Research Article

Optimized multi-axis spiral projection MR fingerprinting with subspace reconstruction for rapid whole-brain high-isotropic-resolution quantitative imaging

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Purpose: To improve image quality and accelerate the acquisition of 3D MR fingerprinting (MRF).

Methods: Building on the multi-axis spiral-projection MRF technique, a subspace reconstruction with locally low-rank constraint and a modified spiral-projection spatiotemporal encoding scheme called tiny golden-angle shuffling were implemented for rapid whole-brain high-resolution quantitative mapping. Reconstruction parameters such as the locally low-rank regularization parameter and the subspace rank were tuned using retrospective in vivo data and simulated examinations. B₀ inhomogeneity correction using multifrequency interpolation was incorporated into the subspace reconstruction to further improve the image quality by mitigating blurring caused by off-resonance effect.

Results: The proposed MRF acquisition and reconstruction framework yields high-quality 1-mm isotropic whole-brain quantitative maps in 2 min at better quality compared with 6-min acquisitions of prior approaches. The proposed method was validated to not induce bias in T₁ and T₂ mapping. High-quality whole-brain MRF data were also obtained at 0.66-mm isotropic resolution in 4 min using the proposed technique, where the increased resolution was shown to improve visualization of subtle brain structures.

Conclusions: The proposed tiny golden-angle shuffling, MRF with optimized spiral-projection trajectory and subspace reconstruction enables high-resolution quantitative mapping in ultrafast acquisition time.

Keywords: MRF, quantitative mapping, subspace reconstruction, trajectory optimization

Abbreviations: MRF, magnetic resonance fingerprinting; FA, flip angle; LLR, locally low rank; SPI, spiral projection imaging; TR, time repetition; TE, time echo; PD, proton density; MFI, multi-frequency interpolation; TGA, tiny-golden-angle; TGAS, tiny-golden-angle-shuffling; PSF, point spread function; iNUFFT, inverse nonuniform Fourier transform; SVD, singular value decomposition; SNR, signal-to-noise ratio; RMSE, root-mean-square deviation; RAM, random-access memory.
1 | INTRODUCTION

Magnetic resonance fingerprinting (MRF) is a rapid quantitative imaging technique for estimating multiple tissue parameters simultaneously and has attracted significant interests as a diagnostic tool in diseases in which the pathological changes are sensitive to related quantitative parameters. The pulse sequence of MRF is usually designed to boost temporal incoherence by varying the acquisition parameters (e.g., flip angle [FA] and TR) and adding a preparatory module (e.g., inversion-preparation pulse and $T_2$-preparation pulse). Studies have demonstrated the repeatability and reproducibility of MRF in both quantitative relaxometry and morphometry. Initially demonstrated for quantitative neuroimaging, MRF has also been deployed and tailored for the imaging of other body parts, such as the heart, abdomen, and ankle.

Recently, there has been tremendous work in the acquisition and modeling of MRF techniques to reduce the total acquisition time. On the reconstruction front, forward model–based regularized reconstructions with carefully designed priors such as the multiscale reconstruction, the sliding-window method, low rank–based reconstruction techniques, spatiotemporal subspace modeling–based reconstruction, and deep learning approaches enable robust reconstructions at high accelerations with limited noise penalty. There have also been studies focused on correcting the reconstructed images influenced by system imperfections, such as imperfect slice-selection profile and $B_1^+$ inhomogeneity, which could affect the accuracy of MRF quantitative mapping and $B_0$ inhomogeneity, which could induce blurring.

On the acquisition front, simultaneous multislice and 3D acquisition techniques have been developed for MRF to achieve higher SNR efficiency compared with 2D acquisition. With higher SNR efficiency, the 3D acquisition achieves quantitative mapping with higher resolution at higher rates of undersampling, thus enabling faster whole-brain mapping. For example, stack-of-spiral encoding scheme with interleaved undersampling in the partition-encoding dimension achieves whole-brain MRF at $1.2 \times 1.2 \times 3 \text{ mm}^3$ resolution in 4.6 min. By augmenting this acquisition with a combined parallel imaging and deep learning reconstruction, 1-mm isotropic resolution whole-brain data can be acquired in 7 min. Another study has proposed to implement hybrid sliding-window and GRAPPA reconstruction on uniform undersampled stack-of-spiral MRF acquisition, which also achieves 1-mm whole-brain MRF in a similar time frame. Rapid quantitative imaging is an active area of research, and a number of other promising acquisition strategies have also been proposed for high-resolution whole-brain quantitative mapping, such as the multitasking technique for $1 \times 1 \times 3.5 \text{ mm}^3$ resolution $T_1/T_2/T_1^\rho$ mapping in 9 min and echo planer time-resolved imaging for 1-mm isotropic resolution $T_1/T_2/T_2^*$ mapping in 3 min.

Our previous work proposed a novel multi-axis spiral-projection-imaging (SPI) acquisition scheme with sliding-window reconstruction to achieve 1-mm isotropic whole-brain quantitative mapping in 5 min, which was also demonstrated to be more robust to rigid head motions when compared with stack-of-spiral-based acquisition schemes.

Building on the previous work, this study incorporates a spatiotemporal subspace modeling reconstruction with locally low rank (LLR) constraint and an optimized spatiotemporal sampling scheme into multi-axis SPI MRF. Compared with conventional sliding-window reconstruction, the subspace reconstruction is shown to provide markedly improved quantitative maps with lower artifacts and higher SNR. The optimized SPI encoding scheme
is designed to increase spatiotemporal incoherence, thus improving the efficacy of LLR, and is validated to be more robust to artifacts at high acceleration rates. The proposed method enables high-quality whole-brain $T_1$, $T_2$, and proton density (PD) mapping at 1-mm isotropic resolution in less than 2 min. A 0.66-mm isotropic resolution scan is also obtained in about 4 min, demonstrating the performance of the proposed method for submillimeter quantitative imaging. Additionally, the multifrequency interpolation (MFI) method\textsuperscript{28,36} is also incorporated into the subspace reconstruction to mitigate blurring in regions with large $B_0$ inhomogeneity.

This work is an extension of our earlier work, which was reported in an abstract at the International Society of Magnetic Resonance in Medicine (ISMRM) 2021.\textsuperscript{37}

2 | METHODS

2.1 | Sequence design

Figure 1A shows the pulse sequence diagram of the proposed method based on our previous work in Cao et al.\textsuperscript{33} A conventional fast imaging with steady state precession–based MRF sequence\textsuperscript{38} is used, in which 500 TRs with varying FA (ranging from $10^\circ$ to $90^\circ$, using a nonselective Fermi pulse for good spectral selection and high SAR efficiency\textsuperscript{39}) are acquired after an adiabatic inversion-preparation pulse, with a TI of 20 ms. Each acquisition period that contains 500 TRs is termed as an “acquisition group” ($G$). When an acquisition group is completed, a resting time of 1.2 s is applied to allow for signal recovery before the next acquisition group. Different acquisition groups are used to acquire different complementary spiral encodings across multiple k-space rotational axes to fill 3D k-space. The TR and TE of the sequence are both fixed at 12 ms and 0.7 ms, respectively.

In our previous work, which uses the tiny-golden-angle (TGA) acquisition along with a sliding window reconstruction, a total of 48 acquisition groups were needed to achieve a stable 1-mm whole-brain quantitative mapping in 5 min and 46 s. In this work, using this acquisition as a reference point for convenience and readability, we will refer to an acquisition with 48 acquisition groups as an $R = 1$ acquisition for 1-mm isotropic resolution.

Based on $R = 1$, faster acquisitions such as $R = 3$ and $R = 6$ were achieved by interleaved undersampling across the acquisition groups dimension. The corresponding sampling patterns could be found in Supporting Information Tables S2 and S3, respectively.

In each TR, a variable-density spiral trajectory\textsuperscript{40,41} with 16-fold in-plane undersampling rate at the center of k-space, and a linearly increasing undersampling rate up to 32-fold at the edge of k-space, are used to achieve an encoding at 1-mm in-plane resolution and an FOV of $220 \times 220 \text{ mm}^2$ with a readout duration of 6.7 ms. The high in-plane acceleration is used to alleviate the potential blurring caused by off-resonance phase accumulated during the readout duration. The slew rate and maximum gradient amplitude used for this spiral trajectory is 100 T/m/s and 40 mT/m, respectively, based on the consideration of compatibility for common clinic scanners.

2.2 | Faster acquisition with higher slew rate

To achieve a faster acquisition, a higher slew rate of 150 T/m/s was used on the GE 3T Premier scanner (GE Healthcare, Madison, WI) (with maximum gradient amplitude of 80 mT/m and slew rate of 200 T/m/s) at the peripheral nerve stimulation threshold. Similar readout duration (7.0 ms here compared with 6.7 ms as mentioned previously), the same 1-mm in-plane resolution and $220 \times 220 \text{ mm}^2$, is achieved using only 12-fold in-plane undersampling rate for center k-space and 24-fold for edge k-space. Therefore, only 36 ($12 \times 3$ for multi-axis rotation scheme) acquisition groups were needed, resulting in a total acquisition time of 4 min and 19 s at $R = 1$, which is 25% faster than the counterpart with a slew rate of 100 T/m/s. Therefore, the acquisition time at $R = 3$ with the higher slew rate needs 1 min and 26 s, which is identical to $R = 4$ using 100 T/m/s.

To assess the performance of the proposed method for submillimeter quantitative imaging, 0.66-mm isotropic resolution SPI-MRF was performed using a 6.8-ms variable-density spiral trajectory with 24-fold in-plane undersampling rate at the center of k-space and 48-fold at the edge of k-space using slew rate of 150 T/m/s. The number of acquisition groups was also increased to 72, resulting in a total acquisition time of 8 min and 38 s at $R = 1$.

The spiral readout durations were kept in a similar range (approximately 6.7 to 7.0 ms) across different acquisitions to alleviate the effect of $B_0$ inhomogeneity and avoid substantial changes in sequence parameters such as TR.

2.3 | Optimized spatiotemporal k/t trajectory

Figure 1B shows the spiral-projection k-space sampling encoding across the first three TRs and 16 acquisition groups for (1) the previously used TGA scheme\textsuperscript{33} and (2) the proposed TGA shuffling (TGAS) scheme. The TGA
FIGURE 1  (A) Sequence diagram. (B) Spiral-projection spatiotemporal encoding with the original tiny-golden-angle (TGA) scheme (left) and the proposed tiny-golden-angle-shuffling (TGAS) scheme (right). (C, D) The k-space coverage of the first three TRs for acquisition groups G1-16, G17-32, and G33-48, where through-plane rotation was implemented around x-axis, y-axis and z-axis, respectively, to achieve multi-axis rotation for better incoherence. FA, flip angle
scheme performs in-plane rotations (i.e., spiral interleaving) in the group dimension and through-plane rotations in the TR dimension. On the other hand, to increase spatiotemporal incoherence, the TGAS scheme intermixes through-plane rotation along both the TR and the group dimensions. Figure 1C shows the color-coded plots of all the spirals that are played out during the first three TRs for the TGA and the TGAS schemes.

As shown in the left panel of Figure 1C, for the first 16 acquisition groups (G1-16) in the TGA scheme, in-plane rotations (around the z-axis) are performed along the acquisition group dimension to obtain 16 spiral interleaves and achieve full sampling at the center of k-space, to provide a disk-like coverage in 3D k-space. Through-plane rotations (around the x-axis) are then performed along the TR dimension using the TGA step of 23.63°. Thus, the disk-like k-space coverage is rotated along with TRs to gradually cover the entire 3D k-space. With the TGA scheme, the in-plane rotation angle \( \Theta_x \) and the through-plane rotation angle \( \Theta_z \) could be described as \( \Theta_x(j) = 23.63° \times j \), \( \Theta_z(i) = 22.5° \times i \), where \( j \) is the TR index and \( i \) is the index of the acquisition group. Here, the angle of 22.5° is determined by the in-plane undersampling rate at the center of k-space of a single spiral interleaf, namely, 360°/16 here for 1-mm isotropic resolution, which would be updated to 360°/24 for the 0.66-mm version. To perform multi-axis rotations, acquisition groups G17-32 and G33-48 are designed to rotate around the y-axis and z-axis for through-plane rotation, respectively (shown on the left side of Figure 1D). An example of the multi-axis TGA trajectory of a representative time point (TR) could be found at the top left of Figure 2A, where all of the 48 spiral interleaves collectively form three orthogonal spiral disks.

In this work, we propose the TGAS spatiotemporal encoding scheme, which shuffles the rotation operations via \( \Theta_x(i, j) = 23.63° \times (i + j) \), \( \Theta_z(i) = 22.5° \times i \), as illustrated in the right panel of Figure 1B. Here, the in-plane and through-plane rotations are intermixed in both the TR and the acquisition group dimensions. This increases the spatiotemporal incoherence and is expected to aid the subspace reconstruction. The advantage of the TGAS over the TGA scheme was validated by both simulation and in vivo experiments in this work. Similar to TGA, TGAS also uses the multi-axis rotations as shown on the right side of Figure 1D.

Figure 2 shows the k-space coverage and point spread function of TGA (blue lines) and TGAS (red lines) trajectory at different acceleration factors. By shuffling the TGA trajectory, the TGAS trajectory is able to cover the 3D k-space more incoherently for each time point, thus improving the point spread function with less sidelobes for the acquisition at each time point, as well as the spatiotemporal incoherence.

### 2.4 Subspace reconstruction

Figure 3A shows the process of the MRF subspace reconstruction. The MRF dictionary was precalculated using the extended phase graph method with the prescribed FAs and TRs. Note that the data acquired from multiple acquisition groups are combined at each TR as in a typical multishot acquisition; the number of time points to be reconstructed from the overall acquisition is identical to the number of TRs within one acquisition group, namely, 500 in this work. Consequently, the dictionary was also compressed in the group’s dimension, leaving 500 time points in total.

The resulting 3D dictionary (\( T_1 \) entries, \( T_2 \) entries and TRs, respectively) was reshaped to two dimensions (entries including all \( T_1 \), \( T_2 \), and TR) and a singular value decomposition was then applied on the reshaped dictionary. The first five temporal principal components were extracted as subspace bases, which correspond to an 11-min and 31-s acquisition.

To determine the number of subspace bases used in the reconstruction, a simulation experiment was performed to test the reconstruction performance with subspace bases ranging from 3 to 7; the results are shown in Supporting Information Figure S1. The simulation data were generated using \( T_1 \), \( T_2 \), and PD maps obtained from the extended phase graph method with the prescribed FAs and TRs respectively. The resulting 3D dictionary (\( T_1 \) entries, \( T_2 \) entries and TRs) could then be solved by

\[
\min_{c} ||PFS\Phi c - y||^2 + \lambda R_r(c),
\]

where \( P \) is the undersampling pattern; \( F \) is the nonuniform Fourier transform (NUFFT); \( S \) are the coil sensitivity maps; \( y \) are the acquired raw data; and \( \lambda \) is the regularization parameter for LLR. The coil sensitivity maps \( S \) were estimated with the ESPIRIT method using the central k-space data combined from all acquired TRs and groups.

To optimize the selection of \( \lambda \) for LLR regularization used in the subspace reconstruction, reference \( T_1 \) and \( T_2 \) maps at 1-mm isotropic resolution were created from an oversampled TGA-SPI-MRF data set (termed as \( R = 0.5 \), which corresponds to an 11-min and 31-s acquisition at 1-mm resolution, with 96 nonoverlapping acquisition groups) using subspace reconstruction without regularization. Retrospective undersampling of this \( R = 0.5 \) data set was then performed along the acquisition group dimension to generate \( R = 3 \) and \( R = 6 \) data sets, which were then...
FIGURE 2  K-space coverage and corresponding point spread function (PSF) (average across x-axis, y-axis, and z-axis) of one TR (A) and five consecutive TRs (B), for TGA and TGAS trajectory at different acceleration factors, from $R = 1$, 3, and 6. The undersampling patterns of $R = 3$ and 6 are found in Supporting Information Tables S2 and S3, respectively.
The Schematic workflow of subspace reconstruction. Five subspace bases were extracted from the MR fingerprinting (MRF) dictionary and used to reconstruct the coefficient maps (at $\times 1$, $\times 2$, $\times 2$, $\times 10$, and $\times 10$ scaling, respectively, for better visualization). The coefficient maps are then used to generate the MRF time-series images and dictionary template matching performed to obtain $T_1$, $T_2$, and proton density (PD) maps. (B) Comparison between sliding-window inverse nonuniform Fourier transform (iNUFFT) and subspace reconstructions, where $T_1$ and $T_2$ maps from 1-mm isotropic acquisitions at acceleration factors $R = 1$ and $R = 3$ are shown. LLR, locally low rank; SVD, singular value decomposition.

Reconstructed with the subspace approach using $\lambda$ ranging from $10^{-6}$ to $10^{-4}$. The difference maps and RMS error of the resulting $T_1$ and $T_2$ maps relative to the reference maps were calculated (shown in Supporting Information Figures S2 and S3). Based on the consideration of SNR and image quality, $\lambda = 3 \times 10^{-5}$ and $5 \times 10^{-5}$ were selected for $R = 3$ and $R = 6$, respectively.

To accelerate the reconstruction and reduce computational requirements, singular-value decomposition coil compression was used for all reconstructions to compress the effective channel count to 12 (for both 48-channel and 64-channel coils used in this work).

To provide a baseline comparison for the subspace reconstruction, the conventional sliding-window inverse NUFFT (iNUFFT) reconstruction was also implemented. All subspace reconstructions used the BART toolbox.

### 2.5 Simulation

In this work, three simulation experiments were performed to determine the number of subspace rank (as described previously) and compare the performance between TGA and TGAS. The $T_1$, $T_2$, and PD maps created from a $R = 0.5$ TGAS-SPI-MRF data set described previously were used as reference and for generating the synthetic MRF time-series images along the TR dimension. To generate simulation data for TGA and TGAS acquisitions, these synthetic images were added with white noise (the amplitude of noise is 25% of the average amplitude of synthetic images) and passed through the forward model, consisting of coil sensitivities and k-space trajectory sampling. The error maps and RMS error were calculated by using these simulated data.
2.6 Template match

The subspace-based compression is also applied to the MRF dictionary, which substantially decreased the matrix size of the dictionary from $160 \times 176 \times 500$ to $160 \times 176 \times 5$, where 160 is the number of $T_1$ entries (corresponding to [20:20:3000 and 3200:200:5000] ms); 176 is the $T_2$ (corresponding to [10:2:200, 220:20:1000, 1050:50:2000, and 2100:100:4000] ms); 500 is the number of TRs within an acquisition group; and 5 is the number of subspace bases. The reconstructed coefficient maps are used directly for template matching with the compressed dictionary, which significantly improves the computation speed of the template matching.\(^{53}\)

2.7 $B_0$ correction

To further improve the image quality, the MFI technique\(^{28,36}\) was incorporated into the subspace reconstruction, with Equation (1) updated as

$$\min_{c_m} \left\| PFS\Phi c_m - e^{-i\omega_m t}y \right\|_2^2 + \lambda R_r(c_m). \quad (2)$$

Where $e^{-i\omega_m t}$ is the conjugate phase demodulation term with time $t$ accumulated during the readout duration at a specific frequency $\omega_m$. In this work, five demodulation frequencies ($\omega_{1-5} = [-200:100:200]$ Hz) were used to cover the typical $B_0$ inhomogeneity range in human neuroimaging on common clinical 3T scanners. Therefore, the coefficient maps with MFI correction $c_{\text{MFI}}$ could be obtained by

$$c_{\text{MFI}}(r) = \sum_{m=1}^{M} W_m(r)c_m(r), \quad (3)$$

where $r$ is the voxel position; $M = 5$ corresponds to $\omega_{1-5}$; and $W_m(r)$ is the weighting coefficient maps, which is the linear interpolation factor of $\omega_{1-5}$ to match the measured $B_0$ inhomogeneity $\Delta B_0$ at $r$.

2.8 $B_1^+$ correction

To improve the accuracy of MRF quantification and account for $B_1^+$ inhomogeneity effects in the MRF data, signal evolution across a range of discretized $B_1^+$ values (e.g., [0.50:0.05:1.50]) were simulated, which enabled the creation of MRF dictionaries with different $B_1^+$ variations. The corresponding dictionary was then selected for use in each spatial location based on a prescanned $B_1^+$ map.\(^{26}\)

2.9 Validation

To validate our proposed method, 5 healthy volunteers were scanned with the approval of the institutional review board with informed consent obtained. Studies were performed on two 3T MAGNETOM Prisma scanners (Siemens Healthcare, Erlangen, Germany) with a 32-channel head receiver coil and a GE 3T Premier MRI scanner with a 48-channel head receiver coil. The matchup between the scanners and the results is listed in the Supporting Information Table S1.

An oversampled $R = 0.5$ 1-mm data set with TGAS trajectory was acquired as a reference to optimize the selection of LLR regularization parameter $\lambda$ and the number of subspace bases used in the reconstruction. Both TGAS and TGA MRF data were also acquired at 1-mm resolution at $R = 1$. Retrospective undersampling (along acquisition group dimension) experiments at acceleration factors of $R = 3$ (1 m 55 s) and $R = 6$ (58 s) were performed to validate the performance of the proposed method to provide a faster acquisition. In addition, 1-mm and 0.66-mm TGAS-SPI-MRF using higher slew rate (150 T/m/s) were also acquired.

To incorporate $B_0$ correction into the subspace reconstruction, an additional $B_0$ field map was acquired using a multi-echo gradient-echo scan with two different TEs (2.6 ms and 4.1 ms) within 1 min. The FOV was $220 \times 220 \times 220$ mm$^3$ to match the MRF acquisition but with a lower resolution of $3.4 \times 3.4 \times 4$ mm$^3$ on the grounds that the $B_0$ field inhomogeneity is relatively smooth, and higher SNR is preferred rather than higher resolution.

To correct the $B_1^+$ inhomogeneity in MRF data, an FOV-matched $B_1^+$ map was obtained using a vendor-supplied $B_1^+$ mapping sequence.\(^{54}\) The FOV was $220 \times 220 \times 220$ mm$^3$, and the scan time for this $B_1^+$ mapping at $3.4 \times 3.4 \times 5$ mm$^3$ resolution was about 60 s.

A phantom (made of agar mixed with MnCl$_2$) with a range of relaxation times similar to brain tissues was scanned using multi-T1 inversion-recovery spin-echo and multi-TE spin-echo sequences as the gold standard methods for $T_1$ and $T_2$ measurement, respectively.

To analyze the $T_1$ and $T_2$ values using different methods or acquired on different MRI systems, synthetic $T_1$-weighted images generated using the measured $T_1$ and PD maps from MRF were used as input for FreeSurfer toolbox\(^{57}\) for brain segmentation. The average $T_1$ and $T_2$ values of gray matter (GM) and white matter (WM) on both bilateral hemispheres were then calculated based on this segmentation.

Computations were performed on a Linux (Ubuntu 20.04) server (with 32 Core i7 Intel Xeon 2.8 GHz CPUs, an Nvidia 2080Ti GPU, and 512GB RAM) using MATLAB R2015b (The MathWorks, Natick, MA, USA).
3 | RESULTS

Figure 3B shows comparisons between the sliding-window iNUFFT and the subspace reconstructions for 1-mm MRF data. At $R = 3$ with TGA acquisition, the $T_1$ and $T_2$ maps from the sliding-window iNUFFT reconstruction show significant artifacts, whereas the $T_1$ and $T_2$ maps from the subspace reconstruction are of good quality and arguably better than the ones obtained from the sliding-window iNUFFT reconstruction at $R = 1$. However, there are some residual artifacts (yellow arrow) in the $T_2$ map from the TGA acquisition at $R = 3$ with subspace reconstruction. For the equivalent TGAS acquisition with subspace reconstruction at $R = 3$, this artifact is absent. The average $T_1$ and $T_2$ values in the WM and GM of these results are listed in the top section of Table 1 (subject 1). The reported values are consistent across methods, particularly with the TGA trajectory and sliding-window iNUFFT reconstruction having previously been validated to agree well with gold-standard quantitative imaging techniques. This indicates that the $T_1$ or $T_2$ maps are consistent when subspace reconstruction and the TGAS trajectory are used.

Figure 4 further compares the performance of 1-mm TGA and TGAS acquisitions, both with subspace reconstruction, at various acceleration factors. The results

|                  | $T_1$ | $T_2$ |
|------------------|-------|-------|
|                  | WM (L) | WM (R) | GM (L) | GM (R) | WM (L) | WM (R) | GM (L) | GM (R) |
| Subject 1 TGA + iNUFFT | 883.2  | 878.3  | 1362.2 | 1366.7 | 60.33  | 59.55  | 81.54  | 80.51  |
| TGA + SubRecon   | 874.3  | 865.9  | 1373.8 | 1362.1 | 61.28  | 62.62  | 82.09  | 82.28  |
| TGAS + SubRecon  | 857.5  | 845.4  | 1362.0 | 1358.8 | 61.92  | 60.45  | 82.09  | 82.28  |
| Subject 2 TGAS (Siemens) | 843.5  | 838.1  | 1323.7 | 1328.1 | 62.71  | 62.13  | 81.18  | 80.51  |
| TGAS (GE)        | 847.7  | 849.1  | 1340.6 | 1352.0 | 62.03  | 60.56  | 80.62  | 79.88  |

Abbreviations: GM, gray matter; L, left; R, right; WM, white matter.

Figure 4 In vivo comparison between the conventional TGA and the proposed TGAS spatiotemporal encodings at $R = 1, 3, 6$, all with subspace reconstruction. The TGA version shows slight artifacts at $R = 3$ (yellow arrow) and strong artifacts at $R = 6$ (red arrow), while the proposed TGAS version maintains good image quality throughout.
from TGA show slight artifacts at $R = 3$ (indicated by yellow arrows with zoomed-in regions) and strong artifacts at $R = 6$ (red arrows). On the other hand, the results from TGAS remain artifact-free and retain high image quality, indicating the superiority of the TGAS acquisition scheme.

Figure 5 shows the simulation results from subspace reconstructions of synthesized TGA and TGAS data at 1-mm isotropic resolution, at $R = 3$ and $R = 6$. The T1 and T2 reference maps obtained from $R = 0.5$ TGA data are also shown for comparison. Similar to the in vivo results, results from TGA show slight artifacts at $R = 3$ and strong artifacts at $R = 6$, while results from TGAS remain artifact-free. With respect to the reference, the results from TGAS shows lower RMS error than those from TGA for both T1 and T2 maps at $R = 3$ and $R = 6$.

To better understand the spatiotemporal incoherence using TGA and TGAS acquisition schemes, multicoil MRF data were simulated using the signal from each of the coefficient maps obtained from a $R = 0.5$ in vivo acquisition. Afterward, each one out of five coefficient components was individually used as system input to calculate the reconstruction response without regularization at $R = 6$. The results are shown in Figure 6. It can be observed that the signal leakages in the TGA acquisition from an active coefficient to the other coefficients (red arrows) are more focused within the brain, whereas

**Figure 5** Simulation comparison between the conventional TGA and the proposed TGAS sampling schemes at $R = 3$ and $R = 6$. RMSE, RMS error
the leakages in the TGAS acquisition are primarily limited to areas outside the brain (yellow arrows). In the zoomed-in Figure 6B, the results from TGA show obvious aliasing artifacts (blue arrows) and corresponding leakages (green yellows). On the other hand, in the TGAS case, visible artifacts are not observed and the leakages are more noise-like.

Figure 7 shows the T1 and T2 maps of 1-mm and 0.66-mm TGAS-SP1-MRF using 100 T/m/s slew rate and 150 T/m/s slew rate. To compare the results of 1-mm resolution with identical acquisition time (1 min and 26 s), $R = 4$ and $R = 3$ were used for low and high slew rate, respectively. Indicated by yellow arrows, using higher slew rate and gradient amplitude could help improve quantitative mapping quality of MRF within the same acquisition time. Considering the SNR of the results, $R = 2$ (4 min and 19 s) was selected for the acquisition with 0.66-mm isotropic resolution. The increased resolution of the 0.66-mm acquisition is shown to better visualize subtle brain structures, indicated by red arrows (from left to right: claustrum, small sulci, and caudate nucleus shown on the T1 maps; and optic radiation, medial occipitotemporal gyrus, and cerebellum shown on the T2 maps), where the zoomed-in figures highlight details in specific regions.

**FIGURE 6** Reconstruction of synthesized MRF data at $R = 6$ from the individual coefficient simulation (e.g., the system input of the “Input1” case used to generate the synthesized MRF data is from a gold-standard coefficient map of the first coefficient component $c_1$) for TGA (A) and TGAS (C) acquisitions, respectively, as well as their zoomed-in maps in the red-box region (B, D). Note that all of the leakage terms (cross terms) are displayed at $\times 10$ scaling in all subfigures.
FIGURE 7  

$T_1$ and $T_2$ maps with zoomed-in regions of the 1-mm and 0.66-mm isotropic resolution data sets. Two different slew rates (100 T/m/s for top row and 150 T/m/s for middle row, respectively) were acquired. $R = 4$ was used for the low-slew-rate acquisition to achieve an identical acquisition time with the high-slew-rate version. Yellow arrows indicate the improvement by using higher slew rate for achieving better image quality within the same acquisition time. The higher resolution in the 0.66-mm data set can aid in better visualization of subtle brain structures, as indicated by the red arrows.

Figure 8 compares the results with and without MFI $B_0$ correction for 1-mm TGAS-SPI-MRF at $R = 3$. It is seen that in regions with strong $B_0$ inhomogeneity ($\Delta B_0$ is about 150 Hz, indicated by the red arrow in the top row), the $T_1$ and $T_2$ maps show substantial distortion. In regions with $\Delta B_0$ around 80 Hz (shown in the middle row), recognized...
FIGURE 9 $T_1$ and $T_2$ maps of 1 subject scanned on a Siemens 3T Prisma (top row) and a GE 3T Premier (middle row) using the proposed TGAS-SPI-MRF. The image was registered to a similar position using FSL MCFLIRT to calculate the difference map (bottom row).

blurring could be found; and in regions with $\Delta B_0$ around 30 Hz (shown in the bottom row) or less, neither distortion or aliasing could be recognized by comparing the $T_1$ and $T_2$ maps with and without $B_0$ correction. An MPRAGE acquisition (the sixth column of Figure 8) was used as reference to demonstrate the effectiveness of $B_0$ correction indicated by the zoomed-in comparison (the seventh column).

Supporting Information Figure S4 shows the results of $B_1^+$ corrections in MRF reconstruction. With the $B_1^+$ correction, the estimated $T_2$ maps in regions indicated by red arrows are more uniform compared with the standard MRF reconstruction without $B_1^+$ corrections.

Supporting Information Figure S5 shows the $T_1$ and $T_2$ maps of the phantom using the proposed method and gold-standard methods. The results demonstrate that the $T_1$ and $T_2$ values measured by the proposed method are consistent with those from the gold-standard methods.

Figure 9 shows the quantitative maps obtained from a single subject scanned at two different sites months apart, using 3T scanners from two different vendors (acquired at $R=3$ for 1-mm TGAS-SPI-MRF). In particular, the subject was scanned on both a Siemens 3T Prisma scanner (Martinos Center, Massachusetts General Hospital, Boston, MA, USA) and a GE 3T Premier scanner (Lucas Center, Stanford University, Stanford, CA, USA), where the results from these scans are shown in the first and second rows, respectively. The difference images obtained after co-registering (using FSL MCFLIRT) these parameter maps from the two scans are shown in the bottom row with $\times10$ scaling. Minimal differences in the GM and WM regions are observed across these scans. The average quantitative values of the bilateral WM and GM are given in Table 1 under Subject 2.

4 | DISCUSSION

In this study, a subspace reconstruction with optimized spatiotemporal trajectory termed TGAS-SPI-MRF was proposed to improve the image quality and accelerate the acquisition speed of SPI-based 3D-MRF. By using low-dimensional temporal subspace and LLR regularization, the reconstruction conditioning as well as the SNR are significantly improved, allowing for higher accelerations. An optimized shuffled 3D spiral-projection trajectory with improved spatiotemporal incoherency further improves the quantitative maps at high acceleration factors of $R=3$ and $R=6$, corresponding to acquisition times of about 2 min and 1 min for 1-mm isotropic resolution, respectively. The results were validated on both the GE Premier and the Siemens Prisma 3T scanners, indicating the robustness and reproducibility of the proposed method. $B_0$ correction using MFI was also incorporated into the subspace reconstruction to mitigate blurring in regions with strong $B_0$ inhomogeneity. Moreover, submillimeter quantitative mapping at 0.66-mm isotropic resolution was also achieved in 4.3 min and was shown to better delineate subtle brain structures. The ability of the
The imperfections from $B_0$ and $B_1^+$ inhomogeneities could also affect the performance of MRF mapping. $B_0$ correction based on the MFI method has been incorporated into the subspace reconstruction and shown to be effective at mitigating blurring caused by off-resonance effect. The imaging results show that even with highly segmented spirals, the image quality can still be degraded by severe $B_0$ inhomogeneity, as in the case when $\Delta B_0$ is higher than 150 Hz. Nonetheless, this can be corrected well using MFI, which will be important in applying TGAS-SPI-MRF to other body parts where $B_0$ inhomogeneity is significantly larger than in the brain. However, the approach requires an additional $B_0$ map acquisition, which took about 1 min in this work for whole brain imaging. Moreover, the results from this study and others$^{26,33}$ have demonstrated that $B_1^+$ correction can improve the quantitative accuracy of MRF,$^{26}$ especially for $T_2$ mapping (because the inversion pulse in an MRF sequence is typically adiabatic, the $T_1$ measurement is less affected than $T_2$, which relies more on the varying flip-angle excitation train). This will also require additional acquisition time. To address this issue, the use of rapid $B_0$ and $B_1^+$ mapping will be explored. PhysiCal is a promising approach that has been recently demonstrated to provide high-quality whole-brain mapping of coil sensitivity, $B_0$, and $B_1^+$ simultaneously in 11 s.$^{62}$ Another direction is to incorporate the mapping of these additional parameters directly into the MRF sequence design and reconstruction, as per the MR field fingerprinting approach.$^{63}$

The TGAS-SPI-MRF approach provides a basis for extremely efficient spatiotemporal sampling, not only for $T_1$ and $T_2$ mapping as demonstrated here, but can also be extended to other applications such as diffusion relaxometry and microstructure mapping (e.g., myelin-water), which we have started to explore.$^{64}$ It could also be adapted for other time-series imaging applications such as perfusion imaging with subspace or model-based reconstruction. Given the short TE and motion robustness features of SPI-based trajectory,$^{65}$ this method should be amendable to body imaging, especially for motion-sensitive parts.

The application of TGAS-SPI-MRF at ultrahigh field, such as at 7 T, would enable a significant increase in SNR to push the achievable spatial resolution to a finer scale and provide robust quantitative assessment of tissue parameters across cortical depths and fine-scale substructures.$^{66,67}$ In addition, because the encoding speed of spiral trajectory is primarily limited by slew rate, novel high-performance gradient systems$^{68-70}$ with higher slew rate and peripheral nerve stimulation threshold could bring benefits to this method as well. For example, the acquisition time of TGAS-SPI-MRF can be further reduced by 2–3 fold.

The subspace reconstruction and LLR regularization improve the reconstruction conditioning as well as SNR. To balance the tradeoff between SNR and image sharpness, the regularization parameters ($\lambda$) of $3 \times 10^{-5}$ and $5 \times 10^{-5}$ were selected for $R = 3$ and $R = 6$, respectively. Moreover, five subspace bases were used in this work to balance between achievable image quality and computational constraints. Both of these parameters ($\lambda$ and the subspace rank) were used consistently in all of the reconstructions shown in this study to achieve stable image quality. This demonstrates that properly tuned selection of these parameters can enable robust results with limited spatial blurring.

One limitation of the proposed method is the computation hardware requirement and the long reconstruction time. Although a coil compression method was used, the reconstruction still took 4–5 h on a Linux Server with about 400 GB of RAM and 1 TB of swap. To mitigate this issue, future work will focus on the development of an efficient reconstruction algorithm with a small memory footprint that can leverage distributed GPU computing. A promising approach in this direction is the use of stochastic optimization, which has recently been applied to a large spatiotemporal MRI reconstruction problem.$^{59}$ The use of deep learning techniques in place of the subspace reconstruction could be another potential solution, which could also help denoise the image to allow for higher-resolution imaging in a faster acquisition time.$^{24}$

Gradient hardware imperfections can cause image artifacts and impact achievable spatial resolution. One of the future works could be exploring the use of field probes$^{60}$ to achieve detailed characterization of eddy current and gradient trajectory imperfections. This information can then be incorporated into the reconstruction$^{61}$ to further improve the image quality and parameter quantitation. Such characterization should help open up the possibility to explore more varied spatiotemporal trajectory, to further increase spatiotemporal incoherence and enable higher accelerations.

The application of TGAS-SPI-MRF at ultrahigh field, such as at 7 T, would enable a significant increase in SNR to push the achievable spatial resolution to a finer scale and provide robust quantitative assessment of tissue parameters across cortical depths and fine-scale substructures.$^{66,67}$ In addition, because the encoding speed of spiral trajectory is primarily limited by slew rate, novel high-performance gradient systems$^{68-70}$ with higher slew rate and peripheral nerve stimulation threshold could bring benefits to this method as well. For example, the acquisition time of TGAS-SPI-MRF can be further reduced by 2–3 fold.
if the usable slew rate is increased to 500–800 T/m/s, which is achievable on those novel gradient systems. Therefore, the combined use of advanced gradient system and ultrahigh-field MRI for TGAS-SPI-MRF acquisition could offer an exciting possibility in rapid mesoscale quantitative imaging of the brain.

5 | CONCLUSIONS

A rapid, high-resolution, whole-brain MRF technique was developed using an optimized TGAS acquisition scheme and subspace reconstruction with LLR regularization. The proposed method can obtain high-quality whole-brain T1, T2, and PD maps with 1-mm isotropic resolution in 2 min at $R = 3$ with similar image quality as its $R = 1$ counterpart, or even 1 min at $R = 6$ with slight compromise on image sharpness. The 0.66-mm submillimeter quantitative mapping has also been achieved with an acquisition time of 4 min and 19 s. The MFI-based $B_0$ correction is also incorporated into the reconstruction to mitigate the blurring caused by off-resonance effect. In vivo experiments on healthy volunteers have been validated across both GE and Siemens platforms.

ACKNOWLEDGMENT

The authors thank Dr. Stefan Skare for his support with sequence programming based on the KS Foundation platform (https://ksfoundationepic.org/). This work was supported by: National Institutes of Health (NIH) research grants: R01EB020613, R01MH116173, R01EB019437, R01EB028797, R01EB016695, U01EB025162, P41EB030006, U01EB026996, and R03EB031175.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

**Table S1.** Matchup between results shown in figures and their corresponding scanners

Note: The Siemens Prisma 1 is located at Martinsos Center, Massachusetts General Hospital, Boston, MA, USA; Siemens Prisma 2 is located at the Center for Brain Imaging Science and Technology, Zhejiang University, Hangzhou, Zhejiang, China; and the GE Premier scanner is located at Lucas Center, Stanford University, Stanford, CA, USA.

**Table S2.** Sampling pattern for an acceleration factor of $R = 3$

Note: The interleaved undersampling is implemented on the acquisition group’s dimension. For example, $[1:3:48]$ groups are acquired at TR$_1$, $[3:3:48]$ groups at TR$_2$, $[2:3:48]$ groups at TR$_3$, and so on.

**Table S3.** Sampling pattern with acceleration factor $R = 6$

Note: The interleaved undersampling is implemented on the acquisition group’s dimension. For example, $[1:6:48]$ groups are acquired for the TR$_1$, $[6:6:48]$ groups for the TR$_2$, $[5:6:48]$ groups for TR$_3$, $[4:6:48]$ groups for TR$_4$, $[3:6:48]$ groups for TR$_5$, $[2:6:48]$ groups for TR$_6$, and so on.

**Figure S1.** $T_1$ and $T_2$ maps using the proposed tiny-golden-angle shuffling (TGAS)–spiral-projection imaging (SPI)–MR fingerprinting (MRF) at $R = 3$ with different numbers of subspace components from 3 to 7 using simulated data

**Figure S2.** $T_1$ and $T_2$ maps using the proposed TGAS-SPI-MRF at $R = 3$ with locally low rank (LLR) regularization parameter $\lambda$ from $10^{-6}$ to $10^{-4}$ using in vivo data

**Figure S3.** $T_1$ and $T_2$ maps using the proposed TGAS-SPI-MRF at $R = 6$ with LLR regularization parameter $\lambda$ from $10^{-6}$ to $10^{-4}$ using in vivo data

**Figure S4.** $T_1$ and $T_2$ maps using the proposed TGAS-SPI-MRF with and without $B_1^+$ correction as well as corresponding $B_1^+$ maps (right-most column). While $T_1$ maps keep consistent, the $B_1^+$ correction helps to improve the uniformity of $T_2$ maps in specific regions (red arrows)

**Figure S5.** (A) $T_1$ and $T_2$ maps of a phantom comprised of 12 tubes with different concentrations of agar and MnCl$_2$, obtained using the proposed method and gold-standard methods. (B) For each tube, the mean values and SDs of the $T_1$ and $T_2$ values from the proposed method are plotted against those from the gold-standard methods. The linear regressions and $R^2$ values are also labeled.
For the inversion-recovery spin echo (IR-SE), the protocol parameters are TR/TE = 6000/20 ms and eight different TIs = 100, 200, 400, 800, 1200, 1600, 2000, and 3200 ms. For the SE, TR was set to 6000 ms, and a total of seven different TEs = 25, 50, 75, 100, 125, 150, and 200 ms were acquired. For both the IR-SE and SE acquisitions, in-plane resolution is 1 × 1 mm² with a slice thickness of 4 mm. The TGAS-SPI-MRF results are reconstructed at R = 6 with 1-mm isotropic resolution.

How to cite this article: Cao X, Liao C, Iyer SS, et al. Optimized multi-axis spiral projection MR fingerprinting with subspace reconstruction for rapid whole-brain high-isotropic-resolution quantitative imaging. Magn Reson Med. 2022;88:133-150. doi: 10.1002/mrm.29194