



## RESEARCH ARTICLE

# Retrospective Brain Motion Correction in Glutamate Chemical Exchange Saturation Transfer (GluCEST) MRI

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### Abstract

**Purpose:** To evaluate the feasibility of motion correction in glutamate chemical exchange saturation transfer (GluCEST) imaging, using a rat model of epileptic seizure.

**Procedures:** Epileptic seizure was induced in six male Wistar rats by intraperitoneal injection of kainic acid (KA). CEST data were obtained using a 7.0 T Bruker MRI scanner before and 3 h after KA injection. Retrospective motion correction was performed in CEST images using a gradient-based motion correction (GradMC) algorithm. GluCEST signals in the hippocampal regions were quantitatively evaluated with and without motion correction.

**Results:** Calculated GluCEST signals differed significantly between the pre-KA injection group, regardless of motion-correction implementation, and the post-KA injection group with motion correction ( $3.662 \pm 1.393\%$  /  $3.726 \pm 1.982\%$  for pre-KA injection group with/without motion correction vs.  $6.996 \pm 1.684\%$  for post-KA injection group with motion correction; all  $P < 0.05$ ).

**Conclusions:** Our results clearly show that GradMC can be used in CEST imaging for efficient correction of seizure-like motion. The GradMC can be further implemented in various CEST imaging techniques to increase the accuracy of analysis.

**Keywords:** Chemical exchange saturation transfer, Gradient-based motion correction, Glutamate, Retrospective motion correction

## Introduction

Movement of the subject during magnetic resonance imaging (MRI) causes quality degradation of the image and misreading in quantitative evaluations [1–3]. The most fundamental reasons for motion effects occurrences in MR images are the long scan times

that are required for high-resolution imaging. Degraded image quality not only causes a change in the anatomical structure but can also have a detrimental impact at the molecular level in quantification analyses. Therefore, performing motion correction prior to image analysis is an important consideration. To date, in order to solve the problems arising from motion effects, numerous studies have been performed using various prospective correction methods during the image acquisition process, as well as retrospective corrections that are performed after image acquisition [1, 4–6]. In addition, the autofocusing (AF) method has been

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introduced as a type of retrospective motion correction that does not require specialized data trajectory strategies, in contrast to prospective methods; however, this method requires reference data from navigator-based trackers in order to cope with a large number of unknown motion parameters [7–9]. Recently, gradient-based motion correction (GradMC), which is a modified form of the AF method, using small random initialization as the initial value for motion trajectory as well as motion trajectory gradient entropy metrics as a cost function, has also been introduced for advanced motion correction [10, 11]. This method iteratively corrects translation and rotation, until image quality can be improved no further.

Chemical exchange saturation transfer (CEST) MRI has been used for molecular level exploration *in vivo* and to detect metabolite content indirectly, based on exchange-related properties [12–14]. In particular, glutamate-CEST (GluCEST) imaging has been shown to be capable of imaging parenchymal glutamate levels in the brain by measuring the exchange of glutamate amine protons with bulk water [15]. GluCEST has been used in investigations in various clinical fields, such as epilepsy, neurodegeneration, schizophrenia, and Huntington’s disease, for determining the glutamate distribution in the disease region of the brain [16–18]. Therefore, the CEST technique, including GluCEST, can be a powerful tool in clinical diagnosis, research, and in the pre-clinical field. However, its main disadvantage is that it requires a relatively long scan time to collect whole-voxel datasets and z-spectrum, while varying the resonance frequency around the water, which causes subject motion during scanning, resulting in image degradation.

In this study, we applied the GradMC algorithm to CEST data to investigate the feasibility of motion correction and to determine how the motion correction procedure affects qualitative and quantitative results in CEST imaging. Motion-corrupted CEST data, obtained using a rat model of epilepsy, were used to reflect arbitrary head motion inside the head coil due to seizure, and data analyses were performed with and without the motion correction algorithm before as well as after epileptic seizure.

## Materials and Methods

### CEST Experiments

All animal experiments were approved by the University of Ulsan Animal Care and Use Committee, and the experiments were performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

For epileptic seizure rat modeling, male Wistar rats ( $n = 6$ , 250–300 g, Orient Bio Inc., Seongnam, Rep. of Korea) were injected intraperitoneally with kainic acid (KA) [19, 20]. All rats were scanned at two time-points: before and 3 h after KA injection. We performed the first scan (pre-injection) after insertion of the intraperitoneal injection line for KA administration with the rat located outside the bore

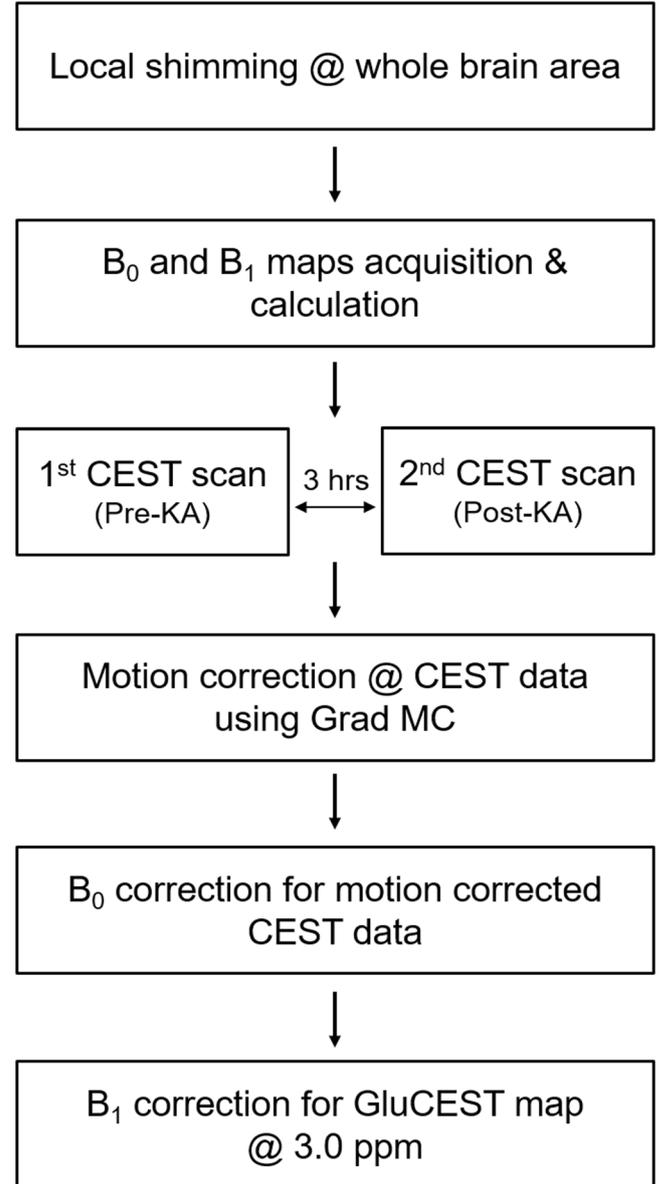
of the MRI system. The second scan (after injection) was performed after a manual injection to minimize the possible position changes during each scan session. All rats therefore remained anesthetized, with 1.5–2.0 % isoflurane in the air, for the total preparation and scanning period (approximately 240 min; 60 min for MR scanning and 180 min for delay after KA injection). The respiration of each rat was monitored online using a small-animal respiratory-gating system (SA Instruments Inc., Stony Brook, NY, USA), and its temperature was maintained at approximately  $37.5 \pm 0.5$  °C using a warm-water circulating flat-bed (CW-05G Heated Circulating Water Bath; MIDSCI, St. Louis, USA) positioned around its body.

Images were acquired using a 7.0 T Bruker pre-clinical MRI scanner (PharmaScan 70/16, Bruker BioSpin GmbH, Germany). We performed local shimming using a region-of-interest (ROI,  $34 \times 34 \times 34$  mm<sup>3</sup>) covering the whole brain area, prior to imaging, to achieve a homogeneous magnetic field and a high signal-to-noise ratio in the MRI system. CEST data were acquired from +3.67 ppm to –3.67 ppm, in 0.33 ppm steps, using the turbo-RARE pulse sequence on a single slice. Each slice contains a well-observed hippocampus region, which is a well-known brain region to evaluate glutamate level changes in epilepsy [18, 21, 22]. The following parameters were implemented: repetition time/echo time = 4200 ms/36.4 ms, field of view =  $30 \times 30$  mm<sup>2</sup>, matrix size =  $96 \times 96$ , slice thickness = 1 mm, echo spacing = 6.1 ms, and RARE factor = 16). A long continuous-wave radiofrequency pulse (power = 5.6  $\mu$ T, and saturation time = 1 s) was used for CEST saturation. For each CEST acquisition, B<sub>0</sub> map, using the double echo-time (1.9 and 2.6 ms) method, and B<sub>1</sub> map, using the double flip-angles (30° and 60°) method, scans were also acquired to correct field inhomogeneities in the CEST data [15, 23].

### Motion Correction and Data Analysis

The GradMC algorithm, which uses the image gradient entropy metric, was applied to the CEST data, and it was constructed using the following equations:  $\mathcal{O}(u) = \mathcal{H}(D_x u) + \mathcal{H}(D_y u)$ ,  $\mathcal{H}(u) = -v^T \ln v$ ,  $v = \sqrt{[(u \odot \bar{u}) / (u^H u)]} \in \mathbb{R}_+^N$ ,  $u \in \mathbb{C}^N$ , where  $D_x$  and  $D_y$  finite difference matrices at x- and y-directions,  $\mathcal{H}(\cdot)$  is a pixel entropy,  $u$  is an unknown image matrix with size of  $n_x \cdot n_y$ , and mathematical operators  $\bar{\cdot}$  and  $\odot$  indicate the complex conjugate and Hadamard product, respectively. Since the rigid-motion transformation matrix ( $A_0$ ) can be applied to a motion-corrupted image matrix  $y$  with the empirical inversion, the equation can also be defined as follows:  $u_0 = F^H A_0 y$ , where  $u_0$  is the resulting image in the spatial domain, and  $F$  is an orthonormal Fourier matrix. Recovered motion parameters are regularized with a quadratic penalty on the differences of consecutive motion

parameters as follows:  $\theta = \arg \min_{\theta \in \Theta} \phi(F^H A_{\theta} y) + \lambda \|D\theta\|^2$ , where  $D \in \{0, \pm 1\}^{6 \cdot T \times 6 \cdot T}$  is a finite difference matrix temporally ordered by phase encodes,  $T$  indicates the number of k-space lines, and  $\lambda \in \mathbb{R}_+$  is a regularization parameter for smoothness (0.2 was used in this study). The translation correction corresponds to the multiplication of each k-space line combined with a linear phase ramp as follows:  $\exp(-2\pi i k_x \theta_t)$ , where  $k_x$  is the Fourier coefficient of the affected view, and  $\theta_t$  is a translation function in the spatial domain. The rotation correction was performed based on a deformed grid, which is determined by rotating the points of each k-space line with by time angles, and interpolation process to predict the values of the rotated point. Additionally, we performed a minimizing cost function using a multi-scale coarse-to-fine approach because the cost function used in this study was highly nonlinear considering logarithms and piecewise interpolation polynomials. Multi-scale coarse-to-fine approach refines the estimated motion parameters step-by-step from coarse to fine scales. Since the central region of the k-space contains lower frequency (high signal intensity), motion produces little offsets in the spatial domain. For this reason, it is easier to estimate and correct the motion in the coarsely sampled image. Therefore, GradMC performs the first iteration to find only the segments in the central region of the k-space surrounded by the unknown motion parameter gaps in the high-frequency views in the motion trajectory, and as the iteration progresses, the gaps reduced until the entire trajectory is recovered. More details of GradMC have been reported elsewhere [10]. We performed motion correction on the CEST data corresponding to each frequency offset, and then applied  $B_0$  and  $B_1$  corrections. For  $B_0$  correction, motion-corrected CEST data were interpolated using a cubic spline, and each voxel value of  $\pm 3.0$  ppm image was replaced by the neighborhood CEST data value, according to the amount of shift in the frequency as calculated from the  $B_0$  map. Finally, GluCEST contrasts were corrected using relative  $B_1$  values that were calculated based on the  $B_1$  map, to correct the  $B_1$  field inhomogeneity [15]. To quantify CEST data, based on the ROI drawn manually in the hippocampus region, magnetization transfer ratio asymmetry ( $MTR_{\text{asym}}$ ) curves from 0 ppm to 3.67 ppm were calculated using the following equation:  $MTR_{\text{asym}}(\Delta\omega) = [S_{\text{sat}}(-\Delta\omega) - S_{\text{sat}}(+\Delta\omega)] / S_{\text{sat}}(-\Delta\omega)$ , where  $\pm \Delta\omega$  are symmetrically located downfield and upfield from the water frequency offset (0 ppm). The GluCEST signal was normalized with  $S_{\text{sat}}(-\Delta\omega)$ , which can increase the dynamic range of the CEST contrast [24]. The quantitative GluCEST signal was evaluated at 3.0 ppm in the  $MTR_{\text{asym}}$  curve, and we implemented the GluCEST map using the GluCEST values computed pixel-by-pixel from the image. Data acquisition and analysis procedures are in Fig. 1. All image processing and motion correction procedures were performed using in-house written MATLAB R2014a (MathWorks, Inc., Natick, MA, USA) scripts.



**Fig. 1.** Flow chart of CEST data acquisition, motion correction and analysis. CEST imaging scans were performed for two-time points: pre-KA and 3 h after KA injection. Then, retrospective motion correction was performed in frequency offsets for each CEST data. The  $B_0$  field inhomogeneities calculated from field mapping were corrected in the motion-corrected CEST data. The relative  $B_1$  map was used to correct the contrast in the glutamate CEST map. All CEST analysis procedures were performed on a voxel-by-voxel basis.

### Statistical Analysis

For statistical analysis, the Wilcoxon rank-sum test was used to compare between the GluCEST signals that were motion corrected in the post-KA group and those signals in the pre-KA group, regardless of the motion correction. Moreover, this test was also used to compare between GluCEST signals

with and without motion correction in each group. A *P* value less than 0.05 was considered significant for all statistical analyses. All statistical analyses were performed using PASW statistics (version 18.0, SPSS Inc., Chicago, IL, USA).

### Results

Figure 2 shows the  $MTR_{asym}$  curves in pre- and post-KA injection groups, with and without motion correction. The  $MTR_{asym}$  curves showed no significant differences in the pre-KA injection group (motion-free; Fig. 2a), regardless of motion correction. The  $MTR_{asym}$  curves in the post-KA injection group (motion-corrupted; Fig. 2b) showed clear differences after the application of motion correction. Notably, after correcting for the seizure-like motion in Fig. 2b, the  $MTR_{asym}$  curves were improved, with clearly reduced signal changes and standard errors.

Figure 3 shows the GluCEST signals in all groups calculated at 3.0 ppm. The GluCEST signals in each paired group was not significantly different (pre-KA injection group, with and without correction;  $3.662 \pm 1.393$  % and  $3.726 \pm 1.982$  %, respectively;  $P=0.773$ , and post-KA injection group, with and without correction;  $6.996 \pm 1.684$  % and  $8.884 \pm 6.401$  %, respectively;  $P=0.989$ ). Since the pre-KA injection group had no motion, it is plausible that there were rarely GluCEST signal changes, irrespective of whether motion correction was applied. In addition, the post-KA injection group did not differ significantly after motion correction due to large range of standard error among the subjects without motion correction. Notably, as we expected, there were clear significant differences when we compared the results of the pre-KA injection group, regardless of motion correction, with those of the post-KA injection group with motion correction ( $3.726 \pm 1.982$  % vs.  $6.996 \pm 1.684$  %;  $P=0.043$ ; without motion correction in the pre-KA injection group, and  $3.662$

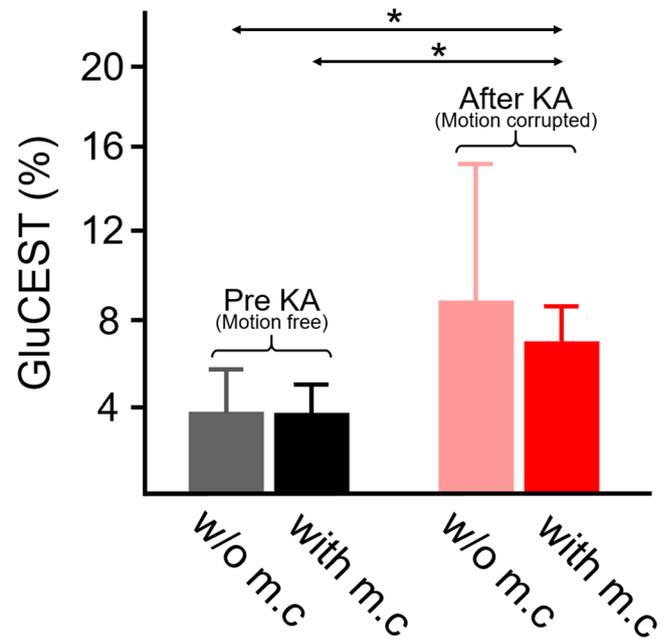


Fig. 3. Quantitative values of GluCEST signal for pre-KA (motion-free) and post-KA (motion-corrupted) injection with and without motion correction. (gray and pink bar plots: without motion correction, and black and red bar plots: with motion correction; \* $P < 0.05$ ).

$\pm 1.393$  % vs.  $6.996 \pm 1.684$  %;  $P=0.037$ ; with motion correction in the pre-KA injection group).

Figure 4 shows the reconstructed GluCEST maps (pre-KA injection group without motion correction, Fig. 4a, and with correction Fig. 4b; post-KA injection group without motion correction Fig. 4c, and with correction Fig. 4d) from a representative rat. In the pre-KA injection group (Fig. 4a, b), there were rarely signal variations, regardless of motion correction, as indicated in Fig. 3. In contrast, in the post-KA injection group, distinctive seizure motion was markedly reduced by motion correction (Fig. 4c, d). Before

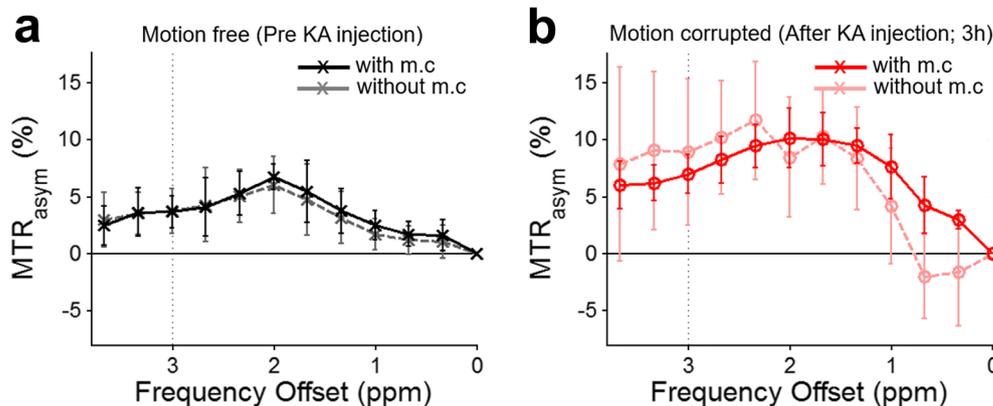
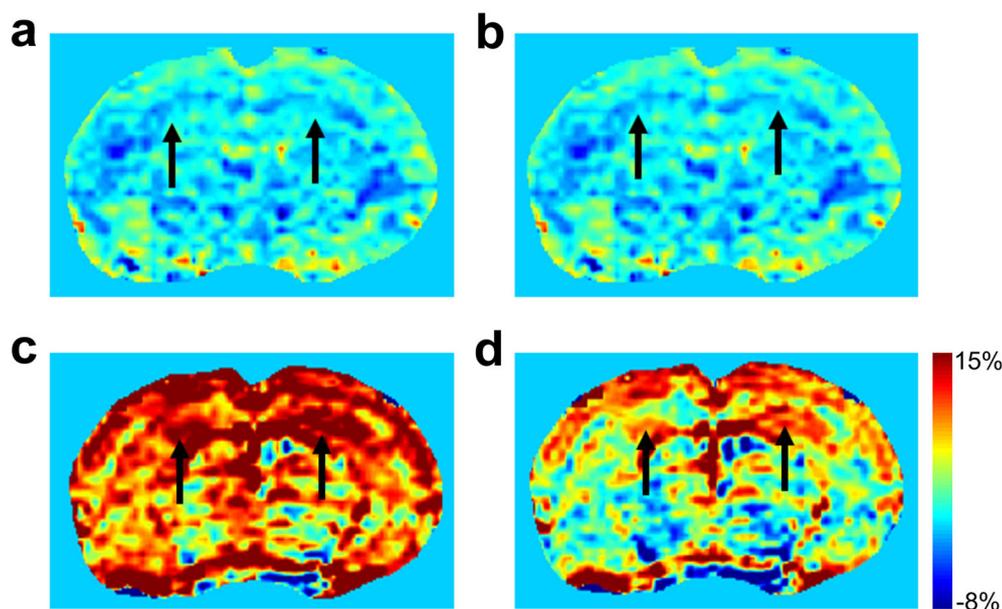


Fig. 2. Conventional  $MTR_{asym}$  curves **a** before (motion free) and **b** 3 h after (motion corrupted) KA injection. Each  $MTR_{asym}$  curve also shows the results before and after motion correction using the GradMC algorithm. (gray [a] and pink [b] dotted lines: without motion correction, and black [a] and red [b] solid lines: with motion correction).



**Fig. 4.** Reconstructed GluCEST maps **a, c** without and **b, d** with motion correction using the GradMC algorithm before (motion free **a, b**) and after (motion corrupted, **c, d**) KA injection. Black arrows indicate the glutamate signal features in the hippocampus region.

motion correction, the whole brain appeared to have high glutamate concentrations, and signals in the hippocampus appeared to be over-estimated (black arrow; Fig. 4c) as compared with the result after motion correction (black arrow, Fig. 4d).

## Discussion

To date, many successful approaches for motion correction have been introduced based on prospective and retrospective techniques [1, 4, 6, 7, 9, 23–26]. Prospective motion corrections can be involved in the use of information that is additionally acquired outside the receiver coil, with the help of motion tracking systems [6, 25, 26]. In a different way, retrospective motion corrections can be performed by constructing reference data by acquiring additional echoes through adjustment of the pulse sequence (navigator), without employing any external tracking systems [4, 7, 9]. These two approaches can ultimately yield motion-corrected results, but they may have limited applicability as they are costly and time-consuming, as additional systems or signals are needed. The GradMC explores possible motion space and selects a point in that space, such that the motion-corrected image yields the minimum value of the cost function [10, 11]. It iteratively corrects the translation and rotation from the initial information of the motion trajectory using the gradient entropy metric as a cost function. Interestingly, the GradMC can be easily applied to image motion correction by using only the acquired MR images, without the need for external motion tracking systems or specially modified pulse sequences.

In the current study, we applied the GradMC method to GluCEST data for evaluating the feasibility of motion correction in CEST imaging. Conventionally, in preclinical and clinical CEST imaging, subjects are constrained by administering anesthesia or by instructing them to remain motionless, which in effect causes motion to be nearly negligible. Therefore, the motion-correction procedure in CEST imaging generally uses an image registration method between the reference image (unsaturated image) and the images acquired at multiple offsets assuming no motion in the reference image. However, as seen in our experiments, it is difficult to perform motion correction using image registration during CEST image acquisition epileptic seizure, because even the reference image was already motion-corrupted. Therefore, instead of using an image registration method, we sought to apply another motion-correction method that can be used practically in CEST imaging in the context of a disorder involving involuntary motion, and selected the GradMC method for this study. Our results clearly showed that the GradMC could be used to correct for motion occurring during CEST imaging in a rat epileptic seizure model. In addition, our results showed negligible differences when applying the GradMC algorithm to motion-free data and found significant differences when applying it to motion-corrupted data, indicating that the GradMC algorithm effectively performed motion correction in this study, as we expected. Although there is no gold standard with which to compare our motion-correction results, in contrast to the numerous studies in which most motion correction algorithms have been applied, the efficacy of our approach can be sufficiently inferred from quantitative analysis and qualitative results from brain mapping images.

This study was designed to evaluate the effects of motion correction in GluCEST imaging. Since this study is limited to a pre-clinical epilepsy model using GluCEST imaging technique, further applications should be considered with various types of CEST imaging such as amide proton transfer, creatine CEST, glycogen CEST in the pre-clinical models, and human patients requiring motion correction to increase quantitative and qualitative accuracy. Moreover, the application of motion correction in this study was utilized single-slice CEST imaging on the hippocampus region. Moreover, future CEST image acquisitions with 2D or 3D multi-slices for applying motion correction and evaluating the level changes of exchangeable protons in detail would extend the results of the current study with the GradMC motion correction algorithm, which can be applied to 3D images as well as 2D images.

## Conclusions

We applied a retrospective motion-correction method, named GradMC, which is capable of blind estimation and correction, to CEST imaging, to evaluate the feasibility of using motion correction in a rat model of epileptic seizure. The overall results clearly indicated that the GradMC could be a useful method for motion-correcting GluCEST images, yielding quantitatively and qualitatively improved results. The GradMC may greatly facilitate motion correction for various types of CEST imaging.

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### Compliance with Ethical Standards

### Conflict of Interest

The authors declare that they have no conflict of interest.

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