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Chemical Exchange Saturation Transfer (CEST) Imaging with Fast Variably-accelerated Sensitivity Encoding (vSENSE)

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Abstract

Purpose—The widespread clinical use of Chemical Exchange Saturation Transfer (CEST) imaging is hampered by relatively long scan times due to its requirement that multiple saturation-offset image frames be acquired. Here, a novel variably-accelerated sensitivity encoding (vSENSE) method is proposed that provides faster CEST acquisitions than conventional SENSE.

Theory and Methods—The vSENSE method fully samples one CEST saturation frame, then undersamples the other frames variably. The fully-sampled frame, in conjunction with newly-proposed incoherence absorption and artifact suppression strategies, improves the accuracy of sensitivity maps and permits higher acceleration factors for the other undersampled frames than regular SENSE. vSENSE is validated in a phantom, a normal volunteer and eight brain tumor patients at 3T.

Results—vSENSE with an acceleration factor of four generated a 3–6 times smaller error on average than conventional SENSE ($P = 0.02$), with acceleration factors of 2–4, as compared to full k -space reconstruction. vSENSE permitted 4-fold acceleration for Amide Proton Transfer (APT)-weighted images, while regular SENSE could only provide a factor of two. When conventional SENSE is used with vSENSE's variable undersampling pattern, erroneous (~9%) z-spectra result.

Conclusion—The vSENSE method enabled twice the acceleration and generated more accurate images than conventional SENSE.

Keywords

chemical exchange saturation transfer (CEST); amide proton transfer (APT); sensitivity encoding (SENSE); variably-accelerated sensitivity encoding (vSENSE); brain tumor

INTRODUCTION

Chemical Exchange Saturation Transfer (CEST) (1-4) is an emerging MRI technique which amplifies the detectability of certain low-concentration metabolites via their interactions

with the abundant water pool. CEST and many of its variants have shown promising results in applications including amide proton transfer (APT) imaging (5) of cancer (6-12) and stroke (13-15), and glucose-CEST in cancer (16,17) etc. However, its routine clinical use is currently limited by relatively long scan times, since CEST typically requires multiple image frames, each acquired with a different saturation offset frequency (6,9,18). Recent advances to quantify CEST signals with z-spectrum fitting (19-23) have further burdened scan times.

Various methods have been developed to accelerate CEST acquisition. These can be classified into sequence-oriented techniques and reconstruction-oriented techniques. The sequence-oriented techniques use either a fast imaging readout, such as GRASE (24), FISP (25), and EPI (26), or use fast CEST saturation schemes, such as SAFARI (27), CERT (28), and VDMP (29). A recent single-voxel UCEPR (30) method that combines ultrafast Z-spectroscopy (31,32) with a PRESS (33) readout, is another sequence-oriented technique. A detailed discussion of these techniques is beyond the scope of this paper. Instead, reconstruction-oriented CEST techniques that include parallel imaging (34-36), SLAM (37-40), keyhole (41,42), and compressed sensing (43,44), are the focus of the present work.

Parallel imaging methods are widespread on modern MRI scanners and can be readily combined with sequence-oriented techniques (24,26). The SLAM method utilizes prior localization knowledge obtained from a scout MRI to directly generate compartmental CEST measurements from arbitrarily-shaped regions of interest (40), with up to 45-fold acceleration factors being reported (37). Although SLAM has a substantially higher signal-to-noise (SNR) efficiency than conventional single-voxel and multi-voxel methods (38), information about tissue heterogeneity within the compartments is lost. This may be detrimental in certain applications in which intra-compartmental information is important. On the other hand, the keyhole method reuses the high-frequency k -space components of one fully-sampled CEST image frame to reconstruct other under-sampled low-resolution CEST frames at different saturation-frequency offsets (41,42). Unlike the undersampling used in parallel imaging techniques which does not reduce the range of k -space spanned, the keyhole method compromises spatial resolution by only sampling central k -space such that errors in quantification may be introduced (45). The third method, compressed sensing, assumes that the underlying image is sparse in a transformed domain and reconstructs the final images with an L^1 -norm regularized minimization process from randomly undersampled k -space (44). However, random undersampling in the frequency-encoding (read-out) dimension, while theoretically possible (43), has not yet proved practical to implement.

The goal of the present work is to fully exploit the potential of parallel imaging—specifically SENSE (35), for CEST imaging. SENSE-CEST is currently limited in practice to an acceleration factor of two in the phase- or slice-encoding direction (9,24) by both reconstruction accuracy and the underlying SNR. The reconstruction accuracy of SENSE depends critically on the accuracy of the sensitivity maps used for unfolding (46). The standard way of generating sensitivity maps (preset by the scanner manufacturer) is to acquire a separate reference scan using a low flip-angle (FA), short echo-time (TE), short repetition-time (TR), low-resolution, large field-of-view (FOV) gradient echo (GRE) sequence, with phased-array receive (47) and body transceive coils. Since the subsequent

CEST scans often use different imaging protocols with different geometric off-sets and orientations from the reference scan, the standard sensitivity maps are rarely accurate. Consequently, the acceleration factor is limited by the need to suppress unfolding artifacts. On the other hand, the importance of SNR for CEST imaging is evidenced by the multiple averages required for acquisitions at ± 3.5 ppm in APT studies (9).

Here, a novel acquisition and reconstruction method, variably-accelerated sensitivity encoding (vSENSE), is proposed to speed up CEST studies. The vSENSE method fully samples one of the CEST saturated frames, from which improved sensitivity maps are generated using newly proposed incoherence absorption and artifact suppression strategies to suppress SENSE unfolding artifacts for the other undersampled frames. Then in the remaining saturation frames, k -space is undersampled variably: less-so for important frequencies (e.g., ± 3.5 ppm for APT imaging), and more-so for other frequencies to provide an SNR comparable to that achieved by averaging (9). With this strategy, vSENSE achieves better accuracy and a higher overall acceleration factor than conventional SENSE, while preserving sufficient SNR for CEST imaging.

THEORY

Image reconstruction with the SENSE algorithm (35) requires solving a linear equation,

$$\mathbf{s}_{Nc \times 1} = \mathbf{SE}_{Nc \times R} \times \mathbf{p}_{R \times 1}, \quad [1]$$

for $\mathbf{p}$, the unfolded image-space data, where $\mathbf{s}$ is the folded image-space data for one voxel after Fourier transform in k -space, Nc is the number of receive coil elements, $\mathbf{SE}$ is the sensitivity encoding matrix, and R is the acquisition acceleration factor reflecting the number of folded voxels. Noise pre-whitening (48) can be included in these $\mathbf{s}$ and $\mathbf{SE}$ matrices. The accuracy of $\mathbf{p}$ depends critically on the accuracy of $\mathbf{p}$, and R , the effect of motion artifacts on $\mathbf{s}$ notwithstanding. For $R=1$, there is no unfolding artifact in the reconstructed matrix, no matter how inaccurate the matrix is. Although the intensities of can be inaccurately rendered if the sensitivity weightings are inaccurate, CEST image intensities are typically normalized by the unsaturated image frame (6,18), or by other saturated frames (49-51) during post-processing. Accordingly, CEST source images acquired with $R=1$ without unfolding artifacts, are treated as accurate here, regardless of the accuracy of the sensitivity weightings. However, unfolding artifacts will appear for $R>1$ when the sensitivities are inaccurate.

Incoherence absorption (IA) to assign sensitivities

One possible approach for obtaining accurate sensitivity maps is to utilize a fully-sampled CEST frame by dividing the root-of-the-sum-of-the-squared (RSS) images of all coil channels, into the image from each channel. Sensitivity maps calculated in this manner share imaging and geometric parameters identical to those of the CEST scan, and thus, can be regarded as accurate. However, three extra aspects must be considered in order to guarantee accurately unfolded images.

First, the raw sensitivity map from the quotient images of the fully-sampled CEST frame needs to be scaled because the RSS image also has a phased-array image shading (52) imposed on it. The scaling map can be calculated by dividing the RSS phased-array image by a body coil image, both obtained from a reference scan, and normalizing it by its maximum value. This scaling map is then applied simultaneously to all the raw sensitivity maps from each individual channel of the fully-sampled CEST image frame. Because its effect factors out of Eq. [1], this process does not introduce any unfolding artifact into the final image, be it accurate or not. Alternatively, other uniformity correction methods (53) such as homomorphic filtering that does not require a reference scan, could be used for scaling. However, the reference scan is fast and is usually implemented automatically at the beginning of any exam session that involves phased-array coils, and often cannot be skipped in any case.

Second, the scaled raw sensitivities can be refined by a locally-weighted (35) polynomial regression (LWPR) or “LOWESS” (54). Here, a “tri-cubic” weighting kernel (54) is used. Fitting can reduce noise in the sensitivity maps. LWPR is implemented in the “support region” in which the object resides, as identified by intensity thresholding applied to the scaled RSS image from the fully-sampled CEST frame. Isolated holes in the support region due to signal dropout (see also below) can be identified via morphological image processing and filled by LWPR.

Third, the extrapolation of sensitivities to the non-support region (i.e., the noise region) is typically implemented in the conventional SENSE method (35) to deal with the bleed of the spatial response function at the object’s edges (55). However, extrapolation does not guarantee accurate unfolded images. For example, Fig. 1 shows that both the scanner- and author-reconstructed images with $R=4$ and conventional SENSE routines exhibit substantial unfolding artifacts, despite extrapolation of the sensitivity maps generated from the reference scan. Therefore we calculate the sensitivities in the non-support region not by extrapolation, but rather, from allocation of the incoherent signal residues. This is called an “incoherence absorption” (IA) approach. Specifically, for a retroactive acceleration factor of two on the fully-sampled CEST image frame,

$$\mathbf{s}_{Nc*1} = \mathbf{SE}_{Nc*2} \times \rho_{2*1} = \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1 + \mathbf{SE}_{Nc*1}^2 \times \rho_{1*1}^2 \quad [2]$$

where $\mathbf{SE}^1$ and $\mathbf{SE}^2$ refer to the sensitivities in two folded (aliased) voxels, with corresponding values of ρ^1 and ρ^2 , respectively.

The IA approach targets the situation in which one of the two voxels is in the support region (voxel 1) and the other is in the non-support region (voxel 2), as shown in Fig. 2(b). Then, we can treat $\mathbf{SE}^1$ as representing the known accurate sensitivities and $\mathbf{SE}^2$ as unknown sensitivities. Ideally, there should be no signal in voxel 2, whereupon Eq. [2] would reduce to $\mathbf{s}_{Nc*1} = \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1$. However, due to bleed from the spatial response function (55) and noise contributions, etc., there will be incoherent contributions to Eq. [2], that can be

estimated as $s_{Nc*1} = \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1$. To isolate the effects of incoherent contributions to signals in the support region, we can assign the sensitivities in voxel 2 as,

$$\mathbf{SE}_{Nc*1}^2 = \frac{s_{Nc*1} - \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1}{\max_{j=1}^{Nc} |s_{j*1} - \mathbf{SE}_{j*1}^1 \times \rho_{1*1}^1|} \times \max_{j=1}^{Nc} |\mathbf{SE}_{j*1}^1| \quad [3]$$

where j refers to the coil element index from 1 to Nc . The $\max_{j=1}^{Nc} |s_{j*1} - \mathbf{SE}_{j*1}^1 \times \rho_{1*1}^1|$ and $\max_{j=1}^{Nc} |\mathbf{SE}_{j*1}^1|$ terms are used to scale the incoherent contributions to the proper sensitivity levels. In Eq. [3], the known sensitivities, $\mathbf{SE}^1$, are from scaled and fitted maps, as shown in Fig. 2b, and the known signal, ρ^1 , is from the regular SENSE reconstruction with $R=1$, using the scaled and fitted maps. For situations in which two folded voxels are both in the support or the non-support regions, their sensitivities do not change. Then, after an iteration of all folded voxels with $R=2$, the fitted sensitivity map, as shown in Fig. 2b, is extended to an intermediate map, as shown in Fig. 2c. In addition, the newly assigned voxels are added to the support region.

Similarly for a retroactive acceleration factor of four,

$$s_{Nc*1} = \mathbf{SE}_{Nc*4} \times \rho_{4*1} = \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1 + \mathbf{SE}_{Nc*1}^2 \times \rho_{1*1}^2 + \mathbf{SE}_{Nc*1}^3 \times \rho_{1*1}^3 + \mathbf{SE}_{Nc*1}^4 \times \rho_{1*1}^4 \quad [4]$$

where $\mathbf{SE}^1$, $\mathbf{SE}^2$, $\mathbf{SE}^3$, and $\mathbf{SE}^4$ refer to sensitivities in four folded voxels, with corresponding values of ρ^1 , ρ^2 , ρ^3 , and ρ^4 , respectively. If, and only if, two voxels (e.g., voxels 3 and 4) of the four folded voxels are in the non-support region, their sensitivities can be assigned as

$$\mathbf{SE}_{Nc*1}^3 = \mathbf{SE}_{Nc*1}^4 = \frac{s_{Nc*1} - \mathbf{SE}_{Nc*1}^1 \times \rho_{1*1}^1 - \mathbf{SE}_{Nc*1}^2 \times \rho_{1*1}^2}{\max_{j=1}^{Nc} |s_{j*1} - \mathbf{SE}_{j*1}^1 \times \rho_{1*1}^1 - \mathbf{SE}_{j*1}^2 \times \rho_{1*1}^2|} \times \max_{j=1}^{Nc} |\mathbf{SE}_{j*1}^1| \quad [5]$$

where the known sensitivities, $\mathbf{SE}^1$ and $\mathbf{SE}^2$, are from intermediate maps, as shown in Fig. 2c and the known signals, ρ^1 and ρ^2 , are from the SENSE reconstruction with $R=1$ using sensitivity maps shown in Fig. 2b. After the second iteration of all folded voxels with $R=4$, the fitted sensitivity map shown in Fig. 2c is extended to the final map shown in Fig. 2d.

The maximum retroactive acceleration factor applied to the fully-sampled CEST image frame should be no less than the maximum acceleration factor intended for the other undersampled frames, and the sensitivities can be assigned analogous to Eq. [5] for cases

where $R > 4$. In the present work, a retroactive acceleration factor of four was sufficient for vSENSE with $R=2$ (Fig. 2e) and $R=4$ (Fig. 2f), resulting in a very small root normalized mean squared error (RNMSE) with respect to the $R=1$ case. The RNMSE is defined as $\|x - y\|_2 / \|x\|_2$, where x is the reference signal, y is a test signal, and $\|\cdot\|_2$ denotes the L^2 norm. Note that identical results obtain for vSENSE with $R=2$ (Fig. 2e) using sensitivity maps from either Fig. 2c or 2d.

Before implementing this incoherence absorption approach, the sensitivities in “null” regions of low signal intensity (e.g. due where surgery and lipid suppression in the scalp result in low signal intensity) must be extrapolated as noted under “second” above. Typically, an intensity threshold of 5% of the maximum value would cause null portions of scalp to be assigned to the non-support region. Since CEST imaging detects signal changes of only 2—3% (9), signal residues measured without properly extrapolating sensitivities in such null regions may be folded into other regions, causing artifacts in the final CEST map. Null regions can be automatically specified by comparing the support region masks calculated from the reference scan (which does not use lipid suppression), with the fully-sampled CEST scan. The null regions are then added to the support region after sensitivity extrapolation using LWPR.

Artifact suppression (AS) to adjust sensitivities

An alternative to IA for suppressing artifacts in the final unfolded images is to use the fully-sampled CEST scan to adjust sensitivity maps in a self-consistent manner we call an “artifact suppression” (AS) approach. First, an initial raw sensitivity map is required. This can be calculated from the fully-sampled CEST image frame and scaled (Fig. 2g) as in the IA approach, or obtained from the reference scan after image co-registration and interpolation. Second, LWPR is used to fit sensitivities in the support region and to extrapolate sensitivities in the non-support region (Fig. 2h). Third, the regular SENSE reconstruction is performed with $R=1$ and the extrapolated sensitivity maps, to produce images without unfolding artifacts.

Fourth, for a retroactive acceleration factor of two (without loss of generality) on the fully sampled frame,

$$\mathbf{s}_{Nc \times 1} = \begin{bmatrix} \mathbf{SE}_{Nc \times 1}^1 & \mathbf{SE}_{Nc \times 1}^2 \end{bmatrix} \times \begin{bmatrix} \rho \rho_{1 \times 1}^1 \\ \rho \rho_{1 \times 1}^2 \end{bmatrix} = \begin{bmatrix} \mathbf{SE}_{Nc \times 1}^1 & \mathbf{SE}_{Nc \times 1}^2 \end{bmatrix} \times \begin{bmatrix} \mathbf{A}_{1 \times 1}^1 & 0 \\ 0 & \mathbf{A}_{1 \times 1}^2 \end{bmatrix} \times \begin{bmatrix} \rho \rho_{1 \times 1}^1 \\ \rho \rho_{1 \times 1}^2 \end{bmatrix}$$

[6]

Here, $\mathbf{SE}^1$ and $\mathbf{SE}^2$ are the potentially inaccurate sensitivities in two folded voxels from the extrapolated sensitivity map. $\mathbf{pp}^1$ and $\mathbf{pp}^2$ are the reconstructed voxel signals solved with $R=2$ and potentially subject to unfolding artifacts, and $\mathbf{p}^1$ and $\mathbf{p}^2$ are the accurate voxel signals solved with $R=1$ above. $\mathbf{A}^1$ and $\mathbf{A}^2$ are scaling factors such that

$\rho\rho_{1*1}^1 = \mathbf{A}_{1*1}^1 \times \rho_{1*1}^1$ and $\rho\rho_{1*1}^2 = \mathbf{A}_{1*1}^2 \times \rho_{1*1}^2$. To ensure the accuracy of unfolded images, the sensitivities are adjusted as follows,

$$\mathbf{s}_{Nc*1} = \begin{bmatrix} \mathbf{SE}_{Nc*1}^1 & \mathbf{SE}_{Nc*1}^2 \end{bmatrix} \times \begin{bmatrix} \rho\rho_{1*1}^1 \\ \rho\rho_{1*1}^2 \end{bmatrix} = \begin{bmatrix} \mathbf{SSE}_{Nc*1}^1 & \mathbf{SSE}_{Nc*1}^2 \end{bmatrix} \times \begin{bmatrix} \rho_{1*1}^1 \\ \rho_{1*1}^2 \end{bmatrix} \quad [7]$$

where $\mathbf{SSE}^1$ and $\mathbf{SSE}^2$ are sensitivities that satisfy $\mathbf{SSE}_{Nc*1}^1 = \mathbf{A}_{1*1}^1 \times \mathbf{SE}_{Nc*1}^1$ and $\mathbf{SSE}_{Nc*1}^2 = \mathbf{A}_{1*1}^2 \times \mathbf{SE}_{Nc*1}^2$.

Fifth, after running through all the folded voxels with $R=2$, the extrapolated sensitivity map is adjusted to the map shown in Fig. 2i, and an artifact-free unfolded image (Fig. 2k) is generated upon SENSE reconstruction. Adjusted sensitivity maps can be generated for $R=4$, using the same strategies as in Eqs. [6–7], which despite exhibiting some non-smoothness (Fig. 2j), yield artifact-free unfolded images (Fig. 2m). Note that adjusted sensitivity maps should be computed for each acceleration factor separately (Fig. 2i and 2j), lest unfolding artifacts ensue (Fig. 2l vs. 2k).

Choice of a starting sensitivity map

The starting sensitivity map for the IA approach can only be computed from the fully-sampled CEST image frame (Figs. 2a–2f). If it is computed from the reference scan, strong unfolding artifacts may occur, as exemplified in Figs. 3a–3e. However, the AS approach can use sensitivities computed from either the fully-sampled CEST frame (Figs. 2g–2m) or the reference scan (Figs. 3f–3k) as the starting sensitivity map. The adjusted map derived from the reference scan (Fig. 3i) exhibits stronger non-smoothness than that derived from the fully-sampled CEST frame (Fig. 2j) due to its inferior accuracy. The more accurate the starting sensitivity maps are, the closer to unity are the scaling factors, $\mathbf{A}^1$ and $\mathbf{A}^2$. To ensure stability, the scaling factors are typically delimited to a range of 0.5–1.5. Note however, that the AS approach will fail if the starting map is mal-defined and substantially different than the correct map. Both the IA and the AS approaches require one of the CEST image frames to be fully sampled while the other frames can be undersampled with any customized pattern. A flowchart for implementing the vSENSE method using the IA and AS approaches is shown in Fig. 4.

METHODS

MRI Experiments

All the phantom and *in vivo* experiments were conducted on a 3 Tesla Philips Achieva MRI system (Best, Netherlands) using a 32-channel-receive head coil. All human studies were approved by the Johns Hopkins Institutional Review Board. One normal volunteer and eight patients with pathology-confirmed brain tumors were recruited, and written informed consent obtained from all participants.

The phantom study was performed on a vendor-provided, doped water phantom. A three-dimensional (3D) SENSE reference scan was implemented at the beginning of the exam in a

coronal orientation (GRE sequence; FA=1° TE=0.8ms; TR=4ms; acquisition resolution=4.7×4.7×3mm³; FOV=450×300×300mm³; number of signal averages, NSA=3). The sequence was run in a combined scan with the phased-array and body coils activated serially for reception, resulting in a total scan-time of 39s. CEST scans were performed with 0.8s duration, 2μT saturation pulses (24), preceding a transaxial two-dimensional (2D) turbo spin-echo (TSE) sequence (FA=90°; TE=7.5ms; TR=3s; acquisition and reconstruction resolution=1×1×2mm³; FOV=256×256×2mm³; turbo-factor=16). The CEST scan was implemented with nine saturation frequencies applied at ±3, ±3.5, ±3.5, and ±4ppm with respect to both the water frequency, and an unsaturated (S₀) acquisition. The total duration of the CEST scan was 7.3min for a SENSE acceleration factor of $R=1$, and 1.9min for $R=4$.

The patient studies also commenced with a SENSE reference scan using the same parameters as those used in the phantom study. Anatomical FLAIR (56) and T₁-weighted (T₁w) images were then acquired from each patient for clinical assessment. The FLAIR images were acquired using an interleaved multi-slice TSE sequence (TE=120ms; TR=11s; inversion recovery delay, TI=2.8s; scan-time=3.9min). The T₁w images were acquired with a 3D MP-RAGE (57) sequence (TE=3.7ms; TR=8ms; TI=805ms; scan-time=3.4min). CEST imaging used the same 0.8s 2μT saturation pulses as above (24), with a fat-suppressed transaxial 2D TSE sequence (FA=90°; TE=6.5ms; TR=3s; acquisition and reconstruction resolution=2.2×2.2×4.4 and 0.83×0.83×4.4mm³, respectively; FOV=212×186×4.4mm³; turbo-factor=84). The CEST scan was implemented using 52 saturation frequencies from 14 to -8ppm relative to water, with a step size of 0.5ppm, plus the S₀ acquisition (20). The image frames at ±3.5ppm were acquired with NSA=4, while the other frequencies used NSA=1, resulting in a total duration of 2.7min with a SENSE factor $R=1$. A 2D TSE “WASSR” (58) sequence with fat-suppression was acquired separately for B₀ inhomogeneity correction (saturation duration=0.4s at 0.5μT; 26 saturation frequencies from 1.5ppm to -1.5ppm in 0.125ppm steps; scan duration=35s including S₀).

Image reconstruction and analysis

All processing and analysis was performed offline using in-house software written in Matlab (Mathworks R2015a, Natick, MA) on a personal laptop computer (2.7GHz).

First, a 4 × 4 transformation matrix, composed of the product of the rotation, translation, flipping, and scaling matrices, was created to transform reference scan images from the viewing coordinate system (here, in a coronal plane) into a fixed Cartesian coordinate system as viewed from the front of the scanner, based on the imaging parameters in the scan header (resolution, FOV, off-centers, angulations, patient orientation, and read-out gradient direction). Another 4 × 4 transformation matrix was similarly generated to transform the CEST scans from the viewing coordinate system (transaxial) into the same fixed Cartesian coordinate system. Co-registered and interpolated reference scan images from the phased-array and body coils, matching the location, resolution, and FOV of the CEST images, were then generated using the two transformation matrices. The reference sensitivity maps were computed by dividing registered images from each of the phased-array coils by registered images from the body coil. As exemplified in the Theory, a support region was created by masking the registered body coil image at a threshold of 5% of its maximum value. A

second-order LWPR with a tri-cubic weighting kernel (54) was used, with a window size of 6 for fitting in the support region and of 24 for extrapolation in the non-support region.

Second, sensitivity maps for the vSENSE method were computed according to the Theory and Fig. 4. The fully-sampled image frame was either the S_0 scan or the 3.5ppm scan. For the IA approach, one set of refined sensitivity maps was calculated after two iterations using $R=2$ and $R=4$ successively, using data from the fully-sampled CEST scan. For one of the 8 patients, a null region was identified and extrapolated following the IA protocol steps (Fig. 4, left-most branch). For the AS approach, two sets of adjusted sensitivity maps were generated for $R=2$ and $R=4$, using starting sensitivity maps from either the reference scan or the fully-sampled CEST scan. For both the IA and AS approaches that started from the fully-sampled scans, the support regions were identified by thresholding the RSS image of all channels at 40% (for the phantom study) or 5% (for human studies) of the maximum values. Fitting and extrapolation using LWPR was performed with the same parameters stated above.

Third, for comparison, sensitivity maps were generated by applying LWPR in the support region, either with or without LWPR extrapolation in the non-support region, and with global fitting (59-61). These sensitivity maps all used the data from the fully-sampled CEST scans after proper scaling, as in the IA and AS methods. Specifically, the thresholding, fitting, and extrapolation steps used settings identical to those described above. The global fitting method tested polynomial orders from 1 to 10, and the order that provided the minimal RNMSE was chosen.

Fourth, for in-house regular SENSE, the k -space was undersampled by increasing the phase-encoding gradient step size constantly throughout all CEST image frames retrospectively. For vSENSE, the k -space was fully-sampled for one frame and variably undersampled for the other frames retrospectively. Images were unfolded by solving Eq. [1] using a truncated singular value decomposition method (62), discarding singular values of less than 1% of the maximum value, using the various sensitivity maps.

The RNMSE of accelerated images derived from each set of sensitivity maps was calculated vs. $R=1$ based on the same maps, except for the AS method, which was compared with the extrapolated maps, as shown in Fig. 2h and Fig. 3g. A linear mixed model was used to compare the RNMSE from different SENSE and vSENSE methods with a compound symmetry covariance type, followed by a post-hoc Bonferroni pairwise comparison (random factor: subject index; fixed factor: reconstruction method) (63). A P -value < 0.05 was considered significant. For patient studies, APT-weighted maps were generated after B_0 correction from the WASSR data (9).

RESULTS

Fig. 5 shows that the accelerated conventional SENSE method (Fig. 5b), using sensitivity maps from the reference scan, had a much greater error (Fig. 5i) than those (Figs. 5j–5n) using sensitivities estimated from the fully-sampled S_0 scan (Figs. 5c–5g). Figs. 5c and 5j confirm (55) that there was a larger error with no extrapolation into the non-support region

than when extrapolation was implemented (Figs. 5d–5g and 5k–5n). For fitting and extrapolation, the local fitting method (Figs. 5e and 5l) substantially outperformed the global fitting method (Figs. 5d and 5k). However, results from the AS (Figs. 5f and 5m) and IA (Figs. 5g and 5n) approaches had the smallest error of all strategies.

Fig. 6 illustrates results from a brain tumor patient, where the currently-standard implementation of SENSE using a separate reference scan (Fig. 6b) resulted in a substantial error (Fig. 6e) as compared to the fully-sampled image (Fig. 6a). Indeed, both the AS (Figs. 6c and 6f) and IA (Figs. 6d and 6g) methods outperformed the conventional SENSE method. As in the normal volunteer results (Fig. 5), the local fitting (see Supporting Information, Figs. S1e and S1l) and global fitting (Figs. S1d and S1k) methods, were both inferior to the AS and IA methods *in vivo*, even though all used the same sensitivity maps calculated from the fully-sampled S_0 frame. In contrast to the phantom results (see Supporting Information, Fig. S2), where the IA approach had a smaller error, the AS method consistently yielded a smaller RNMSE than the IA method in normal volunteers (Fig. 5) and patients (Figs. 6 and S1).

Table 1 lists the results of the 6 possible combinations for implementing the vSENSE method, in all 8 brain tumor patients (the sampling patterns are depicted in Figure S3 of the Supporting Information). The 6 combinations based on the flowchart in Fig. 4 are: the IA approach with either (i) the S_0 scan, or (ii) the 3.5ppm scan fully sampled (columns 4–5); the AS approach with (iii) the fully-sampled S_0 , or (iv) fully-sampled 3.5ppm scan as the starting sensitivity map (columns 6–7) but no reference scan; and the AS approach with either (v) the S_0 scan or (vi) the 3.5ppm scan fully sampled, but using the reference scan as the starting sensitivity map (columns 8–9). Sensitivity maps from all 6 vSENSE strategies (columns 4–9) generated a smaller error ($P < 0.02$) than the regular SENSE method with $R=4$ (column 3) and even with $R=2$ (column 2). Among the six strategies, the AS approach with the S_0 frame fully sampled and using a reference scan (column 8) resulted in a significantly smaller error than the others ($P < 0.02$ vs. columns 4–5; $P \approx 1$ vs. columns 6, 7 and 9). The reduction in error for vSENSE with $R=4$ was 3-fold and 6-fold vs. conventional SENSE with $R=2$ and $R=4$, respectively (columns 8–9 vs. 2–3).

Fig. 7 demonstrates typical results from a case in which conventional SENSE with a constant undersampling factor of four (Fig. 7d), produced corrupted APT-weighted images, as compared to the full k -space results (Fig. 7c; blue and red arrows in the tumor, and periphery indicate SENSE-reconstruction artifacts vs. Fig. 7c). In contrast, the vSENSE method with variable acceleration, generate APT-weighted images (Figs. 7e–7j) consistent with the full k -space data (Fig. 7c), for all six combinations of strategies, as reflected by the results from all patients reported in Table 1.

Fig. 8 demonstrates that the conventional SENSE method with sensitivity maps calculated from the reference scan would produce a substantial error (9.4%) in the compartmental z-spectrum (red in Fig. 8b) vs. the full k -space spectrum (blue in Fig. 8b), if implemented in a variable acceleration fashion, i.e., $R=1$ for the S_0 frame, $R=2$ for the ± 3.5 ppm frames, and $R=4$ for the other CEST saturated frames. On the contrary, the vSENSE method produced z-

spectra (red in Figs. 8c–8h) indistinguishable from the full k -space spectrum (blue in Figs. 8c–8h), using sensitivity maps based on the six different methods reported in Table 1.

Fig. 9 presents a special case where prior surgery and fat suppression caused a local signal null in the scalp (Fig. 9c; orange arrow, on S_0 image). This null region causes substantial artifacts (Fig. 9g; white arrow) if not extrapolated in accordance with Fig. 4. With extrapolation, both the AS (Fig. 9f) and IA (Fig. 9h) approaches yield APT-weighted maps that are consistent with the full k -space map (Fig. 9d), while regular SENSE with $R=4$ shows substantial artifacts (Fig. 9e; red and blue arrows).

DISCUSSION

The core difficulty of sensitivity encoding is obtaining an accurate sensitivity profile. CEST places stringent demands on signal accuracy because the CEST changes *in vivo* are typically only a few percent. Therefore, the application of conventional SENSE to CEST is fraught with potential errors that manifest as artifacts and limit acceleration factors to about 2-fold (Figs. 8-9, Table 1). Nevertheless, long acquisition times are a major hurdle to the clinical translation of CEST imaging. The vSENSE method presented here, addresses these issues with a variable sampling pattern for the different saturation-offset acquisitions that comprise a CEST study, requiring only that one frame is fully sampled. In conjunction with the proposed IA (Fig. 2) or AS (Fig. 3) strategy, the vSENSE method yields significantly better results than those from conventional SENSE implementation (Figs. 5–9 and Table 1). Specifically, conventional SENSE using sensitivity maps calculated from a separate reference scan has significant errors (Table 1, Figure 9), even when used with a variable undersampling pattern (Fig. 8b), while the errors with vSENSE employing IA and AS strategies described here, are on average up to 6 times smaller at $R=4$.

The IA approach assigns the incoherent contributions, based on and without changing the sensitivities in the support region, to sensitivities in the non-support region to isolate their effects on the unfolded images in the support region. This coupling between the sensitivities in the support and non-support regions, requires that the sensitivities in the support region be accurate, that is, a fully-sampled frame and not a separate reference scan is necessary to avoid unfolding artifacts in the support region. In contrast, the AS approach suppresses artifacts in unfolded images by imposing non-smooth artifacts onto the sensitivity maps in both support and non-support regions, without requiring highly accurate sensitivities to start with. Although the IA approach was superior to AS on phantom data, its more stringent requirement on the accuracy of the starting sensitivity maps (Figs. 2–3), limits its performance relative to the AS approach *in vivo* (Table 1), where motion effects cannot be ignored. Nevertheless, IA vSENSE with $R=4$ significantly outperformed regular SENSE with $R=2$ and $R=4$ ($P < 0.02$), as well as vSENSE sensitivity maps estimated from beginning CEST frames (S_0 or 3.5ppm) and then applied to the last CEST frame (14ppm). This demonstrates its robustness to the (relatively limited) range of motion encountered in practice.

One slight complication in the implementation of the IA approach (Fig. 4) is that null regions must be identified when present (Fig. 9). The sensitivities in the support region are

constant through all CEST frames, while the incoherent contributions can vary between the scans. However, as long as the relative intensities of the incoherent contributions from the phased-array coils stay close to the ratios of the assigned sensitivities across individual coil elements, they are generally not folded into the support-region. In Fig. 9, the null region rendered an unstable signal residue that did not follow the relative ratios of assigned sensitivities, which would produce unfolding artifacts in the final CEST map if not extrapolated (Fig. 9g).

The SNR characteristics of vSENSE follow those of the conventional SENSE method (35); see g-factor maps in Figs. S4–S5 of Supporting Information). Here, the ± 3.5 ppm CEST frames were undersampled less than other frames in order to ensure adequate SNR for APT imaging, analogous to the common practice of acquiring more averages at ± 3.5 ppm (9,24). The undersampling pattern is easily adapted for other CEST imaging applications, such as creatine (51) or glucose (16,17) imaging. Note that a smaller RNMSE, as in Table 1, does not necessarily correspond to a higher SNR. Also note that the drastic change of signal intensities between different CEST frames renders the estimation of sensitivity maps from interleaved even and odd k -space lines as in UNFOLD (64), error-prone (see Fig. S6 in Supporting Information). The vSENSE method could also be adopted for other imaging applications that involve repeat application of MRI pulse sequences with varied timing, frequency, gradient strength or duration parameters, such as those deployed in functional, diffusion, perfusion, and relaxation time mapping.

CONCLUSION

In conclusion, the proposed vSENSE method generated more accurate sensitivity maps, permitted a higher overall acceleration factor, and yielded smaller errors than conventional SENSE. As implemented here for CEST imaging, vSENSE essentially doubled the speed and provided more accurate results than conventional SENSE, which, in combination, may provide an important advance for translating CEST to the clinic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Comparison of saturated images at 3.5ppm from a doped water phantom, obtained directly from the scanner's (a-b) and from the authors' in-house (c-d) reconstruction. (a) A SENSE acceleration factor R of 1 was prescribed on the scanner. (b) All scanning settings were identical to those in part (a), except that the R factor was set to 4. For offline, in-house reconstruction, the sensitivity maps were computed from the reference scan after image co-registration and interpolation based on saved geometric parameters. The same sensitivity maps were used for SENSE reconstruction with $R=1$ (c) and $R=4$ (d), using raw k -space data from part (a). The difference between parts (b) and (d) reveal some differences in our implementation of SENSE compared to the scanner's proprietary reconstruction which was inaccessible. The comparison serves as a quality check for in-house implementation.

Figure 2.

Intermediate sensitivity maps calculated from the fully-sampled CEST unsaturated S_0 frame using the incoherence absorption (a-f) and artifact suppression (g-m) approaches. For the IA approach, the raw sensitivity map was first scaled by a scaling map estimated from the reference scan (a), and then fitted using the LWPR method (b). Then, two IA iterations were implemented using retroactive SENSE acceleration factors of two (c) and four (d) successively. The final IA sensitivity map (d) was used to reconstruct images at 3.5ppm, with $R=2$ (e) and $R=4$ (f). The RNMSE in (e) and (f) was computed against the image reconstructed with $R=1$ using maps, as in part (d). For the AS approach, the raw sensitivity map was also first scaled (g), as in the IA approach, and then fitted and extrapolated using the LWPR method (h). Then, two AS maps were generated using retroactive SENSE R factors of two (i) and four (j), respectively. These two AS maps were used to reconstruct images at 3.5ppm with $R=2$ (k, l) and $R=4$ (m), respectively. The RNMSE in (k–m) was computed against the image reconstructed with $R=1$, using maps, as in part (h). Blue arrows indicate differences in sensitivity maps between the two IA iterations. Red arrows denote non-smoothness or unfolding artifacts in the images.

Figure 3.

Intermediate sensitivity maps calculated from the reference scan using the incoherence absorption (a-e) and artifact suppression (f-k) approaches. For the IA approach, the raw sensitivity map was estimated from the reference scan after image co-registration, interpolation, and fitting (a). Then, two IA iterations were implemented using retroactive SENSE acceleration factors of two (b) and four (c) successively. The final IA sensitivity map (c) was used to reconstruct images at 3.5ppm with $R=2$ (d) and $R=4$ (e). The RNMSE in (d) and (e) was computed against the image reconstructed with $R=1$ using maps, as in part (c). For the AS approach, the raw sensitivity map was first estimated (f), as in the IA approach, and then extrapolated using the LWPR method (g). Then, two AS maps were generated using retroactive SENSE R factors of two (h) and four (i), respectively. These two AS maps were used to reconstruct images at 3.5ppm with $R=2$ (j) and $R=4$ (k), respectively. The RNMSE in (j) and (k) was computed against the image reconstructed with $R=1$ using maps, as in part (g). Blue arrows indicate differences in sensitivity maps between the two IA iterations. Red arrows denote non-smoothness or unfolding artifacts in the images.

Figure 4.

Flowchart for implementing the vSENSE method with sensitivity maps computed using either the incoherence absorption approach or the artifact suppression approach. LWPR standards for locally weighted polynomial regression.

Figure 5.

Comparison of saturated images at 6ppm from a normal volunteer using different acceleration factors and sources of sensitivity maps. Parts (a–b) used the reference scan for the sensitivity maps, and regular SENSE reconstruction with a constant undersampling factor. The corresponding unfolding errors for part (b) with $R=4$ vs. part (a) with $R=1$ are shown in part (i). Parts (c–g) used the S_0 frame as the source of sensitivity maps and vSENSE with variable undersampling ($R=1$ for S_0 and $R=4$ for the other frames). Part (c) used sensitivity maps from LWPR only in the support region. Part (d) used sensitivity maps based on a 7th order global polynomial fitting. Part (e) used sensitivity maps from LWPR in both the support and the non-support regions. Part (f) used sensitivity maps derived from the AS approach, while the IA strategy was employed in part (g). Difference maps compared to the $R=1$ result are shown in parts (j–n) for the corresponding sensitivity maps used in parts (c–g), respectively. The k -space undersampling pattern for $R=4$ is shown in part (h; right). Red arrows indicate non-smooth artifacts.

Figure 6.

Comparison of saturated images at 14ppm from a brain tumor patient using different acceleration factors ($R=1$ for part a; $R=4$ for parts b–d) and different sensitivity map sources (from the reference scan for parts a–b; from the S_0 frame for parts c–d). (a–b) For regular SENSE, reconstruction with a constant undersampling factor for all frames was used, with unfolding errors shown in part (e). (c–d) For vSENSE, frames were undersampled variably, i.e., $R=1$ for S_0 and $R=4$ for the other frames, with sensitivity maps from AS (c) and IA (d), respectively. Difference maps in (f–g) were computed against $R=1$ results with corresponding sensitivity maps. Red arrows indicate non-smooth artifacts. (For more details, see Supporting Information, Figure S1).

Figure 7.

Anatomical (a–b) and APT-weighted (c–j) images from a brain tumor patient. APT-weighted images from regular SENSE ($R=1$ for part c; $R=4$ for part d) were obtained using sensitivity maps calculated from the reference scan. APT-weighted images from vSENSE were obtained from variably undersampled data, i.e., $R=1$ for S_0 , $R=2$ for the ± 3.5 ppm frames and $R=4$ for the other frames (parts e, g, i), or $R=1$ for the first 3.5ppm frame, $R=2$ for the rest ± 3.5 ppm frames and $R=4$ for the other frames (parts f, h, j), using either the IA (parts e–f) or the AS (parts g–j) approach. As for the AS approach, the starting sensitivity maps were either from the fully sampled CEST frame (parts g–h) or from the reference scan (parts i–j). (Sampling patterns are depicted in Supporting Information, Figure S3).

Figure 8.

Z-spectra in a selected region of interest obtained from accelerated SENSE and vSENSE (red spectra) vs. full k -space results (blue spectra). Blue z-spectra in parts b–h were from regular SENSE with $R=1$ using sensitivity maps estimated from the reference scan. Both accelerated SENSE and vSENSE used variably undersampled data, i.e., $R=1$ for S_0 , $R=2$ for the ± 3.5 ppm frames and $R=4$ for the other frames (parts b, c, e, g), or $R=1$ for the first 3.5ppm frame, $R=2$ for the rest ± 3.5 ppm frames and $R=4$ for the other frames (parts d, f, h). As for the AS approach, the starting sensitivity maps were either from the fully sampled CEST frame (parts e–f) or from the reference scan (parts g–h).

Figure 9.

Anatomical (a–b), unsaturated CEST frame (c), and APT-weighted (d–h) images from a brain tumor patient. APT-weighted images from regular SENSE ($R=1$ for part d; $R=4$ for part e) were obtained using sensitivity maps calculated from the reference scan. APT-weighted images from vSENSE were obtained from variably undersampled data, i.e., $R=1$ for S_0 , $R=2$ for the ± 3.5 ppm frames and $R=4$ for the other frames (parts f–h), using either the AS approach (parts f) or the IA approach (parts g–h). For the AS approach, the starting sensitivity maps were from the reference scan (parts f). For the IA approach, sensitivity maps were computed either without (part g) or with (part h) the null region, as identified by the orange arrow in part (c).

Table 1

Root normalized mean squared error (RNMSE) for the saturated image at 14ppm from eight brain tumor patients using accelerated SENSE and vSENSE against full k -space results. Images from accelerated SENSE were obtained from constantly undersampled data ($R=1$ for column 2; $R=4$ for column 3) using sensitivity maps calculated from the reference scan. Images from accelerated vSENSE were obtained from variably undersampled data, i.e., $R=1$ for S_0 and $R=4$ for the other frames (columns 4, 6, 8), or $R=1$ for the first 3.5ppm frame and $R=4$ for the other frames (columns 5, 7, 9), using either the IA approach (columns 4–5) or the AS approach (columns 6–9). As for the AS approach, the starting sensitivity maps were either from the fully sampled CEST frame (columns 6–7) or from the reference scan (columns 8–9).

Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9
Patient index	SENSE $R=2$	SENSE $R=4$	IA vSENSE S_0	IA vSENSE 3.5ppm	AS vSENSE S_0	AS vSENSE 3.5ppm	AS vSENSE S_0 , Ref	AS vSENSE 3.5ppm, Ref
1	0.0346	0.0725	0.0194	0.0182	0.0109	0.0084	0.0090	0.0089
2	0.0345	0.0809	0.0186	0.0195	0.0101	0.0106	0.0136	0.0100
3	0.0349	0.0943	0.0177	0.0212	0.0097	0.0203	0.0095	0.0186
4	0.0328	0.0965	0.0125	0.0210	0.0093	0.0161	0.0096	0.0138
5	0.0308	0.0439	0.0297	0.0295	0.0170	0.0123	0.0117	0.0100
6	0.0312	0.0820	0.0164	0.0229	0.0112	0.0153	0.0089	0.0126
7	0.0322	0.0741	0.0205	0.0311	0.0109	0.0128	0.0092	0.0120
8	0.0301	0.0540	0.0217	0.0225	0.0109	0.0141	0.0086	0.0125
Mean $\pm$ Std	0.0326 $\pm$ 0.0019	0.0748 $\pm$ 0.0183	0.0196 $\pm$ 0.0050	0.0232 $\pm$ 0.0046	0.0113 $\pm$ 0.0024	0.0137 $\pm$ 0.0036	0.0100 $\pm$ 0.0017	0.0123 $\pm$ 0.0030