High Spatial Resolution Compressed Sensing (HSPARSE) Functional MRI

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Purpose: To propose a novel compressed sensing (CS) high spatial resolution functional MRI (fMRI) method and demonstrate the advantages and limitations of using CS for high spatial resolution fMRI.

Methods: A randomly undersampled variable density spiral trajectory enabling an acceleration factor of 5.3 was designed with a balanced steady state free precession sequence to achieve high spatial resolution data acquisition. A modified k-t SPARSE method was then implemented and applied with a strategy to optimize regularization parameters for consistent, high quality CS reconstruction.

Results: The proposed method improves spatial resolution by sixfold with 12 to 47% contrast-to-noise ratio (CNR), 33 to 117% F-value improvement and maintains the same temporal resolution. It also achieves high sensitivity of 69 to 99% compared the original ground-truth, small false positive rate of less than 0.05 and low hemodynamic response function distortion across a wide range of CNRs. The proposed method is robust to physiological noise and enables detection of layer-specific activities in vivo, which cannot be resolved using the highest spatial resolution Nyquist acquisition.

Conclusion: The proposed method enables high spatial resolution fMRI that can resolve layer-specific brain activity and demonstrates the significant improvement that CS can bring to high spatial resolution fMRI. **Magn Reson Med 76:440–455, 2016.**
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Key words: compressed sensing; fMRI; high spatial resolution; optogenetic fMRI

INTRODUCTION

Functional MRI (fMRI) has been widely used in neuroscience research and for clinical applications (1–4) since it was developed (5–9). However, achieving high spatial resolution remains a significant challenge in fMRI because it comes at a price of decreased temporal resolution and/or lower contrast-to-noise ratio (CNR). Various methods have been developed to address this problem including development of high magnetic field systems (10–13), improvement of coil sensitivity (14), advancements in pulse sequences (15–17), usage of parallel imaging (18–22), and reconstruction with partial k-space (23–28). However, demands for even higher spatial resolution are common, with examples taken from cortical processing models (29,30) and hippocampal pattern separation (31–33).

Compressed sensing (CS) is an appealing but unexplored method that can be used to further improve the fMRI spatial resolution based on current technologies. By exploiting the significant redundancy in signals (34–37), CS has successfully reconstructed varieties of MRI images (38–48) at a much higher spatiotemporal resolution. CS applications in fMRI have also led to improvements in sensitivity (49,50), temporal resolution (51–57) and robustness (58). There are many advantages of applying CS to high spatial resolution fMRI. Compared with other partial k-space techniques, such as the keyhole reconstruction (25–27), CS allows higher image resolution and contrast (40). CS can also be easily implemented within the limit of available scanner hardware. Importantly, CS can be combined with many other advanced high spatial resolution techniques to further improve the spatial resolution. However, two questions remain: First, how can CS be effectively combined with these techniques under the constraint of CS sampling theory? Second, what are the advantages and drawbacks of using CS for high spatial resolution fMRI?

Here, we demonstrate a novel High SPAtial Resolution compressed SEnsing (HSPARSE) fMRI method and a systematic evaluation of the advantages and limitations of CS high spatial resolution fMRI. We maximized the effective fMRI spatial resolution for the HSPARSE method from multiple aspects: We first optimized the

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contrast with a balanced steady state free precession (b-SSFP) sequence, which enables T_2 microvascular sensitive imaging (59,60) with low spatial distortion (61–64). We then optimized the data acquisition with a randomly undersampled variable density spiral (VDS) (65–67), which enables six-fold spatial resolution improvement with an acceleration factor of 5.3. This ratio is 32% greater than that reported in previous CS fMRI studies with a single coil (49,51). Finally, we reconstructed the dataset with a modified kt-SPARSE method (74).

We then thoroughly evaluated the performance and reliability of the HSPARSE method. Because the CS reconstruction is substantially dependent on the regularization parameters, we first investigated roles of the spatial and temporal regularizations. We then studied the sensitivity, false positive rate, and temporal distortion of the HSPARSE method, and evaluated its performance with physiological noise. We also systematically evaluated the capability of the HSPARSE in detecting functional differences between neighboring active regions (e.g., laminar specificity). Finally, we tested the HSPARSE method in vivo with optogenetic fMRI (ofMRI) (68–71) experiments.

METHODS

Randomly Undersampled, Variable-Density Spiral, b-SSFP Data Acquisition

We designed a randomized undersampling VDS b-SSFP sequence for the HSPARSE fMRI method. Compared with conventional gradient-recalled-echo (GRE) sequence, the b-SSFP sequence provides lower spatial distortion (61–64) and better activity localization with T_2 microvascular sensitivity (59,60). The VDS trajectory also provides high sampling efficiency (65,66) and robustness against motion, off-resonance, and gradient artifacts (67). In addition, using spiral trajectory for CS also results in the highest CNR compared with most CS undersampling trajectories available (72).

A high spatial resolution Nyquist acquisition (Fig. 1b) requires longer acquisition time and results in lower temporal resolution compared with the low spatial resolution Nyquist acquisition (Fig. 1a) with the same field of view (FOV). To enable high spatial resolution without sacrificing the temporal resolution, we first accelerated the sampling by 1.77 times with a three-dimensional (3D) VDS trajectory consisting of 32 k_z locations and 30 interleaves at each k_z location (Figs. 1c,e). Then, 320 interleaves were randomly selected from the 3D VDS trajectory (Figs. 1d,f), which further accelerated the sampling by another factor of 3 and resulted in an overall acceleration factor of 5.3. To obtain more interleaves at the center k-space, the number of interleaves at each k_z slice was designed to follow a Laplacian distribution (mean $\mu = 16$, scaling $b = 11$). The undersampling patterns were also randomized across temporal frames to exploit the fMRI temporal sparsity. However, the total number of interleaves was identical across temporal frames to achieve constant temporal resolution. This design not only enables rapid data acquisition but also successfully achieves the incoherent sampling for effective CS reconstruction.

The HSPARSE passband b-SSFP acquisition scheme was implemented on a 7 Tesla (T) Bruker scanner with a single transmit and receive surface coil using TE = 2 ms, TR = 9.375 ms, and flip angle = 30°. With a 35 × 35 × 16 mm FOV, the sequence was designed to obtain spatial resolution of 0.21 × 0.21 × 0.5 mm and 167 × 167 × 32 matrix size at a 3 s temporal resolution. A fully sampled b-SSFP sequence was also designed with the highest spatial resolution achievable (0.5 × 0.5 × 0.5 mm resolution, 70 × 70 × 32 matrix size) while maintaining the same FOV and temporal resolution. To enable full brain coverage without b-SSFP banding at either resolution, we performed two acquisitions with 0° and 180° phase-cycling angles. The two phase-cycled images were then combined by maximum intensity projection (61).

Accelerated CS fMRI Reconstruction

Similar to CS MRI, spatial sparsity of each fMRI frame can be used to reconstruct an undersampled fMRI dataset (49,55,56):

$$\underset{m}{\operatorname{argmin}} f(m) = \frac{1}{2}||Fm - y||_2^2 + \lambda||\Psi_s m||_1 \quad [1]$$

where F represents the nonuniform Fast Fourier transform (NUFFT) (73) in the spatial domain, m is the 4D image under reconstruction, y is the randomly undersampled 4D kt-space data, λ is the regularization coefficient, and Ψ_s represents a spatial sparsifying transform such as the discrete cosine transform (DCT) or discrete wavelet transform (DWT). As shown by Holland et al (49), the performance of this algorithm is largely dependent on the trajectory design and the algorithm may fail at a large undersampling ratio. Therefore, an alternative constraint using temporal redundancy (39,43,51) has been developed:

$$\underset{m}{\operatorname{argmin}} f(m) = \frac{1}{2}||Fm - y||_2^2 + \lambda||\Psi_t m||_1 \quad [2]$$

where Ψ_t is the sparsifying transform along the temporal dimension. As Zong et al. suggested (51), low complexity transforms such as the Fourier transform and DCT can be applied in block-design fMRI, and more complicated transforms such as the Karhunen Loeve Transform (KLT) and DWT is recommended in complex designs such as event-related fMRI.

In our implementation, we use a modified kt-SPARSE (74) technique where both the temporal and spatial redundancies are exploited:

$$\underset{m}{\operatorname{argmin}} f(m) = \frac{1}{2}||Fm - y||_2^2 + \lambda_1||\Psi_t m||_1 + \lambda_2||\Psi_s m||_1 \quad [3]$$

This cost function allows an acceleration factor and reconstruction quality no worse than methods using only spatial or temporal sparsity constraints because its solution set contains optimal solutions of both the spatial and temporal regularization methods. Compared with the cost function that uses the 4D sparsifying transform, this method also gives higher image contrast, lower noise level, and lower false positive rate (Fig. S1).

We chose DCT for both the spatial and temporal sparsifying transform in our implementation. It has previously been shown that the FT can serve as an effective transform for block-designed CS fMRI (51). Because DCT has a higher

FIG. 1. A randomized, variable-density, undersampled spiral acquisition scheme was designed for the HSPARSE fMRI. **a**: A low spatial resolution Nyquist trajectory only covers a small range of k-space. **b**: To achieve higher spatial resolution without introducing aliasing artifacts or changing the field of view, the k-space coverage can be increased with more interleaves. This inevitably increases the data acquisition time and reduces the temporal resolution. **c,d**: To overcome this problem, a variable density spiral (VDS) trajectory was designed and interleaves were randomly sampled while keeping the total number of interleaves and scan time the same as the low spatial resolution Nyquist scan. **e,f**: For 3D acquisition, the HSPARSE fMRI method randomly selects 320 interleaves from a stack of VDS trajectory consisting 32 k_z locations and 30 interleaves. More interleaves are sampled near the k-space center and the total number of interleaves in each k_z location follows a Laplacian distribution. The sampling pattern was also chosen to be random across temporal frames to exploit the temporal sparsity. However, the total number of interleaves for each time frame was designed to be constant (320 interleaves) to maintain constant temporal resolution over time. Compared with a 3D Nyquist sampled trajectory that has the same spatial resolution, the proposed trajectory achieves a high acceleration factor of 5.3.

compression ratio than the FT (75), therefore, DCT can enable better reconstruction for the block-designed fMRI (35). In addition, DCT also has lower complexity than the data-driven KLT and faster speed than the multilevel decomposition based DWT on a parallel platform (76). To systematically optimize the reconstruction and investigate hundreds of reconstructions under a wide range of regularization parameters, DCT is chosen to facilitate this process.

We applied a fast implementation of the gradient descent method (77) (Figure S2 and Table S1) to solve Eq. [3]. We computed all key processing on a graphics processing unit (GPU), which reduced the reconstruction time from 18 h to 30 min and achieved 34-fold acceleration. Implementation details can be found in the Supporting Information, which is available online.

Optimization of Regularization Parameters

High-speed reconstruction achieved by our GPU parallelization enabled exhaustive testing of the HSPARSE reconstruction across different regularization parameters and phantoms to investigate roles of the spatiotemporal regularizations and to identify optimal parameters for various imaging conditions. Three distinct phantoms (denoted A1, B1, and C1) at a normal (30 dB) and low (25 dB) signal-to-noise ratio (SNR) (Fig. S3a) were designed. The A1 phantom was designed to simulate an in vivo experiment, while B1 and C1 were designed to test across different base images and activation patterns. The base image of the B1 phantom was generated from a rat MRI template (78). Six-cycle 20-s on–40-s off canonical statistical parametric map (SPM) hemodynamic response function (HRF) (79) were added to phantoms in

this and following simulations. The peak HRF amplitudes were set to be 10% modulation of the baseline at the activation pattern center, and decreased with distance following a Gaussian function. After a coarse parameter search to find potential optimal parameter range, the following range of parameters were investigated: λ_1 from 1e-2 to 5e-5 with 8 steps and λ_2 from 5e-3 to 1e-9 with 14 steps. Because values of the λ_1 and λ_2 are dependent on the value of the sampled k-space, we normalized the k-space of each dataset by its corresponding maximum absolute values ($||k_{sig}||_\infty = 1$) to enable comparison of the λ_1 and λ_2 among different reconstructions.

We analyzed the data with five-gamma basis set general linear model (GLM) using the SPM (79). F-test was then conducted and active voxels were recognized as those having an F-value greater than 4.42 ($P < 0.001$). A set of regularization parameters was considered to be in the optimal range if its corresponding CNR, active volume within the designed active region, and mean F-value were greater than that of the ground-truth, and its normalized root mean squared error (NRMSE) between the ground-truth and the HSPARSE reconstructed images was less than 105% of the minimum NRMSE found within the search range. The peak HRF amplitude is calculated as the maximum value of the GLM regressed HRF. And the CNR was estimated as the peak HRF amplitude divided by the standard deviation of the residual time-series.

Evaluation of fMRI Signal Sensitivity and False Positive Rate

To quantitatively evaluate the sensitivity and false positive rate (FPR) of the HSPARSE fMRI method in 3D space, three additional 30 dB phantoms were designed (A2, B2, and C2) in which activity was confined to a single imaging slice with sharp contrast boundaries (Fig. S3b). This single-slice pattern was designed to evaluate the sensitivity and FPR under the most difficult conditions, and we expect higher sensitivity and lower FPR in real application. Four different peak HRF amplitudes (10, 8, 6, and 4%, corresponding to CNR 2.55, 2.05, 1.58, and 1.23) were tested. As shown in Figure 3a, the sensitivity is quantified as the ratio between the number of true positive voxels and the number of true positive plus false negative voxels. The FPR is evaluated as the ratio between the number of false positive voxels and the number of false positive plus true negative voxels in the first to fifth pixel perimeter layer in 3D (Fig. 3b).

Evaluation of HRF Temporal Characteristics

Because temporal redundancy is used to reconstruct images in CS fMRI, reconstruction may introduce a certain amount of temporal distortion into the resulting fMRI signal. Therefore, we evaluated the temporal characteristics of the HSPARSE fMRI signal to determine the nature of the resulting distortion. We designed three phantoms (A3, B3, and C3) with SNR of 30 dB and peak HRF amplitudes of 10, 8, 6 and 4% (Fig. S3c). Each phantom was reconstructed 5 times with independent identical Gaussian distributed noise using previously identified optimal parameters ($\lambda_1 = 5e\text{-}3$ and $\lambda_2 = 1e\text{-}4$).

Evaluation of Robustness to Physiological Noise

Physiological noise in fMRI can lead to decreased sensitivity, increased FPR, and temporal distortion (80), which could be more severe in CS fMRI due to the undersampling. Therefore, we evaluated the robustness of the HSPARSE fMRI with fully sampled in vivo datasets containing physiological noise. However, because a fully sampled high spatial resolution fMRI dataset cannot be acquired without reducing the temporal resolution (due to the fundamental hardware limitations), we acquired the highest spatial resolution fully sampled datasets instead. Three fully sampled in vivo dentate gryus stimulation datasets were acquired. This data was then undersampled by 5.3 times and reconstructed with the HSPARSE method for comparison.

Systematic Evaluation of Spatial Resolution

After separately evaluating spatial and temporal distortions, we next systematically evaluated the capability of the HSPARSE method to detect functional differences between neighboring active regions, such as the laminar specific responses (29,30). Three 35 dB phantoms were designed with increasing difficulty in resolving activations. First, three regions with clear boundaries consisting of signals with distinct peak HRF amplitudes (15, 10, and 5%) (Fig. 6a) or latencies (Fig. 6d) were created. Second, patterns with interleaved layers consisting of signals with different peak HRF amplitudes (12 and 4%, Figure 7a) or latencies (Fig. 7d) were designed. Spatial distortion in the first one may only result in ambiguous region boundary whereas spatial distortion in the second phantom can result in complete loss of layers. Third, we further explored the spatial resolution limit of the HSPARSE fMRI using an activity pattern containing different widths of interleaved signals going down to the single pixel (Figs. 7g,h). These activity patterns were added to six continuous slices for each phantom.

In Vivo Evaluation with Optogenetic Dentate Gyrus Stimulation

Finally, we compared the spatial resolution, sensitivity, and temporal distortion of the HSPARSE method with the highest spatial resolution Nyquist acquisition in vivo by selectively stimulating dentate gyrus excitatory neurons in three rats using optogenetics. We performed optogenetic fMRI (68–71) because it allows precise stimulation of target brain regions, which can result in highly localized activations for evaluating improvements in spatial resolution. The dentate gyrus was targeted (Fig. 8a) due to its unique layered shape (Fig. 8b). It also forms the input structure of the hippocampus and its unique unidirectional nature provides a predictable pattern of activity in hippocampus and downstream structures (81–84), which can help evaluate the spatial resolution of different fMRI methods. More information regarding our surgery protocols can be found in our previous publications (69,71). We acquired the data at 3 s temporal resolution and each dataset included 10 baseline frames and 120 frames of 6-cycle 20s-on-40s-off optical stimulation. After

reconstruction, subject motion was corrected by a GPU based motion correction method (85).

We calculated the peak HRF amplitude for voxels that has an F-value larger than 4.42 ($P < 0.001$) and overlaid the peak HRF amplitude map onto a high-resolution atlas MRI image (86) to enable precise anatomical localization of the activity. Because an equivalent fully sampled high spatial resolution fMRI dataset could not be acquired due to fundamental limitations, the HSPARSE fMRI method was compared with the achievable highest spatial resolution Nyquist image with the same FOV and temporal resolution (NAcq). The SNR of the Nyquist and the HSPARSE images were approximately 30 dB and 25 dB, respectively. Therefore, three HSPARSE datasets were averaged to obtain a high-resolution image with the same SNR as the Nyquist image ($25 + 20\log_{10}\sqrt{3} \approx 30$).

RESULTS

Optimal Regularization Parameters Are Identified

We first assessed the roles of the regularization parameters on the 30 dB A1 phantom reconstruction. As shown in Figure 2a, the reconstructed image quality and fMRI signal depends significantly on the choice of the temporal and spatial regularization parameters. As shown in Figure 2b, although the reconstructed peak HRF amplitude generally decreased for all tested regularization parameters, we found parameter ranges that resulted in higher CNR, mean F-value, and larger active volume within the original designed region than the ground-truth phantom. When these ranges were overlaid, we identified a parameter range of λ_1 between 1e-2 and 5e-3 and λ_2 between 1e-4 and 1e-9 (blue area in Figure 2b lower right) that maximizes the CNR, mean F-value, and the active volume within the original designed active region with low NRMSE. We therefore concluded that this range of parameters is optimal for this phantom.

We performed the same tests at higher noise levels (25 dB) and with different base images (B1 phantom) and activation patterns (C1 phantom) (Fig. S3a). We identified a common range (dark blue range in Fig. 2c) where all the optimal ranges for different phantoms overlapped. For example, for $\lambda_1 = 5e\text{-}3$ and $\lambda_2 = 1e\text{-}4$, which is within this range, CNR improves by 12 to 47%, mean F-value by 33 to 117%, active volume by 36 to 178%, and the NRMSE is less than 0.24. (Figs. 2d–h). The point spread function FWHM also decreased from 0.70 mm for the highest spatial resolution Nyquist image to 0.32 mm (Fig. 2i) for the HSPARSE image with the optimal regularization parameters. Although the average peak HRF amplitude is reduced, we later show that the HRF shape and relative amplitude is maintained after reconstruction.

High Sensitivity and Low False Positive Rate

We evaluated the sensitivity (Fig. 3a) and FPR (Fig. 3b) using the 30 dB A2, B2 and C2 phantoms (Fig. S3b) at four different peak HRF amplitudes (10–4%, corresponding to CNR of 2.55–1.23). Example reconstructions of the three phantoms with 10% peak HRF amplitude are shown in Figure 3c. We find the activities are localized to the original volume of activation and the false positive signals are limited. As shown in Figure 3d, we find the sensitivities of the HSPARSE reconstructed datasets are 69 to 99% of the original datasets on average. We also find the FPRs are small on all perimeter layers and across all tested peak HRF amplitudes, e.g., the FPRs on the 1-pixel perimeter layer (FPR_1) are less than 0.051 and the FPRs on the 2-pixel perimeter layer (FPR_2) are less than 0.01. Because the single-slice activity patterns are designed for testing under the most difficult conditions, higher sensitivity and lower FPR is expected in real applications. Taken together, these data indicate that the HSPARSE reconstruction yields high sensitivity than the ground-truth image with a low FPR.

Low HRF Distortion

We investigated the temporal distortion of the HSPARSE fMRI method with a range of HRFs (peak amplitudes of 10–4%) typically observed in in vivo experiments (Fig. 4a). As shown in Figures 4a,b, although the HRF amplitude is reduced, the HRF shape is maintained with the HSPARSE reconstruction. The HSPARSE reconstructed HRF amplitudes exhibit strong linear correlation with the original HRF amplitudes ($R^2 = 0.98$, Figure 4c), suggesting that the HSPARSE reconstruction linearly scales the original HRF with little distortion to the HRF shape. HRF normalization also confirms that the temporal dynamics are well preserved following the HSPARSE reconstruction, i.e. mean differences between normalized HRFs are less than 0.016 and limits of agreement ($1.96 \times$ standard deviation) are less than 0.08 (Fig. 4d) across all tested peak HRF amplitudes.

HRF characteristics such as the duration of activation and time-to-peak were also compared. The activity duration of the A3 phantom is not significantly different between the original and the HSPARSE reconstructed images for any of the four tested HRF amplitudes (Figure 4e, Wilcoxon ranksum test). For time-to-peak, the maximum mean difference between CS and the original signal of the A3 phantom is 2.4 s (Fig. 4f). Because this time-to-peak difference is less than 3 s, which is the temporal resolution of the data acquisition, the differences could simply be a result of having a limited temporal resolution. We also observed similar results for the B3 and C3 phantoms.

Robust against Physiological Noise

Here, we compared the fully sampled datasets with real physiological noise with their corresponding 5.3 times undersampled HSPARSE images. As shown in Figure 5a, we observed consistent increases in CNR, mean F-value, and active volume following the HSPARSE reconstructions. The NRMSEs between the HSPARSE reconstructed and the fully sampled in vivo datasets are lower than 0.081 across subjects. The HSPARSE reconstructed datasets detect most of the activity in the fully sampled datasets (Fig. 5b). The common active voxels in both images are 90% to 93% of the active voxels in the fully sampled images (Fig. 5c). Additional active voxels are also observed in the HSPARSE reconstructed datasets. Because the ground-truth active region is not available for the in vivo datasets, these additional active voxels

FIG. 2. Optimal range of CS regularization parameters were identified based on quantitative assessments of the reconstructed images. **a**: Example reconstructed images of the A1 phantom (30 dB) with different regularization parameters. Voxels are considered to be active if they exhibit an F-value greater than 4.42 ($P < 0.001$). Lower left panel shows the original ground-truth image. **b**: An optimal regularization parameter range is defined as the region that achieves higher CNR and maximum correlation coefficient, larger active volume within the designed active region compared with the original ground-truth image, and NRMSE of less than 105% of the minimum NRMSE found within the search range. We identified a range of regularization parameters that yields high reconstruction quality (lower right panel, blue area) for the 30 dB A1 phantom. The symbols "^" and "v" in each panel indicate the maximum and minimum values in the corresponding test, respectively. "N/A" indicates an area in which CNR, maximum correlation coefficient, and peak HRF amplitude cannot be computed due to limited activation. 1.02v, 1.05v, and 1.15v indicate the contour lines of 1.02, 1.05, and 1.15 times the minimum NRMSE value. **c**: The optimal ranges for 6 phantoms with different base images, activation patterns and SNRs are overlaid, where we find a set of regularization parameters that provide optimal reconstruction quality for all phantoms tested. **d–h**: With a set of parameters ($\lambda_1 = 5e\text{-}3$ and $\lambda_2 = 1e\text{-}4$) selected from the optimal range, CNR, the active volume within the original ground truth active region, and the maximum correlation coefficient of the reconstructed image are higher than the original phantom with noise, and the NRMSE is less than 0.24 across all phantoms. Although the HRF amplitudes decrease after the CS fMRI reconstruction, we show that the CS fMRI maintains the relative amplitudes and shapes of HRFs in Figure 4. **i**: FWHM of the point spread function is 0.70 mm with the highest spatial resolution Nyquist acquisition while it reduces to 0.32 mm for HSPARSE reconstructed images with optimal regularization parameters. The error bar shows the standard deviation of the CS point spread function across temporal frames.

FIG. 3. HSPARSE fMRI method achieves high signal sensitivity and low false positive rate across a wide range of CNRs and phantoms. **a**: The fMRI signal sensitivity is defined as the number of true positive (TP) voxels over the number of true positive and false negative (FN) voxels. **b**: The false positive rate is defined as the number of false positive (FP) voxels over the number of false positive and true negative (TN) voxels within the 1- to 5-pixel perimeter layers of the designed activation volume (FPR_1 to FPR_5). **c**: Example reconstructions of the A2-C2 phantoms with 10% peak HRF amplitude show that the reconstructed fMRI signals are mainly confined to the designed active area with limited false positive activations outside. **d,e**: Sensitivity (d) and FPR (e) tests were performed on the A2-C2 phantoms with four different peak HRF amplitude of 10–4% (corresponding to CNR of 2.55–1.23). We find the mean sensitivities of the HSPARSE reconstructed datasets are 69 to 99% of the original sensitivities with noise for all tested peak HRF amplitudes. The mean false positive rates are less than 0.051 on the 1-pixel perimeter layer and less than 0.01 on the two-pixel perimeter layer. Error bar represents standard error across the A2-C2 phantoms. Taken together, these data show that the optimal HSPARSE reconstruction results in high sensitivity and low FPR.

could either be false positive detections or a result of the improved CNR. Importantly, these signals are within the one-voxel perimeter layer of the original active region across all subjects, indicating the HSPARSE activity localization is consistent with the fully sampled image. The HSPARSE reconstructed HRFs are linear to the fully sampled HRFs and the correlation coefficients are larger than 0.98 (Fig. 5d). Measures of the activation duration

FIG. 4. HSPARSE reconstruction using optimal regularization parameters maintains HRF temporal characteristics over a range of physiologically relevant HRF amplitudes. **a**: Representative images of the reconstructed A3 phantom are shown with original HRF amplitudes of 4, 6, 8, and 10%. All phantoms were reconstructed 5 times with independent identical Gaussian distributed noise using regularization parameters ($\lambda_1 = 5e\text{-}3$ and $\lambda_1 = 1e\text{-}4$) within the optimal range. **b**: Although the HSPARSE reconstructed HRFs exhibit lower amplitudes than the original HRFs for all tested amplitudes, the HRF shapes are similar after amplitude normalization (inset on upper right). Error bars represent standard deviation across 5 reconstructions. **c**: The correlation analysis indicates that the HSPARSE reconstructed HRF time courses have strong linear correlation to the original HRFs (slope = 0.52, $R^2 = 0.98$). **d**: After the amplitude normalization of all HRFs, the maximum mean difference between the HSPARSE reconstructed and the original HRFs is less than 0.016 and the limits of agreement ($\pm 1.96 \times$standard deviation) are less than 0.080. **e,f**: Similarly, the durations of the HSPARSE reconstructed HRFs are not significantly different from the original HRFs ($P > 0.22$, Wilcoxon ranksum test), and maximum time-to-peak differences (2.40 s) is smaller than the 3 s temporal resolution of the fMRI acquisition. Similar results are seen in B3 and C3 phantoms.

and time-to-peak also confirm that the HRFs from the fully sampled images and the HSPARSE reconstruction are close (Table 1).

Resolves High Spatial Resolution Functional Contrast

We systematically evaluated the HSPARSE method to determine whether it can detect differences between

FIG. 5. HSPARSE fMRI method is robust against real physiological noise. **a**: The HSPARSE fMRI also improves the CNR, maximum correlation coefficient, and active volume compared with their corresponding fully sampled datasets in the presence of real physiological noise. The NRMSE values are less than 0.081 across all subjects. Error bars represent the standard error across voxels of the active area for CNR and maximum correlation coefficient. **b,c**: The images reconstructed with HSPARSE detect the majority of the activity and the active voxels shared between the HSPARSE reconstructions and the fully sampled images consist 90.3 to 93.0% of active voxels from the fully sampled images. Because the ground-truth active region is not available for the in vivo experiment, additional active voxels only detected with HSPARSE reconstruction could either be false positive signal or a result of improved sensitivity due to CNR increase. However, active voxels only detected with HSPARSE reconstruction is limited within the 1-pixel perimeter layers of the active volume detected with the fully sampled dataset. **d**: HRF amplitude reduction from HSPARSE reconstruction has a scaling factor ranging from 0.40 to 0.48. Importantly, the HRFs from the fully sampled datasets and the HSPARSE reconstructions have a strong linear correlation with a minimum correlation coefficient (R^2) of 0.98, demonstrating that HSPARSE reconstruction maintains the temporal characteristics of the fully sampled HRFs.

Table 1
Comparison of Temporal HRF Characteristics between the Original Fully Sampled and HSPARSE Images in the Presence of Physiological Noise

	Time to peak (s)		Duration (s)	
	Orig.	HSPARSE	Orig.	HSPARSE
Subject 1	24	24	20.53	21.94
Subject 2	21	24	23.42	21.75
Subject 3	21	24	33.80	33.61

For all three subjects, the HRF durations are similar and the maximum duration difference is 1.67 s. The first subjects give the same time-to-peak. The rest two subject shows an increase in time-to-peak for the HSPARSE reconstructed image, but the difference is smaller than the 3 s temporal resolution of the acquisition.

functionally distinct yet spatially adjacent regions. The first test was performed on a three-layer phantom with distinct peak HRF amplitudes of 15, 10, and 5% (Fig. 6a). With the highest spatial resolution Nyquist acquisition, the borders between the three layers become obscured (Fig. 6b). However, using the HSPARSE method, the three layers are well preserved with clear boundaries among layers. The HSPARSE raw HRFs and their corresponding first two principal component analysis coefficients also show better separation than those of the Nyquist image (Fig. 6c). We conducted a similar test using the same phantom containing three HRFs with distinct latency (Fig. 6d). Similarly, the borders among three layers become obscured with the Nyquist acquisition (Fig. 6e), while the three layers can be accurately resolved by the HSPARSE method (Fig. 6f).

We performed the second test on a phantom with a pattern containing 6 interleaved layers of high and low (12 and 4%) amplitude activity (Fig. 7a). With the Nyquist acquisition, the layer specificity cannot be resolved (Fig. 7b). However, the HSPARSE fMRI can accurately reconstruct the 6 layers of activation with clear boundaries (Fig. 7c). Similar results were also achieved with two HRFs with distinct latency (Figs. 7d,e).

Finally, we investigated the resolution limit of the HSPARSE fMRI method using an interleaved pattern phantom with minimum layer thickness ranging from 1- to 4-pixels. As shown in Figure 7g, with different peak amplitudes across layers, the HSPARSE method successfully resolves layers down to 1-pixel (0.21 mm) thickness while the Nyquist acquisition can only distinguish the differences down to 3-pixel (0.63 mm). Similarly, the HSPARSE method also shows high spatial resolution down to 1-pixel thickness with layers containing distinct latency but the Nyquist acquisition fails when layer thickness below 3 pixels (Fig. 7h).

With this test, we observed some sinusoidal variations in the HSPARSE reconstructed HRFs (Figures 6c, 7c, and S4c,d, bottom left panel). This is likely due to the DCT regularization and can be reduced by using higher compression ratio transforms such as KLT and DWT. However, importantly, we find that key HRF characteristics and their differences among layers are well preserved.

Resolves In Vivo Layer-Specific Activation Localized to the Dentate Gyrus

We further tested the optimized HSPARSE fMRI method in vivo, using optogenetic stimulation of the rat dentate gyrus. The dentate gyrus was targeted (Fig. 8a) due to its well-defined layered structure (Fig. 8b) and its function as a gate of the unidirectional hippocampal circuit, which can provide predictable activity patterns in hippocampus and downstream structures (81–84). Histological examination confirmed that Channelrhodopsin2-EYFP expression was localized to the dentate gyrus (Fig. 8c), indicating successful targeting of this region for light stimulation. For fMRI, both the Nyquist and HSPARSE reconstructed images reveal activity in the dentate gyrus. However, in both the single and the three times averaged

FIG. 6. HSPARSE fMRI method resolves spatially adjacent yet functionally distinct regions. **a,d**: A rat brain phantom with three layers of distinct peak HRF amplitude/latency in the cortex was designed. HRFs of the three layers and their corresponding principal component decompositions demonstrate clear separation of the three layers. Thicker lines in the HRF plot represent the mean HRF of each layer. **b,e**: Highest spatial resolution Nyquist acquisition results in activity with obscured boundaries between layers. **c,f**: HSPARSE reconstruction correctly identifies the spatial location where the amplitude/time-to-peak transition occurs.

FIG. 7. Resolution limit of the HSPARSE fMRI is identified. **a,d**: A phantom that that is challenging to reconstruct with low spatial resolution was designed with an interleaved pattern consisting of distinct peak HRF amplitude/latency features. **b,e**: The highest spatial resolution Nyquist acquisition completely fails to separate the six interleaved layers. **c,f**: In contrast, the HSPARSE reconstruction successfully resolves the peak HRF amplitude and latency differences for all six layers. **g,h**: To identify the resolution limit of the HSPARSE method, a phantom with interleaved activation layers of variable thickness (4∼1 pixels or 0.84∼0.21 mm) was designed. Layers with distinct peak HRF amplitude/latency can be distinguished down to 3-pixels (0.62 mm) using the Nyquist acquisition and down to a single pixel (0.21 mm) using the HSPARSE method.

HSPARSE images, high peak HRF amplitude (e.g., top 40%) activities were found to be localized precisely following the geometry of the molecular layer in the dentate gyrus while there is no obvious pattern observed in the Nyquist image (Fig. 8d). Nyquist image also shows activity in adjacent CA1. As reported by Angenstein et al, dentate gyrus activity may be localized or, when activity propagates beyond the dentate gyrus, the entire hippocampal circuit is activated together with downstream regions such as the ipsilateral entorhinal cortex and subiculum (82). Because no activity is detected in these downstream regions, it is likely that the adjacent CA1 activity detected by the Nyquist scan reflects a partial volume effect due to low spatial resolution. We observed similar results when the experiments were repeated in two other subjects, indicating the consistency of the proposed HSPARSE method's precise spatial localization ability (Fig. S5).

Finally, we found that HRFs of the single and the three times averaged HSPARSE images and the Nyquist images have strong linear correlation for all three subjects (Figs. 8e,f). This indicates that the temporal characteristics are consistent between the Nyquist and the HSPARSE images. We also found that all time-to-peak differences between the HSPARSE and the Nyquist images are within the 3 s temporal resolution (Table 2). While the durations of activity in two subjects are similar for the HSPARSE and the Nyquist methods on average, the duration is different for one of the subjects. This may be due to biological variation in this subject because the Nyquist and the HSPARSE images were acquired in different imaging sessions. In conclusion, these results demonstrate that HSPARSE can improve localization and identify layer-specific activities in vivo.

DISCUSSION AND CONCLUSIONS

Our study demonstrates that the HSPARSE fMRI can provide approximately six-fold improvement in spatial resolution and resolve layer-specific activations in vivo. The HSPARSE fMRI is shown to support an acceleration factor of 5.3, which is 32% higher than the previously reported CS fMRI studies using a single coil setup (49,51). With the HSPARSE fMRI, we achieve improved CNR, high sensitivity, low FPR, and low HRF distortion, without compromising temporal resolution. The HSPARSE fMRI also shows high robustness against physiological noise, and is capable of resolving layer specific activations. Finally, in vivo experiments reveal that the HSPARSE fMRI enables precise localization of dentate gyrus activity that could not be resolved with the highest spatial resolution Nyquist acquisition.

Optimal Regularization Parameters for HSPARSE fMRI

This is the first comprehensive study on the role of regularization parameters in fMRI reconstruction and their

FIG. 8. HSPARSE fMRI method resolves in vivo layer-specific activity evoked by optogenetic stimulation of dentate gyrus. **a**: Schematic showing optogenetic targeting of the dentate gyrus. **b**: Dentate gyrus has a unique horn shape, with its coronal and axial slices showing "O" and "U" shaped profiles, respectively. **c**: Histological examination verified that the ChR2-EYFP expression is localized to the dentate gyrus region. **d**: The Nyquist acquisition fails to accurately localize dentate gyrus activity and activity occurs on both the dentate gyrus and the CA1. In contrast, both the original and the three times averaged HSPARSE fMRI shows activity localized to the dentate gryus, with the voxels having high peak HRF amplitude precisely following the geometry of the structure's molecular layer. White triangles in the top row indicate the approximate site of stimulation. Active voxels were identified as those having an F-value greater than 4.42 ($P < 0.001$). The active voxels' peak HRF amplitudes were then calculated and overlaid onto a high-resolution MRI atlas, with a threshold at the median plus 1.5 times the standard deviation of all peak HRF amplitudes for clear visualization with good dynamic range. **e,f**: As was seen with the simulations, the HSPARSE-reconstructed HRF amplitudes at the stimulation site are lower than their respective low-resolution scans. However, the HRFs are strongly correlated between the HSPARSE reconstructed and Nyquist sampled images, which suggests that in vivo HSPARSE fMRI maintains the temporal characteristics of in vivo HRFs.

Table 2
Comparison of Temporal Characteristics of HRF between HSPARSE fMRI and Nyquist Acquisition fMRI following Optogenetic Stimulation of the Dentate Gyrus

	Time to peak (s)			Duration (s)		
	NAcq	HSPARSE×1	HSPARSE×3	NAcq	HSPARSE×1	HSPARSE×3
Subject 1	24	21	21	23.47	32.03	26.65
Subject 2	21	24	21	23.26	32.02	33.60
Subject 3	24	21	21	34.71	33.52	34.38

Three subjects were optogenetically stimulated during imaging, using the single (HSPARSE HSPARSE×1) and 3 times averaged (HSPARSE×3) high-resolution HSPARSE fMRI and a highest spatial resolution Nyquist acquisition (NAcq). For each subjects, the time-to-peak difference between the HSPARSE and NAcq images is less than the 3 s temporal resolution. Although the duration of activity is similar between the HSPARSE and NAcq images for subject 1 and 3 on average, the duration is larger in the HSPARSE reconstructed image for subject 2. This difference could be due biological variability because the Nyquist acquisition datasets and the CS datasets were separately acquired in different fMRI imaging sessions.

systematic optimization. As shown in Figure 2, We find the global optimal range does not include the smallest λ_1 or λ_2 values (i.e., $\lambda_1 = 5e\text{-}5$ or $\lambda_2 = 1e\text{-}9$), which indicates neither using only spatial regularization nor using only temporal regularization can achieve the same high quality as the combined method. As shown in Figure 2a, only using the spatial regularization is not enough to eliminate the noise-like aliasing artifact with a high acceleration factor of 5.3. On another hand, while temporal regularization alone can be used to reconstruct the image, the additional spatial regularization can further improve the HRF amplitude and reduce the NRMSE (Fig. 2b). We have also discovered that common optimal parameters can be identified for distinct activity patterns and background images. Because the ground-truth data is not available for real imaging situations, such generalizable optimal regularization parameters are essential for the practical feasibility of the HSPARSE fMRI.

Limitations of HSPARSE and Future Work

A common limitation in the HSPARSE and other CS fMRI methods is that the temporal regularization introduces distortions to the time-series. For example, Zong et al reported decreased HRF amplitudes using a KLT based reconstruction (51). In the HSPARSE fMRI, because the temporal redundancy is also exploited for a high acceleration factor of 5.3, we observe similar HRF amplitude reduction and slight sinusoidal variations in the reconstructed HRFs (e.g., Figures 6c, 7c, S4c,d). However, we find that key HRF characteristics such as the relative peak amplitude difference, latency, time-to-peak, and duration are well preserved.

Although the HSPARSE images have lower HRF amplitudes compared with the same resolution fully sampled images in simulations, in some in vivo experiments, the HSPARSE images show a similar or higher HRF amplitude compared with the highest spatial resolution Nyquist image (Figs. 8e,f). This is likely due to the reduction in partial volume effects due to higher spatial resolution achieved by HSPARSE. Therefore, while the HSPARSE method generally decreases the HRF amplitude, with the decreased partial volume effect, it may produce similar or even higher HRF amplitudes as the Nyquist method.

HSPARSE method is designed for block-designed fMRI. The periodic basis DCT transform we used for the temporal domain may not have enough sparsifying power to reconstruct event-related fMRI signal. Using higher compression ratio transform, such as the KLT or DWT, will allow better reconstruction for aperiodic signals.

The HSPARSE fMRI achieves lower SNR compared with the highest spatial resolution Nyquist acquisition. However, loss of SNR is expected with all high spatial resolution imaging because MRI SNR linearly decreases with the decrease in voxel size. However, because HSPARSE fMRI significantly improves CNR compared with the fully sampled high spatial resolution images, significantly less number of averages is needed to recover the SNR loss from the increased spatial resolution.

The b-SSFP sequence used for the current implementation of the HSPARSE fMRI requires two acquisitions to avoid banding. While this can be a limitation for some studies where experiments cannot be easily repeated, most fMRI studies require repeated acquisition to improve SNR and therefore this is not a significant drawback. In addition, the b-SSFP has added benefits including significantly less spatial distortion than conventional GRE acquisitions (61–64) and high microvascular sensitivity (59,60).

Here, we demonstrate the first method accessing the feasibility and capability of CS for high spatial resolution fMRI. Future improvements in HSPARSE fMRI can include the use of higher compression ratio transforms such as the DWT to further improve reconstruction quality. Other advanced reconstruction such as those used in k-t FOCUSS can also be combined to improve the robustness against motion artifacts.

Applications of HSPARSE fMRI

Although b-SSFP sequence is used for our implementation, the proposed random undersampling spiral acquisition can also be applied to other sequences, such as GRE or spin-echo. In addition, the HSPARSE fMRI can be combined with other high resolution techniques such as parallel imaging to further improve SNR and image resolution. Furthermore, the proposed technique can be generally applied to different field strengths, radiofrequency coils, and gradients, enabling wide application of HSPARSE fMRI.

The HSPARSE will also benefit a wide range of neural circuitry studies. For example, while it has been suggested that the dentate gyrus plays a key role in pattern separation, Nyquist acquisition fMRI failed to test this hypothesis due to insufficient spatial resolution (31–33). Similarly, the HSPARSE fMRI can also resolve cortical layer-specific activities for building cortical processing models (29,30). Given these questions and the need for higher spatial resolution throughout the scientific community, the improvement provided by the HSPARSE method offers an important tool for the advancement of fMRI.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supporting Table S1. Precomputation of Line Search Decompositions Improves the Computational Efficiency of the Gradient Descent Method
Supporting Table S2. GPU-Based HSPARSE fMRI Method Achieves a 34-Fold Improvement in Speed[a]

[a]Three computationally expensive functions, the DCT, NUFFT and iNUFFT, were tested with the proposed GPU method and its parallel CPU counterpart. The proposed GPU methods show 165-, 28-, and 108-fold improvements in speed, respectively, resulting in a 34-fold overall speedup.

Supporting Figure S1. Separating the spatial and temporal sparsity constraints results in higher image contrast, HRF amplitude, and allows lower noise level and false positive rate. **(a-d)** The optimized 4D DCT based CS reconstruction with regularization parameter of λ=1e-2 was first compared with the proposed 3D+1D DCT based method using a phantom. The reconstruction using 3D+1D DCT produces higher mean F-value, image contrast and lower noise level compared with the reconstruction using 4D DCT. Although slightly higher sensitivity is observed in the reconstruction using 4D DCT, the false positive rate of the 4D DCT based method is also much larger than the 3D+1D based method. Furthermore, the reconstruction using 4D DCT also results in smoother and lower amplitude HRFs compared with the HRFs reconstructed with the 3D+1D DCT. **(e-f)** Similarly, the 3D+1D method produces higher mean F-value, contrast and lower noise level in an in vivo dataset. The reconstruction using 3D+1D DCT also allows a higher HRF amplitude, indicating the 3D+1D DCT regularization results in less temporal distortion.

Supporting Figure S2. Design of the GPU accelerated CS reconstruction algorithm. **(a)** Key computationally intensive calculations such as the NUFFT, matrix arithmetic, and DCT were parallelized on a GPU. Because these computations are repeatedly used during the iterative reconstruction loops used in HSPARSE, our GPU parallelization significantly improves the reconstruction speed. The iNUFFT and NUFFT are the most complicated and time-consuming calculations in the HSPRSE reconstruction. **(b)** iNUFFT resamples the gray Cartesian grid onto the blue spiral samples. In our parallel implementation, we assign each GPU core a spiral sample, and each thread inside the GPU core is assigned a Cartesian grid within the corresponding spiral sample's convolution window. During the iNUFFT, each thread first calculates its Cartesian grid's contribution to the given spiral sample, then an efficient binary summation algorithm is performed to sum all values together. **(c)** NUFFT resamples the blue spiral samples back onto the Cartesian grids. In contrast to the iNUFFT, each GPU core is assigned to a spiral sample at a different k_z-location to avoid memory write conflict. Each thread inside the core then retrieves value from the spiral sample point and adds it to the corresponding Cartesian grid inside the convolution window. Because there are thousands of k_z slices in our 4D fMRI datasets, this NUFFT algorithm takes full advantage of the massive number of GPU cores.

Supporting Figure S3. Phantoms used for optimization and testing of HSPARSE fMRI. **(a)** To identify the optimal regularization parameters for reconstruction, three phantoms with two noise levels (25 dB and 30 dB) were generated. The phantoms were designed to first simulate an in vivo fMRI experiment (A1), then to assess the effects of having a distinct base image (B1) and a distinct activation pattern (C1). To simulate more realistic imaging cases, the activation patterns were designed to have decreasing amplitude toward the edge of the activation through Gaussian smoothing (see methods). **(b)** For the assessment of fMRI signal sensitivity and specificity, three 30 dB phantoms were designed to have sharp activation boundaries with activation patterns limited to a single slice. **(c)** To investigate temporal characteristics of the reconstructed HRFs, three additional 30 dB phantoms without Gaussian smoothing were generated that simulated an in vivo fMRI experiment (A3), an experiment with a different base image (B3), and an experiment with a distinct activation pattern (C3).

Supporting Figure S4. Six-cycle time-series and analysis results corresponding to the main figures. **(a,b)** Six-cycle time-series corresponding to Figures 4 and 5. Similar to the analysis performed on the HRFs, the HSPARSE reconstructed six-cycle time-series also show a strong linear correlation with the original ground-truth time-series, which indicates the HSPARSE method maintains high temporal fidelity. **(c,d)** Six-cycle time-series corresponding to Figures 6 and 7. While some sinusoidal variations in the HSPARSE fMRI reconstructed time-series are observed (bottom left panel for both c and d), we find the HSPARSE fMRI preserves the peak amplitude and latency differences between layers, while the highest spatial resolution Nyquist acquisitions fail. HSPARSE also maintains high sensitivity and low FPR. In contrast, Nyquist acquisitions result in high FPR, which could be the result of low spatial resolution induced partial volume effects. **(e)** Six-cycle time-series corresponding to Figure 8. In vivo acquired HSPARSE fMRI six-cycle time-series also show strong linear correlation with the time-series obtained from the highest spatial resolution Nyquist acquisitions for all three subjects, demonstrating that HSPARSE fMRI can provide high temporal fidelity for in vivo experiments.

Supporting Figure S5. Optimized HSPARSE fMRI method consistently resolves layer-specific activity of the dentate gyrus upon optogenetic stimulation. Two additional in vivo experiment results are shown. With the highest spatial resolution Nyquist rate sampled images, activity is observed throughout the hippocampus. In contrast, activities in the HSPARSE reconstructed images are confined to the dentate gyrus. The peak amplitude activities follow the geometry of the molecular layer for all three subjects. The pink area and the red lines delineate the dentate gyrus. The white arrow indicates the site of stimulation.

Supporting Figure S6. The HSPARSE fMRI method is robust to motion within a normal physiological range. (**a**) Five sets of motion profiles with a maximum absolute translation equivalent to 1- to 5-pixels were designed. To simulate realistic motion, the z-dimension translation was restricted to be smaller than the x- and y-dimension translations, and rotations about the x-, y- and z-axis were limited to within $\pm$0.5 degrees. Solid lines represent an example six degree-of-freedom motion profile and shaded areas represent the ranges of translations or rotations in each motion profile. (**b**) The motion corrected HSPARSE images show similar activations as the motion corrected original images when the motion is 1-5 pixels. **(c-d)** When the amount of motion is less than 3-pixels, the HSPARSE reconstructed images are similar to the original image as measured by the mean F-value, sensitivity and false positive rate. However, when motion is larger than 4-pixels, the HSPARSE reconstructed images exhibit decrease in mean F-value and sensitivity. (**e**) Motion profiles of the three experiment subjects indicate that the physiological motion in our in vivo experiments are well within the 4-pixel range of robust reconstruction with the HSPARSE method. They exhibit translations of less than 2.5-pixels and rotations of less than $\pm$0.2 degrees.