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Cluster analysis detection of functional MRI activity in temporal lobe epilepsy

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Abstract

Purpose—The objective of this pilot study was to evaluate the ability of a novel method of cluster analysis, 2dTCA, for identifying and characterizing peak fluctuations in fMRI BOLD signals in the temporal lobes and the default-mode network in temporal lobe epilepsy (TLE) without EEG.

Methods—BOLD fMRI images were acquired in seventeen TLE patients and compared to EEG. The timing of significant transient BOLD peaks was estimated by 2dTCA, and activation maps were determined.

Results—Sixteen subjects (94%) showed apparent temporal lobe activation. Mesial temporal activation was present in 76.4% (13 patients). Temporal lobe or insula activations were detected ipsilateral to the EEG focus in 64.7% (11 patients), bilaterally with no predominance in 29.4% (5 patients), and exclusively contralateral to the EEG focus in none. Eleven subjects showed activation in the so-called default-mode network including posterior cingulate, bilateral posterior parietal cortex, and sometimes anterior cingulate cortex.

Conclusions—These results demonstrate significant positive BOLD fluctuations in the temporal lobes and default-mode regions in a higher percentage of TLE patients than previously reported using other methods. These fluctuations appear physiologically relevant and suggest increased neural activity which may not be detected on scalp EEG, but which may be important in understanding the mechanisms and origins of epileptic discharges.

Keywords

functional MRI; epilepsy; activation; brain; cluster analysis

1. Introduction

Functional MRI (fMRI) is a promising technique for the localization of epileptogenic foci due to its higher spatial resolution in comparison with electroencephalogram (EEG) and other clinical functional imaging methods. In typical fMRI experiments the timing of various stimuli

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are known. The images acquired following the stimuli are statistically compared to images obtained in the absence of the stimuli to determine regions whose blood oxygenation level dependent (BOLD) signal intensity is modulated by the stimuli. The primary difficulty in using fMRI in epilepsy is that the timing of the interictal or ictal seizure activity is random and cannot be controlled.

A method to detect the timing of interictal activity is to combine fMRI acquisitions with scalp EEG recordings. The earliest attempts at monitoring EEG signals in the MRI scanner were performed using EEG-triggered fMRI (Warach et al., 1996; Seeck et al., 1998; Krakow et al., 1999; Symms et al., 1999). Later, filtering techniques allowed for simultaneous EEG/fMRI acquisition (Allen et al., 1998; Allen et al., 2000; Hoffmann et al., 2000; Kim et al., 2004). These methods use scalp EEG to detect the timing of the spikes or other events of interest that occur during the fMRI acquisition and then the image series is analyzed using conventional event-related fMRI methods (Josephs et al., 1997) to localize BOLD activation associated with the spikes or events. This method has been used to localize the BOLD response to interictal scalp EEG discharges in focal epilepsy (Lemieux et al., 2001; Al-Asmi et al., 2003; Diehl et al., 2003; Bagshaw et al., 2004; Gotman et al., 2004; Hamandi et al., 2004; Federico et al., 2005; Kobayashi et al., 2006a; Salek-Haddadi et al., 2006), as well as idiopathic generalized epilepsy (Archer et al., 2003; Salek-Haddadi et al., 2003; Aghakhani et al., 2004; Hamandi et al., 2006; Laufs et al., 2006).

Most of these studies report significant hemodynamic correlates to scalp EEG discharges in approximately 50% of the patients. Many of these are concordant or overlapping with the presumed epileptogenic region providing evidence that transient BOLD signal changes may be a reflection of epileptic neural activity. However, the above method has a number of limitations including that the scalp EEG can record only a fraction of ongoing epileptiform activity, and concomitant EEG makes fMRI cumbersome.

A complementary technique is one that uses a data-driven or exploratory approach to identify the timing of the interictal transient BOLD fMRI signal changes in the imaging data without EEG monitoring. This type of analysis would allow localization of these BOLD signal changes that may not be temporally dependent on scalp EEG recordings, but may be important in identifying the mechanisms and origins of the epileptic discharges, and possibly their propagation.

One such data-driven analysis technique is temporal clustering analysis (TCA) (Liu et al., 2000; Yee and Gao 2002; Gao and Yee 2003; Zhao et al., 2004; Lu et al., 2006). In a previous study, we developed a technique to localize BOLD interictal epileptiform activity using TCA methods (Morgan et al., 2004). We found significantly greater transient BOLD fluctuations in the epileptogenic than in the contralateral hippocampus in six temporal lobe epilepsy patients. In three patients without confirmed localization, the technique determined regions of activity consistent with those suggested by the presurgical assessments. However, Hamandi et al (Hamandi et al., 2005) found that these TCA techniques are highly sensitive to other signal changes that occur during fMRI acquisition such as motion and physiological noise. Our recent development of a two-dimensional TCA technique (2dTCA) addresses this problem by detecting and sorting out separate BOLD responses assumed to be from different sources (Morgan et al., 2007). This method was found to accurately detect multiple transient BOLD signal changes in simulated fMRI datasets.

The objective of this pilot study was to identify regions containing positive, transient fMRI BOLD signal fluctuations in temporal lobe epilepsy patients using 2dTCA without EEG as an initial investigation to understand the potential of this method to provide important and unique information regarding the localization and propagation of interictal discharges. In this group

of patients with temporal lobe epilepsy, we focused on temporal lobe activations and concordance with the epileptogenic region. Additionally, default-mode region activation is also reported, considering recent interest in this network (Archer et al., 2003; Salek-Haddadi et al., 2003; Aghakhani et al., 2004; Gotman et al., 2005; Hamandi et al., 2006; Kobayashi et al., 2006b; Laufs et al., 2006; Salek-Haddadi et al., 2006).

2. Methods

2.1 2dTCA Methods

TCA is a method for determining times at which a significantly large number of voxels have a specific BOLD signal response of interest. In this case, the response of interest is a transient BOLD peak which is defined here as when a voxel experiences a signal change that is at least 1.5 standard deviations higher than its average signal through time. The temporal clustering is done by creating a plot of the number of voxels that individually contain the response of interest at each time point of an imaging series. In other words, a histogram of the number of voxels with significant transient BOLD peaks (y-axis) versus time point in the series (x-axis) is created. We will refer to this as a reference time course (RTC). Peaks in the RTC indicate times when significantly large numbers of voxels experience the signal response of interest. To identify voxels whose signal changes are most similar to the entire RTC, the general linear model (GLM) is used. In the model, the RTC is the regressor of interest, while the motion parameters and a global time course are often used as covariates. This creates a parametric map indicating the magnitude of the linear relationship between each voxel's time course and the RTC, while attempting to account for signal changes due to motion and other global signal changes.

In the conventional TCA technique, one RTC is created for each imaging series or subject and so BOLD responses due to many different stimuli are added together. For example, a response of interest occurring at time points 10 and 30 from source A and responses of interest occurring at time points 20 and 40 from source B are combined into a histogram with peaks at time points 10, 20, 30 and 40. Using the 2dTCA technique, voxels with similar times of signal response of interest are clustered together (Morgan et al., 2007). Multiple histograms are created as columns on a two-dimensional grid. Specifically, time courses from Source A from the example would be used to create one RTC with peaks at time points 10 and 30 in one column of the grid, while time courses from Source B would be used to create a separate RTC with peaks at time points 20 and 40 in another column of the grid (see Figure 1). The similarity measure used to group voxel time courses into columns is the time of the first occurrence of the signal response of interest. All voxels whose first signal response of interest occurs at the same time will be grouped in the same RTC. In this algorithm, the number of RTCs is only limited by the number of time points in the series. However, when implemented, the algorithm combines similar RTCs so that the final result usually is in the range of approximately one to ten, although this is not constrained in the algorithm.

2.2 Subjects

Seventeen consecutive patients (7 M, 10F, age range 22-47; average 40 years) with EEG and clinical evidence of temporal lobe epilepsy were recruited for this study. All were candidates for resective surgery and had the standard clinical assessments performed including the following: detailed seizure history, neurological examination, interictal and ictal scalp-sphenoidal EEG monitoring with analysis of seizure semiology on video, brain MRI, and positron emission tomography (PET) in all but 3 patients (see Table 1). Nine patients underwent epilepsy surgery after fMRI. One patient (TC-17) had a prior right temporal lobectomy followed by a long remission, then recurrence of seizures, with evidence of recurrent right temporal focus.

2.3 MRI scanning

All MRI imaging was performed using a Philips Achieva 3T MRI scanner (Philips Medical Systems, Inc., Best, Netherlands). Subjects remained on their regular medications during the MRI scans. Informed consent was obtained prior to scanning in accordance with Institutional Review Board guidelines. Scanning included a two-dimensional, T1-weighted high-resolution image set for functional overlay covering the whole brain (256×256, FOV = 240 mm, 4.5 mm thick/0.5 mm gap, 30 axial slices), and two to three (depending on time and patient cooperation) T2* weighted gradient-echo, echo planar BOLD fMRI scans with subject instructed to hold still with eyes closed (64×64, 3.75 mm × 3.75 mm, FOV = 240 mm, 4.5 mm thick/0.5 mm gap, TE=35 ms, TR = 2 sec, 200 volumes per series). A three-dimensional, T1-weighted high-resolution image set for post-surgical MRI registration was acquired on some subjects, but not used for this study.

2.4 Image analysis

The fMRI datasets were preprocessed using SPM2 image analysis software [<http://www.fil.ion.ucl.ac.uk/spm/spm2.html>] to correct for slice timing artifact, realign the volumes and spatially smooth with a 7 mm FWHM kernel. Then the fMRI datasets for each subject were analyzed together (concatenated) for BOLD response timing using the 2dTCA algorithm implemented in IDL software (ITT Visual Information Solutions, Inc., Boulder, CO). The resulting RTCs were normalized by subtracting the mean and dividing by the standard deviation. The normalized values indicate variation (number of standard deviations) from the mean without regard for numbers of voxels included in the RTC. The normalized RTCs, the global time course (average time course of all voxels in the brain), and six motion time courses from SPM2 (three translations and three rotations) were used as regressors in the GLM in a fixed-effects analysis (Friston et al., 1995). Initial activation maps were created using each normalized RTC separately as the regressor of interest with a minimum of $t > 4$ with cluster size 5 (approximately $p < 0.01$ corrected for multiple comparisons based on AlphaSim software (Cox and Hyde 1997)). These initial activation maps showed widespread activation over both hemispheres in some subjects, and so the locations of any existing focal peaks of activation were determined. Further, we compared these peak activated regions to two types of activation that have been previously reported in studies involving simultaneous EEG/fMRI in order to provide the general characteristics of the 2dTCA activation across the group. The two types of activation discussed here are temporal lobe activation (Krakow et al., 1999; Krakow et al., 2001b; Al-Asmi et al., 2003; Bagshaw et al., 2004; Kobayashi et al., 2006a) and default-mode network activation (Kobayashi et al., 2006b; Salek-Haddadi et al., 2006).

To identify peak temporal lobe focal activation, activation t -levels were increased from four in increments of one until no activation remained in the temporal lobes. Then the map of the maximum t -level with temporal lobe activation with a cluster size of five was examined for temporal lobe activation and reported as either none, left, right or bilateral and either mesial and/or lateral. If no maps gave temporal lobe activation at the minimum t -level ($p < 0.01$), then the subject was determined to have no temporal lobe activation. If lower t -level activation maps contained bilateral activation, but higher t -level maps showed unilateral activation, then activation in maps containing the unilateral activation was reported. In most cases, if one or more maps showed bilateral activation and another showed unilateral activation, the bilateral maps showed excessively widespread activation that was likely not clinically relevant. If two maps showed different lateralization, then both were reported. We evaluated mesial and lateral temporal lobe activations separately. We also considered activations in the insula adjacent to the superior temporal gyrus.

To be identified as default-mode network activation, an activation map at the minimum t -level or higher must primarily contain default-mode regions (posterior cingulate, bilateral posterior

parietal cortex, and possibly anterior cingulate cortex). This qualitative assessment was reported as either “yes” if a default-mode map existed for this subject, or “no” if not. All reporting of both temporal lobe activation and default-mode activation was done by an investigator naïve to the clinical details of the subject (VLM) and confirmed by a second investigator (BAK).

Activation maps can be generated from many sources in this application. Some sources may be of clinical interest and others may not. Those of no clinical interest include activations related to motion (activity only on edges of brain), to motor areas (activity in primary motor cortex and supplementary motor area), and to visual activity (activity in primary visual cortex in occipital lobe). These yield very typical activation patterns which are easily identified (Morgan et al., 2007). Activations in these regions are presumed due to transient twitches or changes in attention during the scan. Any maps considered due to these sources were identified, but not reported in this work. Similarly, individual foci of activation in regions of the brain outside of the temporal lobe and default-mode network will be analyzed further for a follow-up report.

2.5 Spectral analysis

To investigate the frequency profile of the detected BOLD response resulting in the activation maps identified above (temporal lobe activation and/or default-mode network), the spectral power of the RTC was computed via a Fast-Fourier Transform (FFT). To characterize the response in the temporal lobes, the spectral power of the RTC regressor from each subject identified above with temporal lobe activation was averaged in the frequency domain. The peak average frequency of the BOLD fluctuations was then determined. The same analysis and average was performed over all subjects using the RTC regressor yielding the default-mode network activation.

3. Results

Seventeen epilepsy patients were scanned successfully and the fMRI images were analyzed using the 2dTCA methods described above. The subject demographic information as well as EEG, MRI, PET and surgical results are provided in Table 1. Most of the patients moved considerably during the acquisitions – two patients with ≤ 1 mm translation, ten patients with >1 to 2 mm translation, one patient with >2 to 3 mm translation, and four patients with ≥ 4 mm translation. However, no datasets were discarded due to motion. An average of five RTCs were created by the 2dTCA algorithm across patients (range 1-14). There was no significant correlation between number of RTCs and quantity of translational motion ($cc = -0.025$).

The 2dTCA results are provided in Table 2. Sixteen of seventeen subjects had temporal lobe activation present (94%). Only the patient with the previous temporal resection (TC-17) showed no temporal lobe activation. Mesial temporal activation was present in 13 of 17 (76.4%) patients. Of these patients, eight of 13 had activation ipsilateral to the presumed EEG epileptogenic focus (Figure 2) or bilateral activation with bilateral EEG epileptogenic foci (Figure 3). We included in this group patients TC-1 and TC-15 who showed bilateral mesial temporal activation, but clearly predominant ipsilateral to the EEG epileptogenic focus. None of the 13 patients had mesial temporal activation exclusively contralateral to the EEG focus. The remaining five of 13 patients had bilateral mesial temporal lobe 2dTCA activation (Figure 4).

Lateral temporal lobe or insula activation was present in 4 of 17 (23.5%) patients. Of those four patients, one had bilateral mesial temporal activation also. The patient with insula activation and no mesial temporal activation (TC-4) had activation lateralized to the side of the seizure focus. She was not seizure free after right temporal lobectomy (Figure 5).

Eleven of the seventeen subjects showed clear default-mode network activation including activation in the posterior cingulate, bilateral posterior parietal cortex, and sometimes in the anterior cingulate cortex. Four examples are shown in Figure 6, including maps from subjects TC-4, TC-5 and TC-7 whose temporal lobe activation maps are given in Figures 3-5.

Figure 7 shows the average frequency of the BOLD fluctuations in the temporal lobes and the default-mode network across subjects. The maximum average frequency of the BOLD fluctuations in the temporal lobes and default-mode regions were approximately 0.01 Hz and 0.02 Hz, respectively.

4. Discussion

In this preliminary study we utilized a novel method, 2dTCA, to identify transient BOLD fMRI signal peaks that may be independent of scalp EEG activity in seventeen temporal lobe epilepsy patients. Significant focal activations were found in the temporal lobes and default-mode network regions in many subjects.

4.1 Temporal lobe activations

Positive activation was detected in the temporal lobe in 16 of 17 patients. Mesial or lateral temporal lobe or insula activation was detected ipsilateral to the EEG activity in 64.7% of all subjects and bilateral with no predominance in 29.4% (patients TC-2, TC-7, TC-10, TC-13 and TC-14). Although all our patients had temporal lobe epilepsy demonstrated by a presurgical evaluation, the population was not homogeneous and may have included both lateral and mesial temporal lobe epilepsy. A future study that includes a very homogeneous group of mesial temporal lobe epilepsy with hippocampal sclerosis with seizure freedom after surgery may yield clearer findings.

Our study demonstrated a high incidence of bilateral temporal activation. This is of unknown significance, but may reflect that there is frequently bilateral pathology or bilateral physiological disturbance even with apparently unilateral temporal lobe epilepsy (Ergene et al., 2000; Maton et al., 2001; Concha et al., 2005; Seidenberg et al., 2005; Willmann et al., 2006).

The high yield of activations can be compared to the results of other recently published studies on similar groups of patients using combination EEG/fMRI (Krakow et al., 1999; Krakow et al., 2001a; Al-Asmi et al., 2003; Aghakhani et al., 2004; Federico et al., 2005; Kobayashi et al., 2005; Kobayashi et al., 2006a; Kobayashi et al., 2006c; Salek-Haddadi et al., 2006). In these studies the rate of discarding studies due to low number of interictal spikes during fMRI acquisition is between 0 and approximately 46%. If no number of discarded studies was reported, then the number was assumed to be zero. An average of 65% of the acquired studies showed some fMRI activation or deactivation anywhere in the brain. With our technique, no studies were discarded before analysis, and 94% of subjects showed fMRI activation in the temporal lobes. Across the comparable studies, fMRI activation (or deactivation) was concordant with EEG in an average of 49% of studies as compared with our 64%.

4.2 Default-mode network activation

The default-mode network of the brain first described by Raichle et al. (Raichle et al., 2001), which includes the posterior cingulate cortex, the ventral anterior cingulate cortex, and the bilateral inferior parietal cortex, is postulated to support the baseline attention state of the brain at rest. In healthy subjects these regions are negatively activated using a task-rest paradigm and are functionally connected at rest and during some passive sensory processing (Greicius et al., 2003). Similarly, these regions have demonstrated primarily negative fMRI activation

resulting from epileptic spiking in studies with simultaneous EEG/fMRI in generalized epilepsy (Archer et al., 2003; Salek-Haddadi et al., 2003; Aghakhani et al., 2004; Gotman et al., 2005; Hamandi et al., 2006; Laufs et al., 2006). Kobayashi et al. (Kobayashi et al., 2006b) and Salek-Haddadi et al. (Salek-Haddadi et al., 2006) also found negative activation due to EEG spiking in default-mode regions in approximately 12% and 11.1% of focal epilepsy patients, respectively. Many have postulated that the *negative* activation of the default-mode network following an EEG spike is manifested as a state of altered consciousness resulting from EEG discharges primarily in generalized epilepsy.

In this work, the 2dTCA algorithm detected significant *positive* transient BOLD signal changes in the default-mode network in 11 of the 17 (65%) patients studied. These are novel findings for three reasons: (1) in studies using simultaneous EEG/fMRI, only *negative* BOLD signal changes were detected following EEG spikes, (2) these findings were all in generalized epilepsy patients except for two studies (Kobayashi et al., 2006b; Salek-Haddadi et al., 2006), and (3) the rate of occurrence of negative activation in these focal epilepsy studies has been much lower than found here. The results of this study suggest that the positive default-mode BOLD fluctuations exist in focal epilepsy. However, the regions involved are not clearly related to the temporal epileptogenic focus and the physiological and/or pathological implications are unclear.

4.3 Spectral analysis

The spectral analysis revealed peak power in both regions in the very low frequency range (<0.1 Hz). This is in agreement with spontaneous very low frequency fluctuations of oxyhemoglobin and deoxy-hemoglobin detected in the brain using near infrared spectroscopy (NIRS) at rest (Obrig et al., 2000). Spontaneous BOLD fluctuations have also been measured in this range and are the basis for measurements of steady-state fMRI functional connectivity (Biswal et al., 1995; Biswal et al., 1997a; Biswal et al., 1997b; Kiviniemi et al., 2000; Cordes et al., 2001). However, the fluctuations detected in the present study may differ from the very low frequency oscillations previously reported in that they are represented in the time domain as significant transient signal increases and not simply periodic oscillations. The relationship between this spiking and the known spontaneous BOLD oscillations is not clear. Also, the effect of cardiac signal aliasing on these measurements is also unknown and must be explored further.

4.4 Limitations and potential advantages of 2dTCA

There are many theoretical advantages of the 2dTCA technique. First, it can detect and separate BOLD fluctuations due to multiple sources. This is demonstrated by the temporal lobe and default-mode network activation maps in the same subjects shown in Figures 3-6 and also the two different temporal lobe activation maps detected in the same subject in Figure 3. Another primary advantage is that the 2dTCA method does not require MRI-compatible EEG hardware and software and can detect signals that are independent of scalp EEG spiking. Therefore, if proven clinically useful, this method may be practical for many sites to implement and may be possible at higher field strengths. Processing of 2dTCA algorithm is on the order of several minutes and can be completely automated up to the creation of the activation maps. Further, the typical image acquisition time for combination EEG/fMRI studies is approximately 60-90 minutes for some (Gotman et al., 2004) and 35 minutes for others (Hamandi et al., 2004). In this study, the BOLD acquisition times ranged from 13.3 minutes to 20 minutes.

This method has the potential to detect more BOLD signal responses (interictal activity) than fMRI with EEG for two reasons: (1) no hemodynamic response model is assumed, and (2) 2dTCA may be sensitive to activity not detected by scalp EEG. The definition of the hemodynamic response can significantly affect the accuracy of the EEG techniques as shown

when higher rates of detection result from using a series of gamma functions that peak at different latencies (Bagshaw et al., 2004). It is well recognized that scalp EEG fails to record epileptiform discharges that are generated in deep brain regions, discharges that have an unfavorable dipole orientation, or discharges that involve less than 6 cm² of cerebral cortex. This issue of sensitivity of 2dTCA to activity not detected on the scalp may be explored in a future study including patients with no scalp EEG interictal spiking detected during fMRI acquisition. However, the 94% temporal lobe activation detection rate of this study, as well as the fact that the signals are measured throughout the brain and not at the scalp, suggests that this may be the case.

Conversely, there are some disadvantages of the 2dTCA that need to be addressed. The first is that the EEG correlates of the 2dTCA detected activations remain unknown. These have to be elucidated before validating the technique for clinical application. Understanding the nature of the 2dTCA activations may be furthered with evaluations of EEG/fMRI data analyzed with both conventional and 2dTCA methods.

The criterion for the second clustering is another potential limitation of this algorithm. In the present study the time of first occurrence of the signal response of interest was used to cluster the time series. If the purpose of this clustering was to determine voxels of “activation” then the results would be most sensitive to this criterion. However, the objective of this clustering step is to group similar time course and separate dissimilar ones in a general manner so that the GLM can be used to find the activated voxels. This can be illustrated in the following example. Suppose voxel A and a group of voxels B share the first instance of increase, but no other. They will be in the same cluster (histogram column) even though they are not similar in any other way. However, the linear correlation of voxel A and the RTC (highly correlated with voxel B) will be low, because the RTC has peaks at times when many voxels *share* the response of interest. Therefore, voxel A will not be detected as activated by the GLM using that regressor. On the other hand, if a voxel does not share the first signal increase, but shares many other times of signal increase with a cluster it will still be detected as activated with that regressor due to the GLM. Therefore, even if the similarity measure used here does not separate and identify each voxel into a cluster perfectly, it should still find relevant timing patterns that are shared by many voxels which can be used to find possibly clinically significant activation.

Another disadvantage of the 2dTCA technique is the potentially large number of activation maps generated. Some of these do not yield significant activation and so are easy to ignore, and others show typical visual cortex, motor cortex activation or motion artifacts which may also be considered clinically irrelevant. However, without some *a priori* knowledge some activation maps may not be understood. This is also true for any other data-driven technique, but is also relevant in EEG/fMRI techniques that in current literature also compare activity to expected epileptogenic regions without full understanding of activity present outside these regions. Future studies should aim to elucidate the meanings of these other maps and other regions of activation, perhaps with the hypothesis that these may be related to propagation of discharges or sites of developing seizure foci. Last, the reliability of both EEG/fMRI and 2dTCA activation maps are difficult to calculate. The nonparametric methods proposed by Waites et al. (Waites et al., 2005) for EEG/fMRI activation maps is a potentially useful technique that may also be modified for use in 2dTCA.

4.5 Conclusions

In this pilot study, 2dTCA is used to localize peak BOLD fluctuations in focal temporal lobe epilepsy patients that may be independent of scalp detected EEG discharges. These data showed significant positive BOLD peaks in both the temporal lobes and default-mode regions in a higher percentage of these patients than previously reported using other methods. These fluctuations appear to be physiologically relevant and suggest increased neural activity which

may not be detected on scalp EEG, but which may be important in understanding the mechanisms and origins of epileptic discharges. Future studies will explore negative, in addition to positive, 2dTCA BOLD peaks throughout the brain in epilepsy and healthy controls. Further evaluation of this technique should also explore the physiological basis of 2dTCA BOLD peaks by comparing to EEG, particularly intracranial EEG if this can be performed safely.

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Figure 1.

Graphical depiction of the TCA and 2dTCA algorithms showing how multiple reference time courses are created by the 2dTCA algorithm when multiple different voxel time courses are present in the data. Vox 1 and Vox 2 represent voxels with a similar BOLD response from Source A. Vox 3 and Vox 4 represent voxels with a similar BOLD response that is different than that of Vox 1 and Vox 2 from Source B. The reference time course resulting from the TCA algorithm incorporates peaks from all four voxels, where the reference time courses resulting from the 2dTCA algorithm separate the two different BOLD responses. Arrows indicate timing of responses of interest.

Figure 2. Activation map using 2dTCA regressor from subject TC-6 showing left mesial temporal activation ($t > 5$ cluster size 5) corresponding to her EEG, MRI and PET results.

Figure 3. Activation maps using two different 2dTCA regressors from subject TC-5 showing independent (A) left ($t > 4$ cluster size 5) and (B) right ($t > 6$ cluster size 5) mesial temporal activation corresponding to her bilateral ictal EEG results.

Figure 4. Activation map using 2dTCA regressor from (A) subject TC-10 showing bilateral mesial temporal activation ($t > 7$ cluster size 5) while her EEG, MRI and PET results pointed to a left temporal epileptogenic focus, and (B) from subject TC-7 showing bilateral mesial temporal activation ($t > 6$ cluster size 5) while his EEG showed right temporal seizure onset and PET was normal.

Figure 5. Activation map using 2dTCA regressor from subject TC-4 showing right insula activation ($t > 7$ cluster size 5) with lateralization corresponding to her EEG, MRI and PET results. Insula, rather than mesial temporal lobe activation, is consistent with seizure recurrence after right temporal lobectomy.

Figure 6. Activation map using 2dTCA regressors (top to bottom) from subjects TC-1 ($t > 6$ cluster size 5), TC-4 ($t > 5$ cluster size 5), TC-5 ($t > 4$ cluster size 5), and TC-7 ($t > 6$ cluster size 5) showing default-mode network activation in five axial slices of each subject.

Figure 7. Spectral profile of average BOLD fluctuations calculated from the reference time courses showing activation in the (A) temporal lobes and the (B) default-mode regions. The average was determined across all subjects with the specified activation.

Table 1

Subject demographics and clinical characteristics

ID	Gender/ Age (yrs)	EEG- interictal	EEG- ictal	PET	MRI	Surgery	Outcome
TC-1	M/22	R	R	R	R parahippocampal Gyrus lesion*	R Sel AH	Seizure-free
TC-2	M/40	L	L	N	Left uncal mass*	L Sel AH	Seizure-free
TC-3	F/44	L	L	N	L MTS*	L Sel AH	Postoperative seizure recurrence, with psychogenic seizures by video-EEG
TC-4	F/42	R	R	R	R MTS*	R TLo	Had a postop seizure cluster
TC-5	F/28	L	L>>R	L	L MTS*	L Sel AH	Seizure-free
TC-6	F/35	L	L	L	L MTS*	L Sel AH	seizure recurrence, apparently due to psychogenic seizures
TC-7	M/23	R	R	N	N	-	-
TC-8	M/55	R	R	N/A	R temporal cavernoma*	Lesionectomy	Seizure-free
TC-9	M/27	L	L	L	L MTS*	L Sel AH	Seizure-free
TC-10	F/37	L	L	L	N	-	-
TC-11	M/44	R	R	N	B MTS	-	-
TC-12	F/50	L	L	L	L parietal malformation	-	-
TC-13	F/41	L	L	N	L mesial-basal temporal T2 abnormality	L inferior basal temporal resection	Seizure-free
TC-14	F/37	L	L	N	N	-	-
TC-15	F/46	L	L	N/A	N	-	-
TC-16	M/57	R	R	N	R MTS	-	-
TC-17	F/49	R	-	N/A	Subtotal R temporal lobectomy	-	-

M=Male, F=Female, R=Right, L=Left, B= bilateral, N=Normal, N/A = examination not performed, MTS = mesial temporal sclerosis, * = MRI finding confirmed by tissue pathology, Sel AH= selective amygdalohippocampectomy, TLo = temporal lobectomy, None = no significant activation in that region

Table 2

Summary of 2dtTCA results

ID	# fMRI series	# RTCs	Mesial TL activation	Lateral TL/insula activation	Default-mode network activation
TC-1	3	7	B, R>L	None	Y
TC-2	3	7	B	None	Y
TC-3	3	2	L	None	Y
TC-4	3	5	None	R insula	Y
TC-5	3	15	L and R	R	Y
TC-6	2	8	L	None	Y
TC-7	3	6	B	None	Y
TC-8	3	1	None	R	N
TC-9	3	13	L	None	Y
TC-10	3	1	B	None	N
TC-11	3	5	R	None	Y
TC-12	3	3	L	None	Y
TC-13	3	1	B	None	N
TC-14	3	2	B	None	N
TC-15	3	5	B, L>R	None	Y
TC-16	3	2	None	R	N
TC-17	2	1	None	None	N

R=Right, L=Left, B= bilateral, None = no significant activation in that region, Y=Default-mode network activation was detected, N= Default-mode network activation was detected.