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Magnetic susceptibility induced echo time shifts: Is there a bias in age-related fMRI studies?

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Abstract

Purpose—To evaluate the potential for bias in functional MRI (fMRI) aging studies resulting from age-related differences in magnetic field distributions which can impact echo time and functional contrast.

Materials and Methods—Magnetic field maps were taken on 31 younger adults (age: 22 ± 2.9 years) and 46 older adults (age: 66 ± 4.5 years) on a 3 T scanner. Using the spatial gradients of the magnetic field map for each participant, an echo planar imaging (EPI) trajectory was simulated. The effective echo time, time at which the k-space trajectory is the closest to the center of k-space, was calculated. This was used to examine both within-subject and across-age-group differences in the effective echo time maps. The Blood Oxygenation Level Dependent (BOLD) percent signal change resulting from those echo time shifts was also calculated to determine their impact on fMRI aging studies.

Result—For a single subject, the effective echo time varied as much as ± 5 ms across the brain. An unpaired t-test between the effective echo time across age group resulted in significant differences in several regions of the brain ($p < 0.01$). The difference in echo time was only approximately 1 ms, however which is not expected to have an important impact on BOLD fMRI percent signal change ($< 4\%$).

Conclusion—Susceptibility-induced magnetic field gradients induce local echo time shifts in gradient echo fMRI images, which can cause variable BOLD sensitivity across the brain. However, the age-related differences in BOLD signal are expected to be small for an fMRI study at 3 T.

Keywords

Magnetic Susceptibility; Field Inhomogeneity; Gradient Echo Imaging; K-space Distortions; BOLD; Functional Imaging

INTRODUCTION

Gradient echo (GRE) imaging in magnetic resonance imaging (MRI) is used in an ever-increasing set of applications, including functional MRI (fMRI) using Blood Oxygenation Level Dependent (BOLD) contrast (1), resting state functional connectivity (2), mapping T2* relaxation (3), susceptibility weighted imaging (4), and quantitative susceptibility mapping (5). For these methods, the gradient echo method is used to allow perturbations to the magnetic field to accumulate sufficient phase to either cause signal cancellation in the magnitude images (e.g. BOLD fMRI), or, in susceptibility weighted imaging applications, to enable a measurement of a phase offset from the resulting disruption. For all of these GRE techniques, the ability to quantify the changes in the data and relate it to physiological quantities relies on having accurate information on the timing of the signal, in particular the echo time (TE).

Differences in magnetic susceptibility between air and tissue result in large-scale spatial variations in the main magnetic fields in the body or brain. Accompanying the spatial variation in magnetic field are spatial gradients in the magnetic field strength, which will be referred to as susceptibility-induced magnetic field gradients (SI-MFG). These magnetic field gradients disrupt both the uniformity of the main magnetic field and the linear magnetic field gradients used for spatial encoding in MRI. These disruptions can lead to several artifacts in MRI images, including image distortion, through-plane signal loss, and k-space trajectory distortions (6, 7). The first two artifacts have been extensively studied in the literature and several methods exist to either minimize their effects or to correct image distortions (8, 9, 10, 11). In this work, we focus on the impact of SI-MFG that are in the plane of the imaging scan (referred to as in-plane SI-MFG) on the k-space trajectory. The distortions caused by in-plane SI-MFG on the k-space trajectory can impact BOLD sensitivity.

We considered studies where the two groups being compared might contain significant differences in magnetic field distributions in the brain. In such a study, there is potential for conclusions to be made about differences in brain function that should, instead, be attributed to differences in BOLD sensitivity across the two groups. One type of study that potentially suffers from group-level differences in magnetic field distributions are studies of the aging brain. Aging is accompanied by many changes in the brain (12) including changes in structural organization of the tissues (13), tissue composition (such as iron deposits) (14), and in the average angulation of the head (15). These group-level differences could have a significant impact on the magnetic field distribution across the brain with age, hence leading to age-related k-space trajectory distortions and TE shifts, and potentially to bias in detecting age-related differences in brain function.

In this paper, we explore the impact of in-plane SI-MFG on k-space trajectory and echo time shifts for GRE imaging at the commonly used field strength of 3 T, focusing on the potential impact on aging studies. A method based on acquired field maps is used here to estimate the effective k-space trajectories, taking into account the in-plane SI-MFG. The potential bias induced in the GRE measures for studies across age groups is evaluated by examining the magnetic field distributions in younger adults and older adults collected as part of an aging study. We hypothesized that age-associated changes in the magnetic field maps would result in regions in the brain that experience a significant difference in effective TE for the two age groups. We note that the current work is focused on the impact on BOLD sensitivity of in-plane SI-MFG as opposed to through-plane SI-MFG. The signal dropouts caused by through-plane SI-MFG have been previously studied and techniques exist to minimize their impact on the fMRI results (8, 9).

MATERIALS and METHODS

Echo Shifting Due to In-Plane Susceptibility Gradients

For a proton in an area with spatial gradients in the magnetic field, the in-plane SI-MFG act in the same manner as spatial encoding gradients that are purposefully applied for imaging, resulting in a net imaging or k-space trajectory that is different from the one intended. Importantly, the point at which the trajectory would have refocused, creating a gradient echo, will change resulting in a shift in TE. Due to the spatial variation in the in-plane SI-MFG, each imaging voxel will have its own net k-space trajectory and its own effective TE.

It has been previously observed (7, 16, 17) that in-plane SI-MFG alter the image intensity or image contrast due to the induced echo time shifts and k-space trajectory distortions. Reichenbach et al. (6) noted that the susceptibility-induced k-space trajectory distortions may result in a total signal loss if the k-space trajectory is shifted and skewed far enough such that the center of k-space is not sampled. In addition previous literature has also examined the impact of TE shifts on the BOLD contrast. Deichmann et al. (7) showed that different areas of the brain experienced different TE shifts resulting in a non-uniformity of the BOLD sensitivity across the brain of an individual subject. Mannfolk et al. (17) drew similar conclusions about the variability of the BOLD sensitivity. From acquired field maps, they estimated an increase of the BOLD sensitivity in the hippocampus and a drop in the anterior region of the hippocampus with an echo-planar imaging (EPI) acquisition. Therefore, TE shifts in a GRE image can have a drastic impact on the image contrast, prohibiting extraction of meaningful quantitative results of brain activity.

In order to determine the potential impacts on echo time in an fMRI acquisition, we simulate net k-space trajectories for each voxel based on a susceptibility-gradient-free k-space trajectory and estimated SI-MFG. We refer to the gradient in the field map in the readout or X-direction as G_X and the gradient in the field map in the phase encode or Y-direction as G_Y . The in-plane SI-MFG maps (G_X and G_Y only) were used in the calculation of the net k-space trajectory for each voxel over the entire acquisition. The gradients have been defined as positive from left to right (X-direction) and from anterior to posterior (Y-direction), corresponding to the positive gradient axes for the imaging slice prescription. The net k-space trajectory ($k_{x,net}$, $k_{y,net}$) was estimated using the following formulas:

$$k_{x,net}(t)=k_x(t)+G_X \cdot t \quad k_{y,net}(t)=k_y(t)+G_Y \cdot t \quad [1]$$

$k_x(t)$ and $k_y(t)$ are susceptibility-gradient-free trajectories in the read and phase encoding directions respectively, t is the timing vector for each sample point in the trajectory, and G_X and G_Y are the in-plane SI-MFG. G_X and G_Y have units of Hz/cm and k-space has units of cm^{-1} .

Given the net k-space trajectory for each voxel, the effective TE maps were calculated by determining the point in the k-space trajectory that passed closest to the $(k_x, k_y)=(0,0)$ origin point of k-space. Depending of the in-plane SI-MFG, the effective TE can be very different from the planned or nominal TE.

Experiment Design

All experiments were performed on a Siemens (Erlangen, Germany) Allegra 3 T MRI scanner. All participants signed an informed consent in accordance with the local Institutional Review Board. Field maps were obtained using the vendor-supplied GRE field mapping sequence with echo times of 10 and 12.46 ms, chosen to avoid fat/water frequency differences in the field map. The field map scans were acquired with the same slice prescription that was used in the associated fMRI study, oblique-axial slices aligned with the anterior commissure-posterior commissure (AC-PC) line, a common choice for an fMRI study. 35 slices were imaged with a thickness of 4 mm, enabling full brain coverage. The in-plane spatial resolution of the field map scan was $3.4 \times 3.4 \text{ mm}^2$, matching the spatial resolution of the fMRI scan. Additionally, a T1-weighted anatomical scan was acquired using a magnetization-prepared rapid acquisition of gradient echo (MPRAGE) sequence with TE/TI/TR= 2.3/900/1900 ms and a spatial resolution of $0.9 \times 0.9 \times 0.9 \text{ mm}^3$. To examine the magnetic field distribution across age, field maps were acquired from 31 healthy younger adults (mean age: 22 years; age range: 18–29 years) and 46 healthy older adults (mean age: 66 years; age range: 60–77 years). Two younger subjects were removed from the study due to failure in the image normalization step.

Effective Echo Time Map Estimation

Field maps were obtained with units of Hz. Gradients of the field map were taken by forward differences in the direction of the positive readout- and phase-encode axes associated with the imaging slice prescription. They were calculated in Hz/cm by dividing the first-order differences by the voxel dimension. Given that the field maps are fairly smooth, this differencing method is expected to give accurate estimates of the field map gradients. Field maps and gradient maps were normalized to standard space using FNIRT in FSL (18). Note that the SI-MFG were obtained in subject space prior to normalization, so that the readout and phase-encode directions would be relative to the subject-space, fMRI slice prescription.

G_X and G_Y were then used to calculate the net k-space trajectories and the effective echo time map using Equation 1. An EPI k-space trajectory was simulated with the phase encoding direction defined as the anterior-posterior direction aligned with AC-PC line. The

simulated EPI fMRI acquisition sequence used the following parameters: a nominal echo time of 30 ms, a matrix size of 64 in a 22 cm field of view and a parallel imaging factor of 2. The EPI trajectory had an echo spacing of 0.4 ms, in accordance with our commonly used acquisition parameters. Voxels were discarded from analysis if the net trajectory (imaging plus in-plane SI-MFG) predicted that the center of k-space was not sampled, i.e. that the net k-space trajectory did not pass within 1 k-space sampling distance from the origin of k-space.

Statistical Analysis

Using the EPI acquisition described above and the net k-space trajectory simulation, which includes the voxel-by-voxel susceptibility gradient values, an effective TE map for each subject was estimated. The mean and standard deviation of the effective TE maps were calculated for each age group.

An unpaired t-test on the effective echo time maps translated into standard space was performed to determine if magnetic field differences result in echo time differences between the two groups. We did not include a correction for multiple comparisons but have displayed our results with a stringent threshold of $p < 0.01$. To evaluate the effect size of the difference in effective TE between the two age groups, Cohen's d (19) was also calculated. Several regions of interest were examined where differences in effective TE were significant. We used the value of 0.2 to indicate reasonable effects size for aging fMRI studies (20). A Cohen's d of less than 0.2 was considered negligible whereas as a value larger than 0.2 indicates that the mean effective TE of the younger group was larger than the one of the older group.

We characterized the impact of effective echo time differences on fMRI measurements for the worst-case locations in the brain. For these regions with highly significant differences in echo time, we analyzed the expected BOLD percent signal change. This signal change was placed into the context of typically expected BOLD differences in aging studies. The expected BOLD percent signal change was calculated using the following formula:

$$PSC = \frac{e^{-\frac{TE}{T_{2,activation}^*}} - e^{-\frac{TE}{T_{2,rest}^*}}}{e^{-\frac{TE}{T_{2,rest}^*}}} \quad [2]$$

where a baseline $T2^*$ of 66 ms was assumed (21) and an activation-induced change of $T2^*$ was simulated that yielded activations of 1% and 5% BOLD signal change in the susceptibility-free case.

As head orientation may be one characteristic that leads to magnetic field distribution differences, we also examined the average nod rotation for the young and old group. We performed linear alignment of the high-resolution structural scan (MPRAGE) with the MNI template and extracted the nod rotation angle to determine if there is an age-related difference in rotation of the head.

RESULTS

An example magnetic field distribution and SI-MFG map for a young subject is shown in Figure 1 for a slice including the orbitofrontal cortex. The magnetic field map has values that exceed 100 Hz in the slice shown. The SI-MFG of the field map, G_X , G_Y , and G_Z reach approximately ± 80 Hz/cm. In order to assess the impact of the in-plane SI-MFG on the k-space trajectory, the sign of the in-plane SI-MFG is important relative to the sign of the applied imaging gradients and hence the planned traversal direction through k-space.

The impact of the in-plane SI-MFG in the phase encode direction of an EPI sequence can be seen in Figure 2. Figure 2 shows seven cases of k-space shifts and effective TE resulting from different values of in-plane SI-MFG, G_Y , in the phase encode direction only. The impact of SI-MFG in the X-direction, readout direction, is shown in the supplementary Figure S1. In Figure 2, a G_Y of -40 Hz/cm, which is within the range of SI-MFG values in the brain as observed in Figure 1, can shift the echo time by 8 ms. On the other hand, a G_Y of $+40$ Hz/cm shifts the k-space trajectory so much that the center of k-space is not sampled anymore. We note that the impact of in-plane SI-MFG includes a shift in the starting point of the k-space trajectory due to in-plane SI-MFG effects during the time from the RF excitation to the start of the readout. In addition, the in-plane SI-MFG will skew the trajectory by increasing or decreasing the spacing between the k-space lines depending on whether it is pushing with or against the imaging trajectory. All these effects change the sampling time of the center of k-space (k_x, k_y) = (0,0) and therefore shift the echo time. In the case of in-plane SI-MFG in the readout direction, similar observations can be made as shown in Figure S1 and in (11, 16). For the same value of in-plane SI-MFG, the effect on the k-space trajectory in the readout direction is less impactful than in the phase encoding direction.

The impact on echo time shifts is not just limited to slices at the air/tissue interfaces in the brain, such as the orbitofrontal cortex. Figure 3 shows an example of an estimated effective TE map for the EPI trajectory for one older subject across several axial locations in the brain. All subjects show similar distribution of effective TE across the brain. The slice-value labels correspond to the slice location in mm in the standard MNI space as viewed in FSLview, part of FMRIB's Software Library (www.fmrib.ox.ac.uk/fsl). Regions that resulted in net k-space trajectories that do not sample the center of k-space are denoted by a lack of color overlay. The effective TE is not uniform across the brain in the presence of the in-plane SI-MFG. The deviation from the nominal or planned TE can be significant (± 5 ms). Additionally, the center of k-space is not sampled in regions such as the inferior temporal lobes, known to be regions with significant magnetic field inhomogeneity.

Figure 4 shows the mean effective TE and standard deviation maps for three slices for each age group. As observed previously, the effective TE varies more than ± 5 ms across the brain for both older and younger adults. The variation across space is larger than the standard deviation across all subjects, indicating a good general consistency in the field map and TE values across subjects (22).

An unpaired t-test was performed between the TE maps of the older and younger groups. The thresholded uncorrected p-value map ($p < 0.01$) is shown in Figure 5A, overlaid on the

mean TE image for the same slices as shown in Figure 4. Figure 5B and Figure 5C shows, respectively, the differences and the absolute mean differences in the TE maps between the older and younger groups. Although significant statistical differences between groups were observed around the occipital and temporal lobes, the difference in effective echo time between the two groups was only on the order of 1 ms. Table S1 in the supplementary material describes more precisely the brain regions where significant differences were found. For these regions, Cohen's d was calculated and varies from 0.43 in the superior temporal gyrus to 0.74 in the posterior cingulate. For the middle temporal gyrus, the Cohen's d is negative (-0.41) indicating that the mean effective TE in that region for the older group is bigger than the younger group.

To examine the potential impact of this echo time shift on the fMRI signal, the BOLD percent signal change was estimated for the worst-case shift of 1 msec from the nominal echo time (resulting in an effective echo time of 31 msec), using Equation 2. The percent signal change becomes 1.03% compared to the susceptibility-free case of an initial percent signal change of 1%. In the case of an initial percent signal change of 5%, an increase of 1 ms in echo time due to in-plane SI-MFG will lead to a percent signal change to 5.17%.

Finally, head rotations were examined between the two age groups as a potential source of SI-MFG differences. The average head rotation (nod direction) for older subjects aligning to the MNI template was $-14.3^{\circ} \pm 5.8^{\circ}$ while it was $-8.8^{\circ} \pm 5.2^{\circ}$ for younger subjects. This corresponds to a significant rotation of the head between the two groups due to age (p -value of 6×10^{-5}).

DISCUSSION

SI-MFG exists in the brain due to the large number of air-tissue interfaces in and around the head. These magnetic field gradients introduce local shifts in the k -space trajectory that lead to differences in effective echo time across the brain. The impact of these in-plane SI-MFG may need to be taken into account when using gradient echo imaging as the effective echo time can differ from the intended nominal echo time. As the planned center of the k -space trajectory does not coincide with the center of k -space (k_x, k_y) = (0,0), the signal intensity is altered resulting in a different image contrast. If the k -space trajectory is shifted out of the acquisition window, the majority of the energy of the signal is lost. The impact of in-plane SI-MFG on the BOLD sensitivity can exist even without noticeable changes in image intensity. Deichmann et al. (7) showed that even if the image intensity is acceptable, the BOLD sensitivity can drop considerably. The amount of variation and the impact on quantitative gradient echo measures will depend on the specific pulse sequence and its timing in the coverage of k -space. In our observations, there was significant spatial variations (of around 5 ms) in the effective echo time associated with a BOLD fMRI experiment within the head of each participant. However, across subjects, the magnetic field distribution was highly conserved resulting in a variation of the effective echo time for each location that was much smaller, on the order of 1 ms.

Our original hypothesis addressed possible bias in BOLD fMRI signal due to systematic differences in the field map across age. These systematic differences could result from

different factors such as selective volumetric declines, changes in the angulation of the head and spine leading to changes in head orientation, and accumulation of iron deposits in particular brain regions. The differences in the head rotation that we have observed can be explained by a change of the curvature of the spine with age and could lead to a change in the magnetic field, as previously identified (23). However, our results do not indicate that the difference in the magnetic field distribution with age will have a strong impact on fMRI signal in aging studies at 3 T.

Statistically significant differences do exist in the effective echo time across the two age groups. The Cohen's d coefficients for the regions of interest describe an important effect (>0.2), indicating that there are systematic age-related differences in the magnetic field distribution. However the effective echo time differences are small, approximately 1 ms in the worst case, resulting in a difference of 4% or less in the BOLD percent signal change between the two groups. These variations are only due to SI-MFG and do not represent any underlying differences in neural activity. However, there are two critical factors to consider when assessing the impact of this level of change on an aging fMRI study. First, the ROIs in the current analysis are defined based on maximal changes in echo time. These ROIs are small (20–80 voxels) and would be encompassed by larger ROI's defined by anatomical variations instead of SI-MFG. Second, a variation of 4% in the BOLD percent signal change is small compared to the difference commonly reported in aging studies which is around 10–20% (24) and is smaller than reported BOLD percent signal change standard deviation (25). It is not expected that in-plane SI-MFG will lead to bias in BOLD aging studies. The method that we have used to examine this potential for bias could be applied in future studies to examine specific age-related fMRI comparisons. By collecting field maps and simulating k-space trajectories, future studies could window the maximum age-related differences in echo time and sensitivity and compare them to the magnitude of their age-related fMRI differences.

The method presented here to calculate the net k-space trajectory and the effective echo time is based on accurate field maps and gradients maps. It is important that the field map slices be aligned with the functional imaging slices and that the two datasets are acquired with the same readout and phase encoding directions. In order to determine the gradients in the magnetic field map in each direction, we used a first-order difference operation in the positive direction of the gradient, as this provides the most direct relationship to image encoding gradients and k-space trajectories. We expect that the field maps are smooth and that this operator results in fairly accurate measures of the linear SI-MFG within an imaging voxel. However, higher resolution field map acquisitions could be used to get more localized estimates of the SI-MFG, with spatial derivatives accessible within an imaging voxel. This higher spatial resolution field map may lead to better estimates of the gradients in regions where curvature of the field map is high.

In-plane SI-MFG are often highly correlated with regions with high through-plane SI-MFG. The additional effects from these magnetic field distributions can be very significant and dominate or mask the effects due to the in-plane gradients. Through-plane SI-MFG have been shown to lead to important signal losses due to intra-voxel dephasing. Many techniques

including z-shimming or reducing the slice thickness (8, 9) have been adopted to minimize the signal dropouts in the slice direction.

Some methods have been previously developed to alleviate the impacts of in-plane SI-MFG on the BOLD contrast. Deichmann et al. (7) suggested to use magnetic gradients to compensate for the SI-MFG and mitigate the BOLD sensitivity loss. Weiskopf et al. (16) emphasized the importance of correcting SI-MFG in the readout direction and reduced signal loss by decreasing echo time and increasing spatial resolution in the readout direction. In (26), spiral-in trajectories were compared to spiral-out trajectories to further explore and validate the BOLD sensitivity changes expected for different acquisition strategies. These techniques offer the possibility to adjust the imaging prescription at run-time for a specific subject and targeted ROI. However they are not able to completely eliminate BOLD sensitivity variations across the entire scanning volume and potential bias across the brain can remain in BOLD studies.

In addition to the impact on BOLD fMRI, SI-MFG can have an effect on other techniques that rely on GRE images, such as the estimation of the relaxation parameter $T2^*$ in quantitative imaging techniques. It has been shown that due to SI-MFG the $T2^*$ decay has a more complex behavior than a mono-exponential decay (27, 28). Therefore a model taking into account SI-MFG is crucial for the accurate estimation of $T2^*$.

Our study showed that no substantial bias due to in-plane SI-MFG is expected in BOLD aging studies at 3 T. However, several limitations of the current study should be addressed. First, the study is limited by the small number of subjects involved. Despite the small number of subjects, we did find significantly different regions across age in the field map. However, more sensitivity to these differences would come from a larger study population. Also, all subjects were scanned on the same scanner and with the same field map sequence. Some differences in shimming capabilities would be expected across scanners and this should be investigated in future work. The conclusions drawn in this work are applicable to 3 T scanners, but may be even more important at higher field where larger differences in BOLD signal would be expected if a GRE sequence was used. In addition, though-plane SI-MFG were not the focus of this work and could lead to additional and more significant differences in image contrast across age group due to signal losses. Finally, as described above, the estimates of the effective echo time rely on accurate field maps and SI-MFG maps. By the use of the first-order difference, accurate SI-MFG are difficult to obtain on the edges of the brain using the current approach.

In conclusion, magnetic field inhomogeneities due to air/tissue interfaces around the brain have a strong impact on gradient echo k-space trajectories. In this work, the effects of in-plane SI-MFG on a typical fMRI experiment were examined. A variation in the effective echo time of ± 5 ms was observed across the brain in each individual on a 3 T scanner. When examining older and younger participants, significant age-related differences in the in-plane SI-MFG-induced effective echo time can be seen. However, the magnitude of change in TE is small (~ 1 ms) and no measurable age-related bias in BOLD fMRI signal due to in-plane SI-MFG is expected. In-plane SI-MFG and echo time shifts will become stronger

when using higher field scanners and GRE techniques at high field should be examined for increased sensitivity to SI-MFG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Field map and gradient maps for one slice in the orbitofrontal cortex for one subject.

Figure 2. Impact of in-plane SI-MFG in the phase encoding direction on the k-space trajectory of an EPI sequence. EPI trajectories are simulated with an echo time of 30 ms with typical timing parameters and a positive phase encoding direction of anterior to posterior (up to down). Seven values of SI-MFG in the phase encoding direction were simulated.

Figure 3. Effective TE map for one older subject for an EPI sequence with phase encode axis in the anterior to posterior direction with a planned TE of 30ms. Portions without a color overlay indicate regions in which the k-space distortions are so large that the center of k-space was not sampled. Z-slice locations are in MNI coordinates.

Figure 4. Mean effective TE in ms (A,B) and standard deviation (C,D) maps for the older age group (A,C) and the younger age group (B,D). Three representative slices are shown at MNI coordinates of -6, 10, and 26 mm.

Figure 5.

Comparison of echo time shifts across older and younger subjects. **A.** Thresholded uncorrected p-value maps ($p < 0.01$) overlay on the mean effective TE map demonstrates several regions with significant difference. **B.** Shows the differences between the mean effective TE of the older group and the younger group. **C.** Shows the absolute differences between the mean effective TE between the two age group indicating small differences between old and young subjects.