructure based on signal phase. *P Natl Acad Sci.* 2007; 104:11796–11801.
2. Idiyatullin D, Corum C, Park JY, Garwood M. Fast and quiet MRI using a swept radiofrequency. *J Magn Reson.* 2006; 181:342–349. [PubMed: 16782371]
3. Zhou R, Idiyatullin D, Moeller S, Corum C, Zhang H, Qiao H, Zhong J, Garwood M. SWIFT detection of SPIO-labeled stem cells grafted in the myocardium. *Magn Reson Med.* 2010; 63:1154–1161. [PubMed: 20432286]
4. Lehto LJ, Sierra A, Corum CA, Zhang J, Idiyatullin D, Pitkänen A, Garwood M, Gröhn O. Detection of calcifications *In vivo* and *Ex vivo* After brain injury in rat using SWIFT. *NeuroImage.* 2012; 61:761–772. [PubMed: 22425671]
5. Yao B, Li T, Gelderen Pv, Shmueli K, de Zwart JA, Duyn JH. Susceptibility contrast in high field MRI of human brain as a function of tissue iron content. *Neuroimage.* 2009; 44:1259–1266. [PubMed: 19027861]
6. Carl M, Chiang JA. Investigations of the origin of phase differences seen with ultrashort TE imaging of short T2 meniscal tissue. *Magn Reson Med.* 2012; 67:991–1003. [PubMed: 21898582]
7. Liu C, Li W, Johnson GA, Wu B. High-field (9.4 T) MRI of brain dysmyelination by quantitative mapping of magnetic susceptibility. *Neuroimage.* 2011; 56:930–938. [PubMed: 21320606]
8. Lee J, Shmueli K, Kang B, Yao B, Fukunaga M, van Gelderen P, Palumbo S, Bosetti F, Silva AC, Duyn JH. The contribution of myelin to magnetic susceptibility-weighted contrasts in high-field MRI of the brain. *Neuroimage.* 2012; 59:3967–3975. [PubMed: 22056461]

9. Lodygensky GA, Marques JP, Maddage R, Perroud E, Sizonenko SV, Hüppi PS, Gruetter R. In vivo assessment of myelination by phase imaging at high magnetic field. *Neuroimage*. 2012; 59:1979–1987. [PubMed: 21985911]
10. Denk C, Torres EH, MacKay A, Rauscher A. The influence of white matter fibre orientation on MR signal phase and decay. *NMR Biomed*. 2011; 24:246–252. [PubMed: 21404336]
11. Lee J, Shmueli K, Fukunaga M, van Gelderen P, Merkle H, Silva AC, Duyn JH. Sensitivity of MRI resonance frequency to the orientation of brain tissue microstructure. *P Natl Acad Sci*. 2010; 107:5130–5135.
12. Bender B, Klose U. The in vivo influence of white matter fiber orientation towards B0 on T2* in the human brain. *NMR Biomed*. 2010; 23:1071–1076. [PubMed: 20665897]
13. Sati P, Gelderen Pv, Silva AC, Reich DS, Merkle H, de Zwart JA, Duyn JH. Micro-compartment specific T2* relaxation in the brain. *Neuroimage*. 2013; 15:268–278. [PubMed: 23528924]
14. Liu C. Susceptibility tensor imaging. *Magn Reson Med*. 2010; 63:1471–1477. [PubMed: 20512849]
15. Wharton S, Bowtell R. Fiber orientation-dependent white matter contrast in gradient echo MRI. *P Natl Acad Sci*. 2012; 109:18559–18564.
16. He X, Yablonskiy DA. Biophysical mechanisms of phase contrast in gradient echo MRI. *Proceedings of the National Academy of Sciences*. 2009; 106:13558–13563.
17. Lee J, van Gelderen P, Kuo L, Merkle H, Silva AC, Duyn JH. T2*-based fiber orientation mapping. *Neuroimage*. 2011; 57:225–234. [PubMed: 21549203]
18. de Pasquale F, Cherubini A, Péran P, Caltagirone C, Sabatini U. Influence of white matter fiber orientation on R2* revealed by MRI segmentation. *J Magn Reson Imaging*. 2013; 37:85–91. [PubMed: 22987315]
19. Sati P, Silva AC, van Gelderen P, Gaitan MI, Wohler JE, Jacobson S, Duyn JH, Reich DS. In vivo quantification of T2* anisotropy in white matter fibers in marmoset monkeys. *Neuroimage*. 2012; 59:979–985. [PubMed: 21906687]
20. van Gelderen P, de Zwart JA, Lee J, Sati P, Reich DS, Duyn JH. Nonexponential T2* decay in white matter. *Magn Reson Med*. 2012; 67:110–117. [PubMed: 21630352]
21. Rudko DA, Klassen LM, de Chickera SN, Gati JS, Dekaban GA, Menon RS. Origins of orientation dependence in gray and white matter. *Proc Natl Acad Sci*. 2014; 111:159–167.
22. Wharton S, Bowtell R. Gradient echo based fiber orientation mapping using R2* and frequency difference measurements. *Neuroimage*. 2013; 83:1011–1023. [PubMed: 23906549]
23. Zhong K, Leupold J, von Elverfeldt D, Speck O. The molecular basis for gray and white matter contrast in phase imaging. *Neuroimage*. 2008; 40:1561–1566. [PubMed: 18353683]
24. Luo J, He X, d'Avignon DA, Ackerman JJH, Yablonskiy DA. Protein-induced water 1H MR frequency shifts: Contributions from magnetic susceptibility and exchange effects. *J Magn Reson*. 2010; 202:102–108. [PubMed: 19879785]
25. Shmueli K, Dodd SJ, Li TQ, Duyn JH. The contribution of chemical exchange to MRI frequency shifts in brain tissue. *Magn Reson Med*. 2011; 65:35–43. [PubMed: 20928888]
26. Garwood M, Delabarre L. The return of the frequency sweep: Designing adiabatic pulses for contemporary NMR. *J Magn Reson*. 2001; 153:155–177. [PubMed: 11740891]
27. Weiger M, Hennel F, Pruessmann KP. Sweep MRI with algebraic reconstruction. *Magnetic Resonance in Medicine*. 2010; 64:1685–1696. [PubMed: 20949600]
28. Idiyatullin D, Corum C, Moeller S, Garwood M. Gapped pulses for frequency-swept MRI. *J Magn Reson*. 2008; 193:267–273. [PubMed: 18554969]
29. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YCN. Susceptibility-weighted imaging: Technical aspects and clinical applications, part 1. *Am J Neuroradiol*. 2009; 30:19–30. [PubMed: 19039041]
30. Conturo TE, Smith GD. Signal-to-noise in phase angle reconstruction: Dynamic range extension using phase reference offsets. *Magn Reson Med*. 1990; 15:420–437. [PubMed: 2233221]
31. Hafner S. Fast imaging in liquids and solids with the back-projection low angle shot (BLAST) technique. *Magn Reson Imaging*. 1994; 12:1047–1051. [PubMed: 7997092]

32. Weiger M, Pruessmann KP, Bracher A, Köhler S, Lehmann V, Wolfram U, Hennel F, Rasche V. High-resolution ZTE imaging of human teeth. *NMR Biomed.* 2012; 25:1144–1151. [PubMed: 22290744]
33. Kuethe DO, Adolphi NL, Fukushima E. Short data-acquisition times improve projection images of lung tissue. *Magn Reson Med.* 2007; 57:1058–1064. [PubMed: 17534926]
34. Stanisz G, Kecojevic A, Bronskill M, Henkelman R. Characterizing white matter with magnetization transfer and T2. *Magn Reson Med.* 1999; 42:1128–1136. [PubMed: 10571935]
35. Vavasour IM, Whittall KP, Li DK, MacKay AL. Different magnetization transfer effects exhibited by the short and long T2 components in human brain. *Magn Reson Med.* 2000; 44:860–866. [PubMed: 11108622]

Figure 1.

SWIFT simulation and phantom phase in off-resonance objects. Simulation (solid line) and phantom (circles) data from off-resonant cylindrical objects with (a-c) different acquisition times and (d-f) different relative object sizes by changing the FOV. Simulation results of a “WM stripe” sketched in (g) demonstrating the effect of (h) varying magnitude contrast (GM $T_2^*/T_{acq}=4$, offset = 0 pix, WM $T_2^*/T_{acq}=3$, offset = 0.125 pix, WM width 3 pix) and (i) T_2^* (GM $T_2^*/T_{acq}=4$ and offset = 0 pix, WM width 3 pix, GM-WM magnitude ratio $\text{Mag}_{\text{GM}}/\text{Mag}_{\text{WM}} = 1.15$) in a different type of geometry. The red dot in (g) is the measurement point for the phase (blue line) in the simulation. The scanner frequency drift and shimming has been taken into account based on B0 maps before and after SWIFT imaging in (a-f). This leads to varying off-resonance frequencies for the phantom data points.

Figure 2.

Effect of WM fiber orientation to B_0 on phase. A healthy, perfused rat brain imaged in six different orientations: (a-f) SWIFT phase maps ($T_{acq} = 12$ ms) and (g-l) MGRE3D frequency maps in matching orientations. The long axis of the brain is orientated between (a, f) parallel and (e, l) perpendicular to B_0 . ROIs for Fig 2 in (g): ec = external capsule, ec2 = a second ec ROI, vent = ventricle and gcc = genu of corpus callosum. Asterisks in (a) indicate difference in response of SWIFT and MGRE3D to a large scale B_0 variation.

Figure 3.

Results of the ROI analysis of the effect of WM fiber orientation. (a) SWIFT phase, (b) GRE frequency and (c) their correlation. SWIFT phase and GRE frequency correlate with different orientations ($R^2 = 0.95$). The error bars represent standard deviation inside the ROIs. ec = external capsule, ec2 = a second ec ROI, vent = ventricle and gcc = genu of corpus callosum.

Figure 4.

Effect of an MT preparation on phase images. SWIFT and GRE, respectively, (a, d) phase with MT preparation replaced with a delay, (b, e) phase with MT preparation, (c, f) difference of (a, d) and (b, e). SWIFT $T_{acq} = 12.3$ ms and GRE TE = 12.5 ms. There is a clear increase in phase of WM structures due to the preparation except in mt. ROIs for Fig. 5 in (d): sg = singulum, dhc = dorsal hippocampal commissure, fim = fimbria, mt = mammillothalamic tract and opt = optic tract.

Figure 5.

Results of the ROI analysis of the effect of an MT preparation. (a-c) SWIFT phase with MT preparation replaced by a delay, phase with MT preparation and the difference between without and with MT preparation with three different acquisition times, respectively. (d-f) Matching GRE phase results with five different TEs. sg = singulum, dhc = dorsal hippocampal commissure, fim = fimbria, mt = mammillothalamic tract and opt = optic tract.

Figure 6.

Magnitude images and MTR. SWIFT and GRE magnitude (a, d) without and (b, e) with MT preparation, and (c, f) MTR map, respectively. SWIFT $T_{acq} = 12.3$ ms and GRE TE = 2.8 ms. There is a level difference in the MTR maps, but it is not just a baseline difference.

Figure 7.

Human brain sample imaged at 16.4 T. (a) SWIFT phase with $T_{acq} = 6.14 \text{ ms}$ and (b) GRE phase with $TE = 5.4 \text{ ms}$. Similar features are shown by SWIFT and GRE phase, although SWIFT has a grainier look in the WM. (a) Phase contrast of the U-fibers at the WM-GM interface (arrows) and the line of Gennari (arrow heads) can be seen with both sequences.

Figure 8.
In vivo healthy rat SWIFT images at 16.4 T. (a) Magnitude and (b) phase.

Table 1

The off-resonance frequency of the different ROIs based on the MGRE3D data without and with an MT preparation.

ROI	f_{del} (Hz)	f_{MT} (Hz)
fim	-3.5 ± 1.2	-2.9 ± 1.4
opt	-4.1 ± 1.6	-4.0 ± 2.3
dhc	-3.1 ± 0.7	-3.3 ± 0.8
sg	-3.5 ± 0.6	-3.6 ± 0.8
mt	-2.2 ± 1.1	-1.7 ± 1.1

Table 2
SNR of SWIFT and MGRE3D magnitude images in cortex without and with an MT preparation.

SWIFT sw	15.6 kHz	20.8 kHz	31.3 kHz
Delay	192.9	202.7	177.8
MT	132.4	127.2	119.9
MGRE3D TE	2.7 ms	7.6 ms	12.5 ms
		17.3 ms	22.2 ms
Delay	116.2	101.6	93.4
MT	73.9	66.8	56.2
		52.6	46.1

Table 3

The MTR values of the different ROIs using MGRE3D and SWIFT. Overall, SWIFT MTR values are higher than with MGRE3D.

ROI	MGRE3D	SWIFT 15.6 kHz	SWIFT 20.8 kHz	SWIFT 31.3 kHz
fim	0.49 ± 0.03	0.56 ± 0.04	0.60 ± 0.04	0.56 ± 0.03
opt	0.56 ± 0.04	0.64 ± 0.04	0.67 ± 0.03	0.63 ± 0.03
dhc	0.53 ± 0.02	0.58 ± 0.02	0.62 ± 0.02	0.58 ± 0.02
sg	0.52 ± 0.02	0.56 ± 0.01	0.59 ± 0.01	0.55 ± 0.01
mt	0.53 ± 0.03	0.59 ± 0.04	0.62 ± 0.04	0.58 ± 0.03
cx	0.38 ± 0.01	0.42 ± 0.01	0.44 ± 0.01	0.41 ± 0.01
vent	0.04 ± 0.03	0.02 ± 0.02	0.06 ± 0.04	0.05 ± 0.04