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Accelerating Chemical Exchange Saturation Transfer MRI with Parallel Blind Compressed Sensing

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Abstract

Purpose: CEST is a novel and promising MRI contrast method, but it can be time consuming. Common Parallel Imaging (PI) methods, like SENSE, can lead to reduced quality of CEST. Here, Parallel Blind Compressed Sensing (PBCS), combining BCS and PI, is evaluated for the acceleration of CEST in brain and breast.

Methods: CEST data were collected in phantoms, brain (n=3) and breast (n=2). Retrospective Cartesian undersampling was implemented and the reconstruction results of PBCS-CEST were compared with BCS-CEST and k-t Sparse-SENSE-CEST. The normalized root mean square error (nRMSE) and the high-frequency error norm (HFEN) were used for quantitative comparison.

Results: In phantom and in vivo brain experiments, the acceleration factor of R=10 (24 k-space lines) was achieved and in breast R=5 (30 k-space lines), without compromising the quality of the PBCS-reconstructed MTR_{asym} maps and Z-spectra. PBCS provides better reconstruction quality when compared to BCS, k-t Sparse-SENSE, and SENSE methods using the same number of samples. PBCS over-performs BCS, indicating that the inclusion of coil sensitivity improves the reconstruction of the CEST data.

Conclusion: The PBCS method accelerates CEST without compromising its quality. Compressed Sensing in combination with PI can provide a valuable alternative to PI alone for accelerating CEST experiments.

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SUPPORTING INFORMATION

The material includes results and analysis of the additional datasets.

Keywords

CEST; blind compressed sensing; parallel imaging; parallel blind compressed sensing; CEST acceleration

INTRODUCTION

Chemical exchange saturation transfer (CEST) is a novel contrast mechanism in MRI (1–3) and promising clinical applications are investigated (4–9). The CEST experiment often requires a series of image acquisitions with saturation pulses applied at varying frequencies (10,11) and multiple power levels (12,13). Thus, the entire CEST acquisition can be time consuming.

Currently, Parallel Imaging (PI) has become the standard way of accelerating MR image acquisition (14,15). However, there is emerging evidence that PI leads to deterioration of CEST contrast (16), significantly limiting acceleration options for CEST. Thus, alternative ways to accelerate CEST experiment are direly needed.

Recent successful application of Compressed Sensing (CS) (17,18) in MRI (19) offers an attractive alternative and/or complement to PI methods. However, the successful application of CS to CEST is still very novel, with only one publication to-date(16). The low Contrast-to-Noise (CNR) of the CEST method could hamper the combination (similar to the PI). Thus, there is a need for detailed investigation of CS methods and algorithms in conjunction with CEST.

Recently, several CS MRI methods were investigated for CEST acceleration. Specifically, CS-SENSE-CEST (16) combined Sparse MRI (19) and SENSE (14) in two consecutive steps to reconstruct CEST images. At the recent ISMRM meetings abstracts were presented retrospectively applying Blind Compressed Sensing (BCS) (20–23) for CEST imaging using either Cartesian (24,25) or golden angle radial undersampling (24,26). The novel aspects of our present work are several-fold. First, we retrospectively apply and evaluate the combination of ESPIRiT (27) with BCS (Parallel Blind Compressed Sensing (PBCS)) to accelerate CEST imaging using Cartesian undersampling. While the PBCS method is not novel, its application to CEST is new and the level of success is associated with the salient features of CEST. Second, we are focusing on the *combination* of CS method (i.e. BCS) with PI (i.e. ESPIRiT) for CEST imaging specifically and their *simultaneous* inclusion in the reconstruction (as opposed to the two-step approach in (16)). We demonstrate the possibility of the highly accelerated Cartesian sampling (as opposed to radial) in CEST imaging. Third, we are isolating the specific contribution of PI to the reconstruction of CEST data and comparing the performance of the various reconstruction methods employing CS or PI. Finally, we demonstrate the feasibility of the application of PBCS to breast CEST imaging, hopefully serving as a stepping-stone for the advancement of the methods from brain to the body applications.

THEORY

Here, we briefly describe the PBCS method specifically in conjunction with CEST. In CEST imaging, voxels in the same compartment have similar Z-spectra (29), which show high correlations in the spatial-temporal domain. These Z-spectra can be treated as temporal basis functions in the dictionary. Supporting Figure S1 illustrates the temporal bases decomposition of the desired reconstructed CEST image series $F = UV$, where U is the coefficient matrix, V is temporal bases function matrix. Since the CEST image series is highly correlated, the coefficient matrix U is sparse. In PBCS, the coil sensitivities are initially estimated using the ESPIRiT method (27) with the auto-calibration signal (ACS) part of the unsaturated data. The reconstruction is to minimize the following objective function:

$$\min_{U, V} E(U, V) = \sum_l \left\| F(S_l UV) - d_l \right\|_2^2 + \lambda \|U\|_1 + \eta \|V\|_2^2, \quad [1]$$

where F is the undersampling Fourier operator; d_l is the undersampled k-space data from the l -th coil; S_l is the sensitivity from the l -th coil; $\|U\|_1$ is the L_1 norm; $\|V\|_2^2$ is the energy-regularization term of the temporal bases; λ and η are regularization parameters. Eq.1 is different from the one presented at ISMRM Ref. (26) by explicit inclusion of the coil sensitivity estimation (25) and we assume Cartesian sampling instead of Radial sampling (26). We use the majorize-minimization method (30) to solve this problem.

METHODS

Phantom

The phantom contained five 25 mL tubes filled with Iopamidol (Isovue-M 300, Bracco Diagnostics Inc., Italy) with different pH values (6.0, 6.5, 7.5 and 8.0) and immersed in water bath (31).

In-vivo human

Four volunteers (two females) were recruited for the brain study and two for the breast study. The human studies were approved by the local Institutional Review Board (IRB).

MRI acquisition

All measurements were performed on a 3 Tesla (T) whole-body human scanner (Ingenia, Philips Healthcare, Best, The Netherlands) using a body coil for RF transmit and either a 32-channel head coil (phantom and brain imaging) or 16-channel bilateral breast coil (breast imaging). To test the reconstruction performance under a wider range of experimental conditions, different protocols (based on recent publications Ref. 16,32) were employed to collect brain and breast data.

CEST experiments in phantoms and brain employed a 2D multi-shot Turbo Spin Echo (TSE) sequence with TSE factor=120, FOV=240×240 mm, matrix=240×240, slice thickness=4.4

mm. 31 points in the Z-spectrum in the range ± 1000 Hz were acquired. The saturation train consisted of Sinc-Gauss (SG) shaped RF pulses 49.5 ms each with 0.5 ms pulse intervals and 99% duty cycle enabled by the alternated parallel transmit (33). Two different total saturation times were used: (i) 2 sec/40 pulses (3 experiments) and (ii) 0.5 sec/10 pulses (2 experiments). In the in-vivo study, three power levels (B_{1rms}) were evaluated in three volunteers: 0.7 μ T, 1.2 μ T, and 1.6 μ T. The saturation power for the phantom was 1.6 μ T and one brain dataset with 1.2 μ T only (see below). In each case TR varied to maintain SAR under 90% of the maximum allowed value while TE was at minimum value, resulting in TR range 2668–4684 ms and TE=5.4 ms(n=2) and 6.4 ms(n=1). SPIR (34) was used for fat suppression in-vivo. The water saturation shift referencing (WASSR) method (35) was used for B_0 inhomogeneity correction with the saturation length of 2 sec, $B_{1rms}=0.1$ μ T, and a total of 31 points in the range ± 200 Hz. In addition, overall constant B_0 shift was added to correct for B_0 drift between the scans.

CEST experiments in breast and one brain volunteer employed a 2D multi-shot Turbo Field Echo (TFE) sequence with TFE factor=25(breast) or 120(brain), FOV=210 $\times$ 319 mm(breast) or 240 $\times$ 240 mm(brain), matrix=104 $\times$ 150(breast) or 240 $\times$ 240(brain), slice thickness=5 mm, TE/TR=2.3/5.0 ms, NSA = 2(breast/brain) or 1(brain). The purpose of one brain dataset was to compare the reconstructions of TSE and TFE acquisitions. 33(breast)/31(brain) frequency points in the Z-spectrum in the range ± 770 Hz(breast)/ ± 1000 Hz(brain) were acquired. The saturation train consisted of 10 Hyper-Secant (HS) shaped RF pulses, each 49.5 ms, with 0.5 ms pulse intervals, with $B_{1rms}=1.2$ μ T. The total saturation-acquisition cycle time was 6.3 s per frequency. Separately acquired, Gradient Echo based B_0 mapping sequence was used for the field inhomogeneity correction.

Data Processing and Reconstruction

All of the data were processed using custom developed routines in Matlab (The MathWorks, Natick, MA). The Mutual Information method (36) was used for CEST and WASSR images registration.

The fully sampled k-space data were retrospectively undersampled using a variable-density random sampling pattern (19), to simulate accelerated acquisitions. Specifically, we chose samples randomly with sampling density scaling according to a power of distance from the k-space center (Figure 1a). The following reduction factors (R) and corresponding number of k-space lines (N_k) were tested for TSE/TFE brain/phantoms: R(N_k)=4(60), 5(48), 6(40), 8(30), 10(24) and for TFE breast: R(N_k)=5(30).

The reconstruction using information from all channels took a prohibitively long time. Hence, in all datasets, coil compression was performed on the raw k-space data using the singular value decomposition method (37) to combine the 32-coil brain data and 16-coil breast data into 8 and 4 virtual coils, respectively, prior to the image reconstruction process.

The sum-of-squares (SOS) reconstruction from fully sampled data and the corresponding magnetization transfer rate asymmetry (MTR_{asym}) maps were used as the gold standard for visual and quantitative comparison. For phantom MTR_{asym} (4.2ppm) maps were calculated. For brain MTR_{asym} (3.5ppm) and for breast MTR_{asym} (1ppm), MTR_{asym} (2ppm) and

$MTR_{\text{asym}}(3.5\text{ppm})$ were calculated. In each case the maps were calculated by integrating $\pm 0.4\text{ppm}$ around the nominal frequency.

The absolute difference maps were obtained between the fully sampled images and the undersampled reconstructed images. A quantitative comparison was provided in terms of the normalized Root Mean Squared Error (nRMSE):

$$\text{nRMSE} = \frac{1}{\max(f_{\text{Full}}) - \min(f_{\text{Full}})} \sqrt{\frac{\sum_{m=1}^M \sum_{n=1}^N |\hat{f}(m, n) - f_{\text{Full}}(m, n)|^2}{MN}}, \quad [2]$$

where f_{Full} and $\hat{f}$ are the $M \times N$ MTR_{asym} maps reconstructed using the fully sampled data and the undersampled data, respectively. The nRMSE of the ROI-averaged Z-spectrum for different reconstruction methods were also calculated similar to Eq. [2], where f_{Full} and $\hat{f}$ were the Z-spectra of the fully sampled and reconstructed data, respectively.

To quantify the quality of the resolution and reconstruction of fine features for different methods, the High-Frequency Error Norm (HFEN) was used (38):

$$\text{HFEN} = \frac{\|LG(f_{\text{Full}}) - LG(\hat{f})\|_F^2}{\|LG(f_{\text{Full}})\|_F^2}, \quad [3]$$

where LG is the Laplacian of Gaussian filter that can capture the edges of the image. We used the same filter parameters as (38).

For parameters λ and η selection, we used one of the brain datasets to find a set of parameters with the smallest reconstruction nRMSE and the same optimized parameters were used in all datasets. For k-t Sparse SENSE: $\tau = 10^{-2}$, $\sigma = 10^{-3}$; for PBCS: $\lambda = 10^{-3}$, $\eta = 10^{-8}$, $\gamma = 10^{-2}$, $\delta = 40$; and for BCS: $\lambda = 10^{-2}$, $\eta = 10^{-8}$. All datasets were scaled to have similar magnitude prior to reconstruction, using division by the mean value of the whole image data for each dataset. This ensured robust regularization parameters for different datasets. All the reconstruction algorithms were fully optimized.

RESULTS

Phantom Results

Figure 1a and Supporting Figure S2 compare the MTR_{asym} maps (4.2 ppm) reconstructed with fully sampled, PBCS, BCS and k-t Sparse SENSE for the phantom experiment at reduction factors $R=5$ and 10. Images reconstructed with PBCS had the lowest reconstruction error. Figure 1b compares the ROI-averaged Z-spectra reconstructed using different methods at $R=10$. The Z-spectra of BCS and k-t Sparse SENSE are close to the fully sampled curve for most of the range but deviate more than PBCS at the fast-changing part, such as the frequencies around 550 Hz and 0 Hz. This is where exchanging peaks are located and these frequencies are the most important for MTR_{asym} evaluation. Deviation at

these frequencies leads to artifacts in the MTR_{asym} maps. The better agreement between fully sampled and PBCS reconstructed data indicates better performance of PBCS at the areas of fast changing temporal/frequency information. The nRMSE of the reconstructed Z-spectra are also shown in the Figure 1b for comparison, demonstrating the least error with PBCS method compared with the other two methods. Deviations observed at the very edges ($\pm 1000\text{Hz}$) of the Z-spectra are associated with the interpolation errors.

In Vivo Results

Figures 2–4 compare the results obtained using images reconstructed with different methods at highest R (lowest N_k) achieved: $R(N_k)=10(24)$ for the TSE brain datasets and $R=5(30)$ for breast. Figures 2a–4a compare the MTR_{asym} maps (3.5 ppm), while Figures 2b–4b compare the Bland-Altman plots (39) and Correlation Plots of the three methods at reduction factor $R=10$ (brain) or $R=5$ (breast).

In all cases the reconstructed MTR_{asym} maps of k-t Sparse SENSE show aliasing due to the high reduction factors. BCS gives good reconstruction visually, however quantitative values show a larger reconstruction error than PBCS. The nRMSE of BCS and k-t Sparse SENSE are larger than that of PBCS at highest reduction factors shown ($R(N_y)=10(24)$ brain and $R=5(32)$ breast). This observation is consistent with visual inspection. For all the methods, areas around ventricles showed larger nRMSE. This might be due to the faster spatial changes in these areas or due to small motion-induced sensitivity estimation errors.

While PBCS gives better fidelity to the fully sampled maps, slight resolution deterioration becomes apparent at $R=10$ for brain (Figures 2a and 3a). Similarly, breast dataset reconstruction at $R(N_y)=6(25)$ was unsuccessful (hence, is not shown). The resolution deteriorates at higher R s for all the methods tested here, with the worst quality deterioration in k-t Sparse SENSE. Overall, while the deterioration is present, it could be minimized in PBCS by using slightly lower reduction factor, e.g. $R=8$ in brain (see Figure 5).

From the Bland-Altman plots in Figures 2b–4b, PBCS has the lowest standard deviation compared with the other two methods. BCS also leads to relatively small standard deviation, but k-t Sparse SENSE deviates a lot from the fully sampled case. From the Correlation Plots, PBCS has the highest r^2 value, but BCS and k-t Sparse SENSE have lower r^2 values. These results are consistent with other datasets (see Supporting Figures S3–S12).

DISCUSSION

To have a better overview of the performance of the different methods Figure 5 displays nRMSE and HFEN for different reduction factors from the same dataset in Figure 3. Both, nRMSE and HFEN illustrate better performance of PBCS vs BCS and k-t Sparse SENSE. Moreover, all the methods deteriorate with increasing acceleration factor (and fewer numbers of k-space lines used in the reconstruction), however, the PBCS deterioration is the slowest.

From the Bland-Altman plots (Figures 2–4) the limits of agreement between fully sampled data and undersampled data gradually increase from PBCS, to BCS to k-t Sparse SENSE.

Viewed from a different perspective, this indicates increased spread of the MTR_{asym} values, which is an indirect indication of the increase in noise measurement. Thus, the images reconstructed with BCS and k-t Sparse SENSE vs PBCS become increasingly noisier.

From the data shown, PBCS outperforms other reconstruction methods tested here, regardless of the saturation parameters or off-resonance frequency. Since the major difference between PBCS and BCS is the inclusion of the coil sensitivity from the reference image in the reconstruction, we conclude that it is the ultimate factor improving performance of PBCS over BCS in CEST data.

To validate this point further, we compared spatial-temporal constraint reconstruction (STCR) (40) with k-t Sparse SENSE, which combines STCR and sensitivity encoding (14). Similar to PBCS vs BCS, k-t Sparse SENSE outperforms STCR (Supporting Figure S13). This observation reinforces our conclusion that the improved performance of PBCS in CEST data stems from the inclusion of the coil sensitivity information.

To further expand the discussion of potential advantages of CS vs PI in CEST imaging, we re-created the SENSE reconstruction using the uniform sampling pattern and reduction factors $R(N_y) = 2(120)$ and $4(60)$ (Supporting Figure S14). From the figure, the performance of SENSE-CEST degrades quickly at the reduction factor $R=4$. This is in agreement with previous observations (16). At the same time, PBCS gives good quality reconstructions for the same dataset at reduction factor $R=10$ (Supporting Figure S7).

Reduction factor $R=10$ could be achieved in brain TSE datasets and the lower $R = 5$ was achieved in breast. However, the number of k-space lines used for reconstruction is comparable: 24 in brain vs 30 in breast. While different anatomies and acquisitions cannot be compared directly, the small increase needed in breast data may stem from reduced SNR in breast datasets, where TFE with NSA=2 was used in acquisition. To validate this point, additional brain data was acquired with TSE and TFE protocols (Supporting Figures S15 and 16), while keeping the other parameters the same. Indeed, only $R(N_y)=6(40)$ could be achieved in TFE acquisition. Increasing the SNR by increasing NSA to 2 lead to $R(N_y)=8(30)$ (Supporting Figure S17).

To test the influence of the acquisition resolution on the reconstruction quality, smaller matrix size experiment was conducted in phantoms (Supporting Figure S18). At the first glance, only lower reduction factor ($R=8$) could be achieved (Figures 1 vs Supporting Figure S18). However, when comparing reduction factors corresponding to the similar number of k-space lines used for reconstruction, i.e. $R(N_y)=8(30)$ for large matrix and $R(N_y)=4(32)$ for smaller matrix size, similar quality and identical nRMSE of 0.0027 was obtained. Thus, reduction in the acquisition matrix size does not affect the results.

Practically, motion has detrimental effects on CEST. Acceleration methods, such as investigated here, may reduce this problem, by allowing faster acquisitions, thus reducing motion artifacts.

The biggest contributor to the long experimental time of CEST can be the saturation pulse itself. The 2D undersampling schemes may reduce acquisition time (28) and thus the overall

experimental time. The biggest impact would be in the cases when a single shot acquisitions are prohibitive (e.g. due to associated blurring), and where CS undersampling could replace multi-shot acquisitions with a single-shot. The real advantages of CS undersampling would be in the expansion of the methods to 3D CEST(41,42).

We speculate that the acceleration using recent multi-band methods might be possible for CEST, but would require separate evaluation. Currently, work is in progress to evaluate the Compressed Sensing based prospective random Cartesian undersampling scheme (28), to be discussed in a separate publication.

CONCLUSION

We used a sensitivity weighted Parallel Blind Compressed Sensing algorithm to retrospectively accelerate CEST imaging. This method provides better CEST reconstructions at high reduction factors up to $R=10$ (with as little as 24 k-space lines) compared with other state-of-the-art methods (including PI and CS alone) investigated here. The acceleration factor would be subjected to the practical requirements and CEST experiments specifics. A combination of CS with PI can provide an invaluable alternative to PI for accelerating CEST.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) The comparison of the MTR_{asymp} maps reconstructed with fully sampled (left top corner), PBCS (second column), BCS (third column) and k-t Sparse SENSE (fourth column) at reduction factors $R = 10$ in a phantom containing Iopamidol tubes with different pH values (6.0, 6.5, 7.0, 7.5, 8.0). The absolute value of difference *times 3* of the fully sampled MTR_{asymp} maps are shown in the second row. The undersampling pattern for $R = 10$ is also shown on the left side of the second row. (b) The reconstructed Z-spectra and MTR_{asymp} curves for three pH values (6.0, 7.0, 8.0) at the reduction factor $R = 10$ using PBCS (black), BCS (dotted blue), and kt Sparse SENSE (green), compared to Z-spectra from the fully sampled data (red). The nRMSE of the reconstructed Z-spectra of PBCS (E_P), BCS (E_B), and k-t Sparse SENSE (E_K) are shown for comparison.

Figure 2.

The results of in vivo human brain CEST experiment using long saturation (2 s). **(a)** The MTR_{asym} color maps (top row) of (from left to right) fully sampled (first column), PBCS (second column), BCS (third column) and k-t Sparse SENSE (forth column) reconstruction for $B_{1rms}=0.7\mu T$. The absolute value of difference *times 3* of the fully sampled MTR_{asym} maps shown using gray scale (bottom row). The columns continue the same order as in the top row. All the results were obtained using the reduction factor $R = 10$. The nRMSE values are also shown on each map/image. **(b)** Further analysis of the in vivo brain CEST experimental data shown in (a). **Top row:** all ROI pixels Bland-Altman plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three power levels 1.6 μT (red squares), 1.2 μT (green squares) and 0.7 μT (blue squares). The horizontal axis

stand for the pixel value in the ROI of the MTR_{asym} map (lower right corner). The vertical axis stand for the difference between the reconstructed MTR_{asym} map and the fully sampled MTR_{asym} map in the ROI. **Bottom row:** all ROI pixels Correlation Plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three power levels 1.6 μT (red squares), 1.2 μT (green squares) and 0.7 μT (blue squares). The ROI used is shown in the insert at the lower right corner.

Figure 3.

The results of in vivo human brain CEST experiment using short saturation (0.5 s). **(a)** The MTR_{asym} color maps (top row) of (from left to right) fully sampled (first column), PBCS (second column), BCS (third column) and k-t Sparse SENSE (forth column) reconstruction for $B_{1rms}=1.6 \mu T$. The absolute value of difference *times 3* of the fully sampled MTR_{asym} maps shown using gray scale (bottom row). The columns continue the same order as in the top row. All the results were obtained using the reduction factor $R = 10$. The nRMSE values are also shown on each map/image. **(b)** Further analysis of the in vivo brain CEST experimental data shown in (a). **Top row:** all ROI pixels Bland-Altman plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three power levels 1.6 μT (red squares), 1.2 μT (green squares) and 0.7 μT (blue squares). The horizontal axis

stand for the pixel value in the ROI of the MTR_{asym} map (lower right corner). The vertical axis stand for the difference between the reconstructed MTR_{asym} map and the fully sampled MTR_{asym} map in the ROI. **Bottom row:** all ROI pixels Correlation Plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three power levels 1.6 μT (red squares), 1.2 μT (green squares) and 0.7 μT (blue squares). The ROI used is shown in the insert at the lower right corner.

Figure 4.

The results of in vivo human breast CEST experiment using short saturation (0.5 s). **(a)** The MTR_{asym} color maps (top row) of (from left to right) fully sampled (first column), PBCS (second column), BCS (third column) and k-t Sparse SENSE (forth column) reconstruction for $B_{1rms}=1.2 \mu T$. The absolute value of difference of the fully sampled MTR_{asym} maps shown using gray scale (bottom row). The columns continue the same order as in (a). All the results were obtained using a reduction factor $R = 5$. The nRMSE values are also shown on each map/image. **(b)** Further analysis of the in vivo breast CEST experimental results shown in (a). **Top row:** all ROI pixels Bland-Altman plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three frequency ranges 1ppm (red squares), 2ppm (green squares) and 3.5ppm (blue squares). The horizontal axis stand for the pixel value in the ROI of the MTR_{asym} map (lower right corner). The vertical axis stand for the difference between the reconstructed MTR_{asym} map and the fully sampled MTR_{asym} map in the ROI. **Bottom row:** all ROI pixels Correlation Plots for PBCS (left), BCS (center) and k-t Sparse SENSE (right) reconstructions from three frequency ranges 1ppm (red squares), 2ppm (green squares) and 3.5ppm (blue squares). The ROI used is shown in the insert at the lower right corner.

Figure 5.

The influence of the reduction factors $R = 4, 6, 8, 10$ on the reconstructed image quality, assessed using (a) the reconstruction error (nRMSE) and (b) high-frequency error (HFEN) on one set of the in vivo human brain data with saturation power of $0.7 \mu\text{T}$. The data reconstructed using: PBCS (red), BCS (green) and k-t Sparse SENSE (blue).