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An Empirical Investigation of Motion Effects in eMRI of Interictal Epileptiform Spikes

P. Sundaram¹, R. M. Mulkern¹, W. M. Wells³, C. Triantafyllou⁵, T. Loddenkemper², E. J. Bubrick⁴, and D. Orbach¹

¹Department of Radiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

²Department of Neurology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

³Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

⁴Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

⁵A. A. Martinos Imaging Center, McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract

We recently developed a functional neuroimaging technique called encephalographic magnetic resonance imaging (eMRI). Our method acquires rapid single-shot gradient-echo echo-planar MRI (repetition time, TR = 47 ms); it attempts to measure an MR signal more directly linked to neuronal electromagnetic activity than existing methods. To increase the likelihood of detecting such an MR signal, we recorded concurrent MRI and scalp electroencephalography (EEG) during fast (20–200 ms), localized, high amplitude (> 50 μ V on EEG) cortical discharges in a cohort of focal epilepsy patients. Seen on EEG as interictal spikes, these discharges occur in between seizures and induced easily detectable MR magnitude and phase changes concurrent with the spikes with a lag of milliseconds to tens of milliseconds. Due to the time scale of the responses, localized changes in blood flow or hemoglobin oxygenation are unlikely to cause the MR signal changes that we observed.

While the precise underlying mechanisms are unclear, in this study we empirically investigate one potentially important confounding variable – motion. Head motion in the scanner affects both EEG and MR recording. It can produce brief “spike-like” artifacts on EEG and induce large MR signal changes similar to our interictal spike-related signal changes.

In order to explore the possibility that interictal spikes were associated with head motions (though such an association had never been reported), we had previously tracked head position in epilepsy patients during interictal spikes and explicitly demonstrated a lack of associated head motion. However, that study was performed outside the MR scanner and the root-mean-square error in the

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Corresponding Author: Darren B. Orbach, MD PhD, Department of Radiology, Children's Hospital Boston, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115 Phone: 617-355-5012, Darren.Orbach@childrens.harvard.edu.

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head position measurement was 0.7 mm. The large inaccuracy in this measurement therefore did not definitively rule out motion as a possible signal generator. In this study, we instructed healthy subjects to make deliberate brief (< 500 ms) head motions inside the MR scanner and imaged these head motions with concurrent EEG and MRI. We compared these artifactual MR and EEG data to genuine interictal spikes. While per-voxel MR and per-electrode EEG time courses for the motion case can mimic the corresponding time courses associated with a genuine interictal spike, head motion can be unambiguously differentiated from interictal spikes via scalp EEG potential maps. Motion induces widespread changes in scalp potential, whereas interictal spikes are localized and have a regional fall-off in amplitude. These findings make bulk head motion an unlikely generator of the large spike-related MR signal changes that we had observed. Further work is required to precisely identify the underlying mechanisms.

Keywords

interictal spike; eMRI; electroencephalography; gradient-echo EPI; head motion

Introduction

We recently developed a functional neuroimaging technique called encephalographic MRI (eMRI). Our method acquires rapid gradient-echo echo-planar imaging (EPI) and attempts to measure an MR signal more directly linked to neuronal electromagnetic activity than BOLD-fMRI. One potential contrast mechanism is based on the modulation of MR phase by local magnetic fields and has been successfully demonstrated by other investigators in phantom experiments. For a gradient-echo sequence, this phase change, $\Delta\phi$, is given as

$$\Delta\phi = \gamma \Delta B_z TE \quad (0)$$

where ΔB_z is the component of the local magnetic field along B_0 , γ is the gyromagnetic ratio, and TE is the echo time. For reliable detection of the MR signal of interest, we imaged fast (20–200 ms), localized, high amplitude (> 50 μV on EEG) cortical discharges in a cohort of focal epilepsy patients. These “interictal” discharges occur in between seizures, and result from extreme synchronization of the postsynaptic potentials of a large number of simultaneously firing contiguous neurons. On EEG, they are seen as interictal spikes (Figure 1). To achieve high temporal resolution, we used single-slice imaging; our TR of 47 ms yielded approximately 21 images per second.

We found easily detectable MR magnitude and phase changes concurrent with the interictal EEG spikes with a lag on the order of milliseconds to tens of milliseconds. The spike-related MR magnitude signal changes were large in amplitude, ranging from 33% to 100% above the mean and had morphology similar to the interictal spike. The EEG signal was well-modeled by the temporal derivative of the MR phase change time course, suggesting a tight linkage between the MR phase changes and the magnetic field changes induced by local neuronal activity. We did not observe any such fast signal changes in healthy subjects, nor were they seen in the epileptic group during EEG segments in which no interictal spikes were present. Given the time scale of the observed MR responses, on the order of a few hundreds of milliseconds, localized changes in blood flow and hemoglobin oxygenation are unlikely to cause the observed signal changes. While the precise mechanisms underlying the spike-related MR signal changes are unclear, in this study, we empirically investigate one potentially important confounding variable – bulk head motion.

We explored the issue of head motion briefly in our earlier work by recording concurrent scalp EEG and head motion. However, those studies were performed outside the MR scanner and the root-mean-square error in the measurement of head displacement was 0.7 mm. We note that even a tiny head motion during an interictal spike may well generate large MR signal changes. The inaccuracy in our earlier study therefore does not definitively rule out motion as a possible source of the signal changes observed in the epilepsy patients. In this study, we set out to preclude head motion as a possible source via (1) deliberate healthy subject head motion experiments, (2) head motion simulations, and (3) comparison of EEG scalp potentials maps for motion and spikes.

Bulk Head Motion during Simultaneous EEG-fMRI

Bulk Head Motion and EEG

With careful immobilization of the subject's head and electrode wires, high quality simultaneous EEG and MRI can be acquired. However, B₀, the static magnetic field of the MR scanner (3 tesla, in our case), is a challenging environment for EEG recording. Even if the head is securely restrained, tiny head movements can produce brief EEG artifacts that may be hundreds of microvolts in amplitude. Gross head motions cause a change in the area of the inter-electrode circuit loops normal to B₀. By Faraday's law, this magnetic flux change induces an electromotive force (emf) in the EEG electrode leads. Modeling the EEG leads as closed wire loops connected to a high-impedance amplifier, the induced voltage, V, may be given by a surface integral,

$$V = - \frac{\partial}{\partial t} \left(\int B_0 \cdot dS \right) \quad (0)$$

where dS is the normal vector to an incremental area of the scalp surface. In order to calculate the actual EEG artifact voltages observed at the amplifier, the head volume conductor must be included in the wire loop, making it difficult to define the actual area over which the flux change occurs. However, electroencephalographers can readily identify movement artifacts on EEG (and do so daily) due to lack of an electrophysiological field, i.e. the distribution of EEG responses across the scalp does not comport with a generator in the brain.

Bulk Head Motion and the MR signal

Bulk head motion accompanying interictal spikes could cause large MR magnitude signal increases similar to our results due to motion-related inflow of unsaturated spins into the imaging plane. During imaging, the spins in the slice of interest are repeatedly excited once per TR. Since T₁ ≫ TR, there is incomplete relaxation between successive RF excitations, with the spins reaching a pseudo-steady state rather than returning to equilibrium. Assuming perfect spoiling, the steady-state raw MR signal, S_{steady-state}, may be given as,

$$S_{steady-state} = \frac{M_0 \sin \theta (1 - e^{-TR/T_1})}{(1 - \cos \theta e^{-TR/T_1})} e^{-TE/T_2^*} \quad (0)$$

where M₀ is the equilibrium magnetization, θ is the flip angle, T₁ is the longitudinal relaxation time and T₂^{*} is the apparent T₂. Any change in head position relative to the slice profile will perturb this steady state, and a transition to a new steady state will occur. This transient state, which can last for several acquisitions following the displacement, will affect

both MR magnitude and phase. The MR magnitude component of these motion-related effects has been studied in the context of image realignment in BOLD-fMRI. The effect of head motion on MR phase depends on the direction of the motion with respect to the time-varying gradient magnetic fields of the scanner. Susceptibility-induced inhomogeneities in the magnetic field will also be affected by head motion. These effects have been modeled by Drobnyak et al. in the development of their fMRI simulator.

Subjects and Methods

Subjects

All subjects signed informed consent forms approved by our Institutional Review Board. We imaged 15 patients (7 male, 8 female; ages 20–57) with medically refractory focal epilepsy, referred by the Brigham and Women's Hospital Epilepsy Center. These patients were known to have frequent, high amplitude interictal discharges on EEG. One epilepsy patient was imaged twice, with the two scans 1 year apart. We also imaged 3 healthy volunteers in the same age range. One healthy subject was imaged twice, with the two scans obtained one year apart.

MRI Acquisition

All imaging was performed at 3-T, using either a GE Signa (General Electric, Milwaukee, USA, for all the epilepsy patients and 6/9 healthy volunteers) with an 8-channel phased-array head coil, or a Siemens Magnetom Trio (Siemens Healthcare, Erlangen, Germany; for 3/9 healthy volunteers) with a 12-channel head coil. We acquired concurrent EEG and MRI for all subjects using a single-slice gradient-echo EPI sequence. MR scan parameters were: TR = 47 ms, TE = 22 ms, flip angle = 20°, image matrix = 64 X 64, field-of-view (FOV) = 28 cm, slice thickness = 5 mm, in-plane pixel size = $4.375 \times 4.375 \text{ mm}^2$, and bandwidth per pixel = 2.2 kHz. We used identical scan parameters on both GE and Siemens scanners except for the TR; on the Siemens scanner, we used TR = 48 ms.

For all subjects, we acquired single-slice images at multiple axial positions. For the epilepsy patients, we positioned the axial slices to sample their suspected epilepsy foci as reported by the epileptologists. With our chosen TR, our sampling rate was approximately 21 images per second. For a given slice position, each acquisition block consisted of either 512 (on the GE) or 700 (on the Siemens) consecutive images. We acquired 10–15 such blocks for each axial position. For each time point, we reconstructed magnitude and phase difference images from per-coil complex data as described in previous work. The mean MRI scan time per subject was 30.4 min.

We also acquired anatomical images using a T1-weighted 3-D inversion recovery spoiled gradient-recalled echo sequence with TR = 7.2 ms, TE = 2.9 ms, inversion time = 600 ms, flip angle = 10°, image matrix = 256×256 , and FOV = 30 cm. Unless instructed otherwise, all subjects were asked to relax and lie still during the scan with their head immobilized with sponge cushions.

EEG Recording During MRI

We recorded either 32-channel or 64-channel EEG continuously during imaging, using an MR-compatible EEG amplifier (BrainAmp MR, BrainProducts, Munich, Germany). EEG was sampled at 5000 Hz. The EEG cap (Easycap, GmbH, Herrsching, Germany) had either 29 or 60 scalp electrodes, and one placed on the back for electrocardiogram. The electrodes were sintered Ag/AgCl rings filled with a conductive gel for good scalp contact (impedance < 10 k Ω). The EEG amplifier was securely positioned on the table behind the subject's head. The amplifier transmitted digitized EEG signals (16 bit, resolution 0.5 μV , $\pm 16.48 \text{ mV}$

dynamic range) to a recording computer in the control room via a fiber optic cable. Electric potentials at all electrodes were measured with the electrode FCz as the reference.

EEG recorded inside the MR scanner is contaminated with two artifacts: gradient artifacts due to the rapid gradient switching during imaging, and cardioballistic artifacts due to pulsatile movement of blood. We removed both artifacts using the artifact template subtraction algorithm implemented in the Vision Analyzer software (BrainProducts, Munich, Germany). The denoised EEGs were stored at 250 Hz. For further EEG processing, we used Matlab 7.1 (MathWorks, Natick, MA) and EEGLAB 6.01.

Epilepsy Patient Scans

We acquired concurrent EEG-MRI in 15 epilepsy patients. Subjects were instructed to lie still and relax during the scan. A board-certified epileptologist with expertise in EEG and epilepsy, reviewed the EEGs and identified interictal spikes while blinded to the MR images. The EEG findings were evaluated according to the following factors: morphology, frequency, localization on EEG, reactivity, symmetry, and synchrony, taking into account the baseline state of alertness. These features were used to distinguish between movement EEG artifact and intracranial epileptiform discharges. We analyzed the MR magnitude and phase images corresponding to these data and looked for interictal spike-related signal changes.

Healthy Subject Head Motion Scans

To compare MR and EEG signal changes during brief head motion with interictal spike-related signal changes, we acquired concurrent EEG and MRI during bulk head motion in 3 healthy subjects. The subjects were instructed to lie still for a period and then either nod their head slightly ($< 1^\circ$ back-and-forth head rotation about the left-right axis) for brief periods of time (< 0.5 s). We analyzed the MR magnitude and phase data separately and looked for head motion-related signal changes. We also examined scalp potential maps and time courses of the EEG signal changes induced by the head motion. We used the Vision Analyzer software (BrainProducts, Munich, Germany) to render the scalp potential maps in multiple head views (top, left, right, back, front).

Temporal Alignment of MRI and EEG

At each TR, a single TTL pulse was sent from the MR scanner to the EEG amplifier. Temporal alignment of the MRI voxel time courses and the concurrently recorded EEG was performed using in-house software, and was based solely on these TTL timing markers. EEG was recorded continuously and did not trigger the MR acquisition.

Analysis of MR Images

We examined the MR magnitude and phase difference time courses corresponding to healthy subject head motion and the interictal spikes identified by the epileptologists. In all cases, we calculated percent MR magnitude signal changes by subtracting from the images an average reference magnitude image corresponding to a quiet time segment without bulk head motion or interictal spikes. We also reconstructed MR phase difference images using a quiet time instant as the reference. For all data, we detected voxels showing high-amplitude (signal change > 3 times standard deviation above the baseline), fast (< 500 ms) MR signal changes, using in-house software. These MR magnitude and phase signal time courses were plotted on the same time axis as the concurrently recorded EEG. We analyzed the MR magnitude and phase data separately. We did not perform image registration since we acquired single-slice data.

Comparison of Scalp EEG Potential Maps for Head Motion and Interictal Spikes

To quantify the difference between scalp EEG potential maps for head motion and interictal spikes, we collected 20 instances each of head motion-induced spikes and genuine interictal spikes. For each group, we manually identified the time instant corresponding to the peak amplitude of the spike. As a measure of the spread in scalp potentials, we computed the standard deviation in the scalp potentials at the spike instant for both motion-induced spikes and interictal spikes.

Head Motion Simulations

In order to understand the type of head motion that could induce fast MR signal changes on the order of hundreds of milliseconds, we performed simulations of two types of head motions: an ‘out-of-plane’ rotation about the left-right axis, and a ‘back-and-forth’ head rotation about the same axis. In the ‘out-of-plane’ rotation case, the head does not return to its original position after the brief rotation, whereas in the ‘back-and-forth’ case, the head returns to its original position after the brief rotation. In both cases, we used a 1° degree head rotation about the left-right axis. The ‘out-of-plane’ rotation was 200 ms in duration, while the ‘back-and-forth’ rotation was 400 ms in duration.

We performed both simulations using the MR simulator POSSUM, which is based on solving Bloch equations for a given set of scan parameters and a geometric definition of the imaging sample. We used the T1-weighted scan from one of the healthy subjects in our study to define the imaging geometry. As with the real MR scans, we performed single-slice imaging simulations. We selected a single axial slice, and used the following MR scan parameters: TR = 60 ms, TE = 22 ms, flip angle = 20° , image matrix = 64×64 , voxel size = $5 \times 5 \times 5 \text{ mm}^3$. We did not account for image noise and susceptibility in our simulations. We examined the time courses of the MR magnitude signal changes corresponding to the brief prescribed head rotations.

Results

MR Responses to Interictal Spikes

As previously described, we observed fast, high-amplitude MR magnitude and phase responses concurrent with every interictal epileptiform spike in the epilepsy patients. No such signal changes were seen in healthy subjects.

Comparison of EEG and MRI Responses to Head Motion and Interictal Spikes

We found that at the level of a single electrode or a single voxel, the EEG and MR responses to head motion can mimic the corresponding responses to genuine interictal spike events. However, we can differentiate head motion from interictal spikes based on the spatial distribution of the scalp EEG potential maps. We found that head motion induces widespread changes in scalp potential. In comparison, the scalp potential maps for the interictal spikes are localized and show a regional fall-off in potential so as to constitute an electrophysiological field.

In Figures 2(a-b), we compare EEG and percent-change MR magnitude time courses at the level of a single electrode (Figure 2a), and a single voxel (Figure 2b), for the case of healthy subject head motion and a genuine interictal spike, respectively. We centered the motion and spike-related time courses about their peak to highlight their similar morphology. We can see that at the level of a single electrode or a single voxel, the artifactual head motion-related EEG and MR time courses show fast changes that evolve over hundreds of milliseconds, and can be challenging to differentiate from the corresponding responses associated with

interictal spikes. However, head motion and interictal spikes can be differentiated via scalp EEG potential maps, as shown in Figure 2(c) corresponding to the peak response time (*).

We observe similar trends in Figures 3 and 4, which show 3-second segments of eMRI data for the case of an interictal spike in an epilepsy patient and healthy subject head motion respectively. Comparison of the EEG scalp potential maps in Figures 3(c) and 4(c) confirm that head motion can in fact be differentiated from interictal spikes based on the broad scalp involvement on the EEG potential maps. We also note that in Figures 3(b) and 4(b), the spatial distribution of the MR magnitude and phase changes in the head motion case are more diffuse and less localized than in the interictal spike case.

Comparison of Scalp EEG Potential Maps for Head Motion and Interictal Spikes

We found that the scalp potential maps corresponding to the motion-induced spikes showed widespread changes in scalp potential. The scalp potential maps corresponding to interictal spikes have a regional fall-off and are localized. This is reflected in the standard deviation calculations for the scalp potentials corresponding to these two groups. The scalp potential maps corresponding to motion-induced spikes showed large standard deviation in potentials ranging from $\pm 170 \mu\text{V}$ to $\pm 871 \mu\text{V}$ with an average standard deviation of $\pm 449 \mu\text{V}$ across the scalp. In comparison, the scalp potential maps corresponding to interictal spikes showed small standard deviation in potentials ranging from $\pm 12 \mu\text{V}$ to $\pm 99 \mu\text{V}$ with an average standard deviation of $\pm 64 \mu\text{V}$.

Head Motion Simulations

We found that head motion induced changes in the MR magnitude time courses in both the 'out-of-plane' case, and in the 'back-and-forth' head rotation case. Figures 5(a-b) show MR magnitude (percent-change) time courses at the same image voxel for the 'out-of-plane' rotation, and the 'back-and-forth' rotation respectively. We found that on an individual voxel-level, the time scale of the changes caused by the 'back-and-forth' motion are high-amplitude and fast, and on the order of hundreds of milliseconds. In comparison, the 'out-of-plane' head motion induced high amplitude MR magnitude changes that decayed slowly over 3–4 seconds, depending upon the T1 value of the sample.

Discussion

We previously described fast MR magnitude and phase changes concurrent with interictal epileptiform spikes. These signal changes were only observed during EEG spike events in epilepsy patients, and no such changes were observed in healthy subjects. In this study, we set out to rule out bulk head motion as a possible source of the observed signal changes. While a review of the epilepsy literature did not reveal any reports on involuntary head motion related to interictal spikes, we still needed to preclude motion as a signal source since even tiny head movements during spikes may well cause large MR signal changes. In order to do this we measured head motion during spikes outside the scanner in the earlier work. Since that measurement had a large positional error of 0.7 mm, in this study we asked healthy subjects to make deliberate movements during scanning to see if any of the induced MR signal changes resembled those of the genuine interictal spike case.

The healthy subject head motion experiments showed that while it is possible to induce fast MR and EEG signal changes through head motion, we can differentiate head motion from genuine interictal spikes based on the spatial distribution of the scalp EEG potential maps. Head motion induces diffuse changes in EEG with broad scalp involvement, i.e. the topography of these EEG motion artifacts will not constitute an electrophysiological field since there is no localized signal fall-off. Although it is difficult to differentiate these from

the real interictal spikes by looking only at individual electrode or individual voxel time courses (as seen in Figure 2), the two cases can be unambiguously differentiated by detailed morphological and topographical analysis of the EEG. In our previous work, we acquired concurrent EEG and head motion tracking outside the scanner, to explicitly investigate whether interictal spikes were associated with head motions, and found the EEG spike activity to be uncorrelated with head motion (correlation coefficient, $r = 0.00043$). The combination of previously reported interictal spike-related changes on MR seen only in epilepsy patients and never in controls, the current analysis of EEG and MR characteristics of head motion, and the previously reported concurrent EEG-head motion tracking experiments in epilepsy patients make bulk head motion an unlikely generator of the large interictal spike-related MR signal changes in the epilepsy patients.

While bulk head motion is an unlikely source, our MR simulations of head motion suggest that a focal ‘back-and-forth’ brain tissue motion may well cause MR signal changes on the time scales that we observed. However, focal micro-motions of brain tissue and cerebrospinal fluid related to epileptiform spikes have never been reported. Interestingly, a recent study of Lorentz effect imaging of ionic currents in solution demonstrated large MR magnitude signal increases potentially related to the bulk motion of water molecules induced by ionic flow. For a detailed discussion on other possible mechanisms, we refer the reader to our earlier work .

Conclusion

We recently described fast MR magnitude and phase changes concurrent with interictal epileptiform spikes. In this study, we empirically investigated bulk head motion as a possible source of the large spike-related MR signal changes. We instructed healthy subjects to make brief head motions inside the scanner and acquired concurrent EEG and MRI corresponding to these motions. We compared the motion-induced eMRI signal changes to the corresponding changes induced by genuine interictal spikes. We found that while it may be challenging to differentiate head motion from interictal spikes based on single electrode EEG and single voxel MR time courses, we are able to distinguish between them based on scalp EEG potential maps. Head motion induces broad scalp-wide changes in potential while interictal spikes cause local changes in scalp potential. Electroencephalographers routinely differentiate motion-related EEG artifacts from genuine interictal spikes based on the presence of a localized electrophysiological field. These results confirm our initial reported findings, which demonstrated that interictal spikes are associated with fast MR signal changes, and exclude bulk head motion artifact as a source of those changes.

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Figure 1.

Figure 1(a). Example of an interictal epileptiform spike as seen on referential EEG. The signal shown was measured at the left frontal electrode (F7). The spike is seen at 13.1 s, and is clearly distinguishable from the background activity. This is an example of an interictal discharge, i.e., it occurs in between seizures. (b) shows the same 5 s EEG segment as in (a), on a bipolar montage. The left frontal spike is seen again at 13.1 s. This is evidenced by a downward deflection at Fp1-F7, and the upward deflection at F7-T7. This localized phase reversal constitutes an electrophysiological field, and is used by electroencephalographers to identify interictal spikes on EEG.

Figure 2.

Differentiating head motion from genuine interictal spikes. We note that it can be challenging to distinguish between the two cases based on single-electrode EEG and single-voxel MR time courses. However, we can differentiate between them based on their scalp EEG potential maps. In (a), the percent change in MR magnitude induced by a head nod in a healthy subject (red graph) mimics the MR magnitude signal change associated with a genuine interictal spike (black graph). The two MR magnitude time courses are plotted centered about their peak value, for comparison. In (b), the motion-related EEG time course (red graph) has similar morphology to the spike-related EEG time course (black graph). While the MR and EEG time courses for the two cases appear similar, we can differentiate between them via scalp EEG potential maps (in (c)). The potential maps (5 views shown) are plotted for the interictal spike and the head motion case at the time indicated by * in (a). We see that head motion induces widespread changes in scalp potential. In comparison, interictal spikes are localized and have a regional fall-off.

Figure 3.

eMRI of a genuine interictal spike in an epilepsy patient. The left-temporal EEG spike ((a), top panel) induces fast signal changes in MR magnitude ((a), middle panel) and MR phase ((a), bottom panel). In (b), images M(a-e) and P(a-e) show percent change in MR magnitude and MR phase change in radians at times (a-e) respectively. In (c), plots E(a-e) show distribution of EEG scalp potential (in μV) at times (a-e) respectively. For each time point, five head views are shown. We note that the interictal spike causes localized changes in scalp potential.

Figure 4. eMRI of healthy subject head nod. Head motion induces signal changes in EEG ((a), top panel), MR magnitude ((b), middle panel) and MR phase ((c), bottom panel). In (b), images M(a-e) and P(a-e) show percent change in MR magnitude and MR phase change in radians at times (a-e) respectively. In (c), the maps E(a-e) show distribution of EEG scalp potential corresponding to times (a-e). For each time point, five views are shown. We note that head motion causes broad changes in scalp potential, with huge variations across the scalp.

Figure 5. Simulations comparing the MR-magnitude response to an “out-of-plane” head rotation (a) with the corresponding response to a “back-and-forth” head rotation (b). In both cases, the motion was a 1° rotation about the left-right axis. In (a) and (b), we plot the MR magnitude time course corresponding to the same image voxel. We note that “back-and-forth” head motions can cause fast MR magnitude changes on the time scale of hundreds of milliseconds but the “out-of-plane” head motions induce slower signal changes that decay over several seconds back to a pseudo-steady state.