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Two-dimensional temporal clustering analysis for patients with epilepsy: detecting epilepsy-related information in EEG-fMRI concordant, discordant and spike -less patients

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Abstract

EEG acquired simultaneously with fMRI (EEG-fMRI) is a multimodal method that has shown promise in mapping the seizure onset zone in patients with focal epilepsy. However, there are many instances when this method is unsuccessful or not applicable, and other data driven fMRI methods may be utilized. One such method is the two-dimensional temporal clustering analysis (2dTCA). In this study we compared the classic EEG-fMRI and 2dTCA performance in mapping regions related to the seizure onset region in 18 focal epilepsy patients (12 presenting interictal epileptiform discharges (IEDs), during EEG-fMRI acquisition) with Engel I or II surgical outcome. Activation maps of both 2dTCA timing outputs (positive and negative histograms) and EEG detected IEDs were computed and compared to the region of epilepsy surgical resection. Patients were evaluated in three categories based on frequency of EEG detected spiking during the MRI. EEG-fMRI maps were concordant to the epilepsy region in 5/12 subjects, four with frequent IEDs on EEG. The 2dTCA was successful in mapping 13/18 patients including 3/6 with no IEDs detected (10/12 with IEDs detected). The epilepsy-related activities were successfully mapped by both methods in only 4/12 patients. This work suggests that the epilepsy -related information detected by each method may be different: while EEG -fMRI is more accurate in patients with high rather than lower numbers of EEG detected IEDs; 2dTCA can be useful in evaluating patients even when no concurrent EEG spikes are detected or EEG-fMRI is not effective. Therefore, our results support that 2dTCA might be an alternative for mapping epilepsy-related BOLD activity in negative EEG-fMRI(6/7 patients) and spike -less patients.

1 INTRODUCTION

The primary goal of the presurgical evaluation of epilepsy patients is to accurately localize the epileptic activity in the brain. Different noninvasive techniques have arisen as potential solutions to this challenge in patients in whom a divergent diagnosis is obtained with conventional assessments. One of the most explored methods is functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990). The fMRI signal is a blood oxygenation level dependent (BOLD) signal which can localize regions where neuronal activity produces significant hemodynamic changes with respect to the baseline fMRI signal (Ogawa 1990, Logothetis 2001). In epilepsy, these changes are usually associated with the interictal epileptiform discharges (IEDs), which are expected to be consistent with or overlap with the epileptic activity being investigated in the presurgical evaluation (Thornton et al., 2010).

The classic simultaneous EEG-fMRI analysis has proven to be a useful tool for mapping the IED-related BOLD activity in many instances (Gotman et al. 2006; Hamandi et al. 2004; Salek-Haddadi et al. 2006). Here, the timing of the interictal spikes are detected by the scalp EEG while simultaneously acquiring fMRI images. Then, the IEDs are localized as regions with fMRI signal changes concurrent with their timing. The main advantage of this multimodal acquisition is the utilization of the high temporal resolution of EEG and high spatial resolution of fMRI. However, EEG-fMRI has several disadvantages/challenges such as: (1) It requires the acquisition of simultaneous EEG-fMRI data, which needs specific MRI-compatible EEG hardware and software and experienced staff for its implementation, (2) The analysis relies on IED detection, and (3) The analysis generally does not consider the variability of the Hemodynamic Response Function (HRF) due to differences in IED shape, frequency and amplitude. Therefore, while generally considered the gold standard for localizing IEDs with fMRI, classic EEG-fMRI analysis may be insensitive to the BOLD epilepsy-related activity in many patients.

As an alternative to the classical EEG-fMRI analysis, other techniques have been proposed in the context of mapping the BOLD responses related to epilepsy independently of the IED detection by the simultaneous EEG. The Independent Component Analysis (ICA) is a data driven method that spatially decomposes the fMRI data into spatial maps without *a priori* information or strong assumptions about the fMRI data set (McKeown, 1998). The Independent Components (ICs) were found to map BOLD activities related to normal brain activities during tasks (McKeown, 1998), the default mode networks during resting state fMRI acquisitions (Fox, 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Rondinoni et al 2013) and also for mapping the epileptic BOLD-related activity (Rodionov et al., 2007; Moeller et al., 2011; Maziero et al., 2015). Particularly in epilepsy, the ICA had shown sensitivity for mapping BOLD activity related to the IEDs detected during EEG-fMRI acquisitions. However, ICA usually decomposes the fMRI data of patients with epilepsy in to a high number of ICs, which complicates the process of classifying these ICs as BOLD IED-related, scanner or physiological noise, head motion or BOLD activity not related to epilepsy.

The two-dimensional Temporal Clustering Analysis (2dTCA) (Morgan et al., 2008) is another data-driven method proposed specifically for detecting transient BOLD-related

activity independently of *a priori* information. Briefly, the 2dTCA extracts BOLD-related activities from the fMRI data series based on the assumption that T2* fluctuations must be inside a reasonable range to be considered as BOLD-related (Handwerker et al., 2004); otherwise they will be related to artifacts such as motion and susceptibility. The method groups time courses exhibiting transient fluctuations, the assumed response to an IED, at the same time in histograms composed by the number of voxels exhibiting these fluctuations at each fMRI volume. Theoretically, different sources of activity are represented by different histograms that exhibit temporal and spatial similarity among their signal fluctuations. So while ICA and 2dTCA are both data-driven, the potential advantage of 2dTCA is that only BOLD signals with specific characteristics (percent signal change over certain time period, etc.) are considered by 2dTCA which may reduce the number of resulting components to be considered. The 2dTCA showed promising results mapping BOLD activities related to transient tasks executed by healthy subjects (Morgan et al., 2009) and also to detect epileptogenic BOLD-related activities in groups of patients with temporal lobe epilepsy without EEG data inside the MR scanner (Morgan et al., 2010). However, the applicability and sensitivity of the method have been questioned when it is applied in individual fMRI datasets of epileptic patients (Khatamian et al., 2011). The authors compared the maps obtained by 2dTCA to those obtained by classical EEG-fMRI. They reported that the classical EEG-fMRI and 2dTCA found similar results when applied in data of patients whose prolonged interictal events have been recorded by the simultaneous EEG. The authors also concluded that 2dTCA would be interesting only for validating the results found by other methods (Khatamian et al., 2011). However, the data analyzed in their study were restricted to patients showing IEDs during the simultaneous EEG-fMRI acquisition and those in which the classic EEG-fMRI was able to map coherent epileptic BOLD activities.

To our knowledge the 2dTCA has never been evaluated for mapping epileptic-related activity in patients whose fMRI is expected to improve the epilepsy diagnosis, such as in patients with inconclusive (not sensitive/discordant) EEG-fMRI results, or those where the EEG-fMRI analysis is not possible (patients with no IEDs during fMRI acquisition). Besides that, 2dTCA is often based on the detection of positive variations, in relation to the baseline of T2* signals. Here, we propose to evaluate and compare the sensitivity of classic EEG-fMRI and 2dTCA methods to localize epileptic activity in a group of focal epilepsy patients with and without IEDs presented during simultaneous EEG-fMRI acquisition as a more objective measure of their general usefulness in individual presurgical evaluations. Specifically, for the first time, we evaluate how 2dTCA can provide information for patients with negative EEG-fMRI results or where this analysis is not possible. In addition, the evaluation will include 2dTCA maps resulting from both negative and positive BOLD signal changes in order to discuss whether negative histograms provide useful information about epilepsy.

2 METHODS

2.1 Patient description

We acquired EEG-fMRI data of patients with focal epilepsy from the Ribeirão Preto Epilepsy Surgery Center. Patients were enrolled during pre-surgical evaluation following

previously described protocols (Velasco et al. 2011), which is based on video-EEG, MRI, *foramen ovale* electrodes, ictal single photon emission computed tomography (SPECT) and positron emission tomography (PET). A total of 18 patients (12 M, mean = 38 yrs $\pm$ 11 yrs) (Table 1) were considered eligible by the following selection criteria: (1) the surgery follow up 18 months after surgery was Engel score I–II (Engel et al., 1993) and (2) no large head movement (fMRI data with movements greater than 2mm volume -to-volume, based on realignment parameters, were excluded). The study was approved by the local Medical Ethics Committee of the Clinical Hospital of Ribeirão Preto and written informed consent was obtained from all patients.

2.2 Healthy subjects description

We also acquired resting state EEG -fMRI data in 4 male healthy subjects (mean age = 24 yrs $\pm$ 2 yrs). These subjects were considered eligible by the following selection criteria: (1) no report of neurological illness; (2) normal EEG (3) no large head movement (fMRI data with movements greater than 2mm volume -to-volume, based on realignment parameters, were excluded). The study was approved by the local Medical Ethics Committee of the Clinical Hospital of Ribeirão Preto and written informed consent was obtained from all subjects.

2.3 MRI acquisition

All images were acquired at Hospital das Clínicas, Ribeirão Preto, São Paulo, Brazil using a 3.0T Achieva MRI scanner (Philips Healthcare, Best, Netherlands). The T2* weighted gradient-echo echo-planar imaging (EPI) sequence was acquired using an eight channel SENSE head coil with the following parameters: 32 ascending slices ($2.8 \times 2.8 \times 4$ mm³) covering the whole brain without slice gap, slice/volume TR = 62.5/2000 ms, TE = 30 ms, flip angle = 90°. Each fMRI run was composed of 600 volumes, obtained in 20 minutes. All patients were instructed to keep their eyes closed during the fMRI acquisitions. High resolution T1-weighted anatomical images were acquired with a 3D-TFE sequence: TR/TE = 6.75/3.1 ms, FA = 8°, inversion delay = 900 ms, shot interval = 2000 ms, isotropic voxels of 1 mm and SENSE = 1.

2.4 EEG data acquisition and processing

EEG was recorded using an MR-compatible EEG system (Brain Products, Gilching, Germany). A 63-electrode (Ag/AgCl, internal resistance of 5k Ω and reference at FCz) EEG cap (Easycap, Herrsching, Germany) was used according to the 10–10 international system. An additional channel for ECG was recorded in order to remove physiological artifacts. The Gradient and pulse artifacts were removed offline using the average artifact subtraction (AAS) method (Allen et al. 1998; Allen et al. 2000). The subjects did not present significant head motion during the simultaneous acquisitions, therefore we have applied volume-wise based AAS (Maziero et al., 2016). The gradient artifact-corrected EEG data were down sampled from 5000Hz to 250Hz. The IED times were identified and marked by an experienced neurophysiologist. The IEDs were grouped based on their laterality.

We classified the patients into three different groups according to the number of IEDs identified by the neurophysiologist. This classification was based on a previous study

(Saleki-Haddadi et al., 2006) where the authors reported EEG-fMRI to detect epilepsy-related BOLD changes in a patient who had 12 IEDs detected during simultaneous EEG-fMRI acquisition of 35 minutes. Our runs were composed of 20 minutes of EEG-fMRI acquisition, therefore a comparable number of IEDs to our study would be 7. Here, we considered any patient presenting more than 7 IEDs in a single hemisphere in one run of EEG-fMRI acquisition as a frequent IED patient in order to group the patients as follows:

- I.** Frequent IEDs: Seven patients presenting more than 7 IEDs in a single hemisphere in a single run of the simultaneous EEG-fMRI acquisition were included in this group.
- II.** Infrequent IEDs: Five patients presenting between 1 and 7 IEDs in a single hemisphere during a single run of the simultaneous EEG-fMRI were included in this group.
- III.** No IEDs visually detected: Six patients did not have any IED detected during the simultaneous EEG-fMRI acquisitions and were included in this group.

2.5 Images pre-processing

All image pre-processing was done in SPM 12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>) using Matlab 2013a (The MathWorks, Natick, USA). The fMRI data from healthy subjects and patients were corrected for slice timing artifact, motion corrected, co-registered to the anatomical images and spatially normalized to the MNI atlas. The anatomical images were also normalized to the MNI atlas and segmented into white and grey matter. The latter was used for generating a mask for including only voxels within the grey matter, which were further analyzed by 2dTCA and EEG-fMRI. The fMRI images were interpolated to iso-voxels ($3 \times 3 \times 3 \text{ mm}^3$), spatially smoothed by a Gaussian filter of FWHM= 6 mm and temporal high-pass filtered at 0.008 Hz.

2.6 fMRI analysis by two-dimensional Temporal Clustering Analysis (2dTCA)

As described by previous studies (Morgan et al., 2008; Khatamian et al., 2011) the 2dTCA method applies two steps for excluding background and non-interesting voxels before clustering them temporally (see Morgan et al., 2008 for more details). The first step is to exclude voxels showing $T2^*$ fluctuations outside an expected BOLD-response range, which is established by the user. Here, we assumed this range to be between 0.5–8 percent of BOLD signal mean through time. Previous studies (Morgan et al., 2010; Khatamian et al., 2011; Lopes et al., 2012) were interested only in positive changes. Here, we applied 2dTCA algorithm for both positive and negative fluctuations. The second step is to exclude all voxels that do not have transient changes larger than 1.5 standard deviations of their temporal average when all volumes acquired are considered. Both thresholds were chosen based on the BOLD-related fluctuations expected to be detected by fMRI studies (Handwerker et al., 2004) and also due to the interest in detecting transient (spike) BOLD activities using 2dTCA.

The goal of the 2dTCA is to identify time points across the fMRI acquisition where spikes in the signal, defined above as greater than 1.5 standard deviations above/below the mean, occur. In the simplest case this can be done by creating a histogram of the number of voxels

in the volume that are experiencing a spike at each time point. In 2dTCA a second clustering is done which separates groups of voxels with similar spiking patterns into separate histograms. Consider the example of an fMRI volumetric time series in which one set of voxels experience spikes at some time points t_1 and t_2 , while another set of voxels spike at times t_3 and t_4 . The original TCA methods (Liu et al., 2000) would create a single histogram with peaks at times t_1 , t_2 , t_3 and t_4 . However, the 2dTCA algorithm would create two histograms with peaks at t_1 and t_2 in one and peaks at t_3 and t_4 in the other. Therefore, for each fMRI time series(run) from each subject, the number of histograms created by the 2dTCA algorithm depends on the number of sets of voxels with similar spiking patterns.

Therefore, the output of the 2dTCA algorithm is a set of histograms indicating number of voxels meeting the above two criteria [0.5 to 8% signal change and greater than 1.5 standard deviations above/below (for negative histograms)the temporal mean] at each TR. The length of the histogram is the number of TRs in one run. Different timing profiles are represented by different histogram outputs; therefore, multiple histograms are created per run. The number of histograms can vary from run to run and from subject to subject. The resulting histograms were then used individually as temporal predictors for applying the general linear model (GLM)in SPM 12. We included the motion effects (using the 6 scan realignment parameters)as confounds for the GLM analysis. The 2dTCA is a data-driven method which does not require the simultaneous EEG data; therefore, all the 18 patients were analyzed with this method.

2.7 Classical EEG-fMRI analysis: predictor construction

Twelve patients from groups I and II had IEDs recorded during EEG-fMRI; therefore, they were included in the classical EEG-fMRI analysis. For each patient and type of IED, a predictor was modeled as stick functions convolved with the canonical hemodynamic response function (Glover et al., 1999). For patients #1, #3, #4, #6, #8, #10, #11 and #12 we obtained only one predictor per run of fMRI, due to the unilateral discharges presented during the EEG-fMRI acquisition (Table 1). However, for patients #2, #5 and #9 we derived between one and three predictors, depending on the presence of bilateral discharges in each run acquired (Table 1). For example, patient #2 had only left discharges in the first run and so only one predictor was obtained for that run; however had bilateral discharges during the second run resulting in one predictor considering right discharges, one considering left and one considering right and left together. We also included the motion effects (using the 6 scan realignment parameters) as confounds for the GLM analysis. The GLM was applied to each predictor individually.

2.8 Computing t-score maps

For both methods(IED-based or 2dTCA histograms), we only evaluated maps with $t > 0$. This was done based on the assumption that the positive BOLD response related to epileptic sources is more likely to correspond to electro-clinical findings than the negative BOLD changes, as reported by others studies (Salek-Haddadi et al., 2006; Rodionov et al., 2007). This means that for the negative 2dTCA histograms the GLM analysis identified any positive BOLD changes concurrent with transient focal negative BOLD spikes. The t -maps produced by each approach were initially thresholded at t -values with equivalent p (FWE

corrected) <0.05 and cluster size $k>5$. However, this threshold was observed to be very restrictive for the IED-derived EEG-fMRI maps, resulting in few maps with supra-threshold voxels (only one concordant to patient's epilepsy information). Therefore, we assumed a threshold of $t>3.1$ (equivalent to $p<0.001$, uncorrected) for the maps produced by classical EEG-fMRI. Then, we evaluated the number of resultant maps for the two different significance thresholds and for various cluster size thresholds of 5, 10, 15 and 30 voxels.

2.9 Classifying t-score maps

All t-maps obtained for each run/patient were visually classified into five categories as follows: (1) Epilepsy concordant maps, as described below in section 2.10; (2) Resting state networks (RSN) related maps according to literature (Damoiseaux et al., 2006; De Luca et al., 2006; Mantini 2007; Shirer et al., 2012), where we compared each map provided by 2dTCA to the examples provided by the above references (for specific details about all the RSN that we have considered in our study please read Damoiseaux et al., 2006; De Luca et al., 2006; Mantini 2007; Shirer et al., 2012). Although these studies report a larger number of RSN, in our study we found maps associated with default mode network (DMN), visual, auditory, dorsal attention, and motor processes. Additionally, we have also detected maps described in a previous study (Shirer et al., 2012) as language related – involving the superior temporal (BA 22), inferior frontal (BA 45); and medial prefrontal cortex -posterior cingulate cortex (PCC/MPFC) – showing clusters in the superior temporal area (BA 22), cingulate (BA23) and superior frontal lobe (BA 9 and 10) (Damoiseaux et al., 2006, Shirer et al., 2012); (3) Discordant maps presenting consistent activation of clusters mapping gray matter regions different than RSN related regions or the surgery cavity; (4) Artefact related maps were selected based on previous descriptions (De Martino et al., 2007), where maps related to motion residual artefacts, EPI susceptibility artefacts, vessel artefacts (e.g. physiological related, presenting peaks at large vessels) and also maps showing high levels of spatially distributed noise were considered as artefact-related; (5) Not sensitive or informative maps which were maps not presenting supra-threshold voxels or presenting supra-threshold voxels spread all over the brain (e.g. in white matter, ventricles and cerebellum). An example of each category is illustrated (Figure 1) for patient #9, a left temporal lobe epilepsy patient. For the healthy subjects (HS) the t-score maps were classified into categories 2, 4 and 5. Any other map not classified within those three categories was considered as a false positive (epilepsy concordant or discordant).

2.10 Epilepsy concordant maps

Each t-map was evaluated based on its concordance to the surgery location and the surgery outcome (Engel score I-II) of each patient. The concordance was evaluated by adapting a procedure previously applied by us and others (Grouiller et al., 2011, Maziero et al., 2015). We compared the first, second and third global maxima of each t-map produced by both approaches and its relation to the surgery cavity/indication and surgery outcome. We considered the epilepsy-related area as the resection area and its immediate proximity, which was assumed to be 15mm from resection margins/indication and within the same sublobar cortical region (Grouiller et al., 2011, Maziero et al., 2015). Therefore, any map presenting from the first to the third t-maximum cluster inside this region was considered as epilepsy-related, the cluster matching the criteria was called epilepsy-concordant cluster.

2.11 Temporal analysis of concordant clusters

The fMRI time courses from each voxel within the epilepsy-concordant cluster resulting from 2dTCA were extracted from the fMRI data of each patient. This process resulted in the so-called 2dTCA-concordant time courses (2dTCA-tcs). The time courses were used for calculating the temporal correlation between 2dTCA-tcs and the EEG-based temporal predictor determined by convolving the IEDs with the hemodynamic response function. This was done in order to determine whether the maps resulting from 2dTCA were BOLD responses related to the IEDs detected by the scalp EEG. This was only computed for the patients from Groups I and II (IEDs detected while scanning). The analyses were done in Matlab 2013a (The MathWorks, Natick, USA).

3 RESULTS

We analyzed data of 18 patients with focal epilepsy whose surgery outcome was Engel I or II (Table 1). The 2dTCA analysis was performed on all 18 patients. Twelve of these patients showed IEDs during the simultaneous EEG-fMRI acquisition and had classic EEG-fMRI analysis performed. The classic EEG-fMRI analysis best performance (Table 2) was for the smallest threshold ($p(\text{unc}) < 0.001$ and $k > 5$ voxels). Of the five patients with epilepsy concordant maps, four patients were from group I (frequent IEDs) and one patient from group II (infrequent IEDs). The 2dTCA had its best performance at the threshold level of $p(\text{FWE}) < 0.05$ and $k > 5$ voxels (Table 2). The 2dTCA analysis resulted in epilepsy-concordant maps for thirteen patients in its best performance (Table 2). The 2dTCA epilepsy concordant maps were resultant from six patients from group I, four patients from group II, and three patients from group III. The 2dTCA method mapped epilepsy-related activity in four of the five patients in whom the classic EEG-fMRI analysis produced concordant maps. The 2dTCA method provided maps of epilepsy-related activity in 6/7 patients (from groups I and II) in whom classic EEG-fMRI was negative. Considering groups I and II, EEG-fMRI analysis provided maps of epilepsy-related activity in one of the two patients whom 2dTCA did not result in concordant maps.

The number of activation maps resultant from 2dTCA considering all patients and runs was 177 ranging from 3 and 16 per patient (Table 3). Considering our classification categories, the method generated 17/177 (9.6%) epilepsy concordant maps, 32/177 (18.1%) discordant (5 of those maps were related to temporal lobe network structures, such as insula and thalamus or to the contralateral temporal lobe), 26/177 (14.7%) related to RSN, 36/177 (20.3%) related to artefacts and 66/177 (37.2%) not informative or not sensitive maps. From the 17 epilepsy concordant maps 11 were obtained from negative histograms. For the EEG-fMRI analysis there were 29 maps distributed between 1 and 6 per patient (Table 3), considering 12 patients. Considering our classification categories the method produced 5/29 (17.2%) epilepsy concordant maps, 14/29 (48.3%) discordant, 3/29 (10.3%) artefact related maps and 7/29 (24.1%) were not informative or not sensitive maps.

3.1 Frequent IEDs (group I)

The number of IEDs detected in the run where each method provided epilepsy-related maps varied from 16–84 for 2dTCA and from 16–104 for the classic EEG-fMRI results (Table 1).

Some examples are shown in Figure 2. Both methods provided epilepsy-related maps for patients #2, #4 and #6. For both methods we also verified significant t-score clusters not related to the surgery cavity in some cases.

Two subjects from group I presented bi-temporal IEDs (Subjects #2 and #5). The bilateral IEDs were visually detected only in the second fMRI run in both cases. The 2dTCA method has provided three epilepsy-related maps for patient #2, all of them mapping both temporal lobes with the highest t-score value on the right temporal lobe (one example is presented in figure 2A), within the resection cavity.

3.2 Infrequent IEDs (group II)

The number of IEDs detected in the run where the 2dTCA provided the epilepsy-related maps varied from 3–7 and from 1–7 for the classic EEG-fMRI results (Table 1). Some examples are shown in Figure 3. Both methods provided epilepsy-related maps only for patient #12. For both methods we also verified significant t-score clusters not related to the surgery cavity in some cases. For patient #10, the 2dTCA method has provided a epilepsy-related map with activation in both temporal lobes. The highest t-score value was found within the resection cavity in the right temporal lobe (Fig. 3A).

3.3 No IEDs visually detected (group III)

The 2dTCA provided epileptic -related maps for 3 out of 6 patients without IEDs on the EEG-fMRI acquisition (Fig. 4). The classic EEG -fMRI could not be performed due to the absence of IEDs in the EEG data acquired simultaneously to the fMRI. Three out of four epilepsy related maps in this group came from negative 2dTCA histograms. For this group we found one contralateral map resultant of 2dTCA analysis of Patient 18. The map presents supra-threshold voxels on the left temporal lobe for a patient whom a surgery in the right temporal lobe provided an outcome Engel I (information updated in the 18th month follow up).

3.4 Healthy Subjects

The 2dTCA analysis of four runs of fMRI (each one from a different health subject) provided 32 histograms/t-score maps. Twelve of these maps were classified as RSN (37.5%), 15 as artefacts (46.9%) and five as not informative or not sensitive maps (15.6%). None of the maps presented information that could be assumed as epilepsy related. Some examples of the maps classified as RSN are presented in Figure 5. Most of the RSN maps were found to be related to default mode network (DMN), visual, auditory, dorsal attention, motor processes, language and PCC/MPFC.

3.5 Temporal correlation between each 2dTCA-tcs and EEG-based predictor

From ten patients (Groups I and II) there were 14 epilepsy-related maps resulting from 2dTCA, only two had significant temporal correlation ($p < 0.05$) between the 2dTCA-tcs and the EEG-based temporal predictor. These patients were the #1 (run 1, $R=0.14$ and $p=0.001$) and #2 (run 1, $R=0.13$ and $p=0.002$) which both had frequent IEDs.

4 DISCUSSION

In this work we systematically compared EEG-fMRI and 2dTCA (based on positive and negative BOLD signal histograms) for localizing interictal epileptic activity non-invasively with MRI. Accuracy was based on spatial concordance with surgical resection area in patients with Engel I and II (seizure free/rare disabling seizures) outcome. The classical EEG-fMRI analysis produced 5/12 (41.6%) concordant maps considering the patients from groups I (frequent IEDs) and II (infrequent IEDs), this percentage is consistent with a previous study (Thornton et al., 2010), where the authors reported a concordance between EEG-fMRI maps and the seizure onset region in 33% of their patients in whom IEDs were detected during the simultaneous EEG-fMRI acquisitions. The classic EEG-fMRI analysis was not applied to six of our patients, due to the absence of IEDs recorded during the simultaneous acquisition. On the other hand, the 2dTCA analysis provided concordant maps in 13/18 (72.2%) patients, 10 from the groups I (frequent IEDs) and II (infrequent IEDs) and 3 from the group III (no IEDs). In four patients (#2, #4, #6 and #12) both methods did provide epilepsy concordant maps, while in one patient (#7) EEG-fMRI was alone successful.

A previous study (Khatamian et al., 2011) reported that 2dTCA has a poor performance in mapping the regions mapped by the classical EEG-fMRI analysis for patients with few IEDs recorded by the simultaneous EEG. In our results, we verified that 2dTCA provided concordant maps in 4/5 patients from group II, which is inconsistent with the previous report. We believe that the primary reason for this difference is based on the patient inclusion criteria applied in their study, where only patients with concordant EEG-fMRI maps were included in the analysis. If only those patients with concordant EEG maps from group II are considered, then 2dTCA resulted in a concordant map in the one patient where EEG-fMRI also resulted in a concordant map.

Another difference between this study and previous ones implementing 2dTCA and EEG-fMRI is the use of negative BOLD signal histograms. This refers to the search for fMRI signal spiking that have specific negative percent signal change and decrease in signal below the mean through time (negative transient signal changes). In this work, the 2dTCA was used to calculate the negative histograms, and then concurrent positive BOLD changes were identified with the $t > 0$ contrast in the GLM. In doing such, smaller regions of increased signal were identified that corresponded in time with larger regions of decreased signal detected by the 2dTCA algorithm (which is biased towards spatially large signal changes). The idea that positive and negative BOLD responses to epileptic activity are sometimes concurrent was described by Kobayashi et al. (2006). Their work and others' (Salek-Haddadi et al., 2006; Rodionov et al., 2007) suggested that widespread deactivations (negative signal changes) concurrent in time with activations (positive signal changes) may illustrate the effect of the epileptic discharge on the rest of the brain, and are remote to the epileptic activity. Our results show that in 8 patients only the negative histograms yielded positive activation concordant with the resection region which further supports this theory. Three patients had both a positive and negative histogram that were concordant (patients # 2, #6 and #10), while 2 patients had positive histograms alone which were concordant with the

resection. More work is needed to characterize the differences between the negative and positive histograms and BOLD signal changes.

Our results have consistently shown evidences that the epilepsy-related information detected by each method may be different. Firstly, we have noticed that only 4/12 patients presenting IEDs were mapped by both methods, even in such cases the spatial overlap among the areas mapped by each of them are small, if any. In addition, 2dTCA provided epilepsy-related maps in six of seven patients whom EEG-fMRI was negative and EEG-fMRI provided concordant maps in one of two patients whom 2dTCA was negative. Secondly, there were temporal correlation between 2dTCA-tcs and EEG-based temporal predictor in only two patients (patients #1 and #2). However none of these temporal correlation were strong (highest $R=0.14$).

The fMRI data analysis is strongly dependent on thresholding the statistical maps. Although some statistical conventions are often applied, such as for $p\text{-value}<0.05$, it is often complicated to set a threshold capable of correcting the multiple comparisons without being too restrictive of the data; and even more complicated when different analysis methods are compared. In our study we set the thresholds individually for each method based on the performance of each at different thresholds ($p(\text{uncorrected})<0.001$ and $p(\text{FWE})<0.05$) and the minimum number of voxels composing a cluster (5, 10, 15, 30 and 60) above that threshold. In our results, the 2dTCA presented a better performance at a threshold of $p(\text{FWE})<0.05$ (Table 2) and the classic EEG-fMRI at $p(\text{unc})<0.001$. We believe that this difference is due to 2dTCA data driven assumption that only considers the $T2^*$ variations and looks for times at which large numbers of voxels are spiking in signal intensity together. On the other hand the EEG-fMRI analysis is based on the fusion between IEDs-detected by EEG and the assumption of a related HRF detected by the $T2^*$ variations, which might reduce its statistical power due to the many assumptions related to the neuro-vascular coupling for its application. The use of multiple HRFs could probably provide more epilepsy-concordant maps for the EEG-fMRI analysis. It is important to note that even if only the 1st global maximum of the map is considered, there are concordant maps in 8/18 patients for the 2dTCA analysis. It is also important to note that independently of the threshold applied (Table 2), the 2dTCA analysis provided a higher number of epilepsy-related maps than the EEG-fMRI, and also that usually the patients/regions mapped were not the same.

One of the most challenging issues in EEG-fMRI analysis of patients with epilepsy is dealing with patients with no concurrent IEDs during the fMRI (Group III). There are a few approaches for dealing with this issue, such as the method proposed by Gruiller et al (2011). In their approach, the authors proposed using the averaged IED topography from out of scanner EEG acquisitions for producing a correlation-based predictor based on the spatial correlation between that topography and the topography of each EEG time point acquired simultaneously to the EEG. However, this approach has the tradeoff of needing the detection of a considerable number of IEDs outside the scanner to provide adequate signal to noise ratio for the averaged topography. This may be rare in patients such those from group III, who are often submitted to up 72–100 hours of video-EEG and often have just a few IEDs detected by the EEG and visually coded by the neurophysiologists. Besides that, IEDs

generated by deep structures of the brain (such as mesial temporal lobe) can be undetectable by scalp-EEG (Velasco et al., 2006; Tao and Baldwin 2007), which might also decrease the approach's sensitivity. On the other hand, the 2dTCA is a data driven method capable of mapping epileptic-related BOLD activity independent of the detection of IEDs. This is illustrated by the results obtained for patients from group III (Fig. 4), where concordant maps were found.

Data driven methods often result in multiple maps when they are applied to fMRI data of epilepsy patients. The number of maps increases the difficulty of choosing which map is derived from the BOLD signal related to the electrical activity of interest. In a previous study about ICA (Maziero et al., 2015), we found that its decomposition resulted in a range of ICs varying from 80 to 225 for each patient with epilepsy per run of fMRI, similar numbers were reported by other groups (Rodionov et al., 2007, LeVan and Gotman, 2009; LeVan et al., 2010). In the current study the 2dTCA algorithm produced between 3 and 16 maps per patient (177 considering all the patients and runs). These numbers were dramatically reduced by a visual verification where RSN-related, artefactual, not informative and not sensitive maps were excluded. The most difficult discriminations were required to separate the 49 remaining maps into epilepsy concordant and discordant. However, as any other pre-surgical evaluation method applied to epilepsy, the convergence of 2dTCA with other information such as EEG and MRI (when a lesion is detected) was verified to be helpful. We believe that the use of Electrical Source Imaging (ESI), previously applied to select epilepsy-related ICs (Maziero et al., 2015), might help in such task. However ESI accuracy lies on many parameters, such as the number of electrodes used for acquiring the data and also the method chosen for calculating the electromagnetism inverse problem (Maziero et al., 2014), which is a topic for further investigation.

Another issue in analyzing fMRI data with different techniques is to compare their sensitivity and specificity. We have defined sensitivity in two ways. First, we computed sensitivity as the number of true positive maps for each method. For this we assumed that the artefactual ICs and those of no-interest to epilepsy are easily identifiable with either method, and so are ignored. This sensitivity is then computed by dividing the number of maps classified as epilepsy concordant by the total concordant and discordant maps obtained by each method. In that scenario the sensitivities are 34.6% and 26.3% for 2dTCA and EEG-fMRI, respectively. Second, we computed the sensitivity as the true positive rate of the method to identify an accurate epilepsy concordant map. With this metric, the sensitivity of 2dTCA would be 72.2% while 41.6% for EEG-fMRI. This is only considering cases where EEG-fMRI could be applied. If we calculate EEG-fMRI sensitivity in mapping epilepsy-related BOLD activities considering all the patients invited for studies/scanned this number would be 27.7% (5 out of 18 patients). Similarly, we can derive a metric of specificity based on the number of discordant maps divided by the number of concordant and discordant maps derived by each method. This metric would result in a specificity of 65.3% for 2dTCA and 73.6% for EEG-fMRI. Taken together these results highlight the need to incorporate these methods in the context of all the presurgical testing as a confirmatory measure. While 2dTCA may provide an accurate epilepsy concordant map in more instances than EEG-fMRI, the potential number of false positive maps is high with both methods.

In the current study we have also applied 2dTCA to analyze resting state fMRI data of four healthy subjects. This analysis was meant to help in identifying RSN-related maps (i.e. default mode network, auditory, visual and dorsal/ventral attention process) and for providing information about epilepsy-discordant maps that could result from the method. No map was classified as epilepsy discordant (false-positive) in this group, suggesting that 2dTCA does not often detect presumed epilepsy-related maps by chance. The results for the group of healthy subjects were also useful to provide examples of how 2dTCA detects different RSN-related BOLD responses. The auditory map is especially important in this study, because its activations are expected to be found in the inferior regions of parietal lobes and superior gyrus of temporal lobes. Therefore, maps presenting activations on the latter regions could be often misclassified as temporal lobe epilepsy-related. Approaches such as spatial overlap between RSN maps detected in healthy subjects and maps resulting from analyzing patients could be interesting to decrease misclassification of potential RSN as epilepsy discordant or concordant. However they need to be considered carefully because the epileptiform discharges can modify the synchronization of regions that compose a RSN in healthy subjects (Centeno et al., 2014).

We believe that further investigation on the excluded maps could reveal BOLD alterations related to fluctuations in wakefulness/arousal such as those described in previous studies (Tagliazucchi and Laufs, 2014; Chang et al., 2016; Wong et al., 2016). Although the authors described how these fluctuations may affect the brain connectivity, it still is unknown how they may affect clustering approaches. Furthermore, the likelihood of detection of these potentially low frequency fluctuations by 2dTCA is low. Alternatively, while it may seem possible that 2dTCA may be sensitive to BOLD changes related to sleep spindles detected in EEG (Caporro et al., 2011), we did not find evidence of this in our data. This suggests that the hemodynamic response related to those waves may not be detectable by 2dTCA.

Finally, our results have consistently shown evidence that the epilepsy-related information detected by each method may be different. Firstly, we have noticed that only 4/12 patients presenting IEDs were mapped by both methods, even in such cases the spatial overlap among the areas mapped by each of them are small or even inexistent. Secondly, there were temporal correlation between 2dTCA-tcs and EEG-based temporal predictor in only two patients (patients #1 and #2). However none of these temporal correlation were strong (highest $R=0.14$). This is a strong indicator that a wider use of fMRI for mapping epilepsy-related activity can be achieved by combining different modalities such as ICA, EEG-fMRI and 2dTCA. In fact, in this study 14/18 patients are concordantly mapped when both methods are considered. This is an important result towards improving fMRI application in clinical practice of epilepsy, which often has its use mostly restricted to cognitive mapping. Besides that, it is clear that the data driven methods can provide insights about mapping the epilepsy-related BOLD activity where EEG-fMRI equipment/expertise is not available.

5 CONCLUSION

In this work we compared the 2dTCA algorithm to the classic EEG-fMRI approach to localize epileptic activity in 18 focal epilepsy patients with Engel I and II surgical outcomes.

Accuracy was quantified as concordance with resection area. While we believe that both of these methods are most useful when used in conjunction with other presurgical evaluations, our results provide a few suggestions. First, a conservative t-map threshold provides more accurate results for the 2dTCA algorithm, while a less stringent threshold should be used for the EEG-fMRI method. Second, negative 2dTCA histograms with positive t-maps are useful in many cases. Finally, while EEG-fMRI is most accurate in patients with high numbers of IEDs detected on concurrent EEG, 2dTCA can be useful in evaluating patients even when no concurrent EEG spikes are detected or EEG-fMRI is not effective.

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Figure 1.

Illustration of the five categories considered for classifying the t-score maps of a patient with left temporal lobe epilepsy (Engel-Ia after surgery). The images are presented in neurological convention (right on right). The t -score maps are threshold at $p(\text{FWE}) > 0.05$ and with a minimum cluster size $k > 5$. The borders of the surgical resection are shown in green, and the cluster matching the concordant criteria is indicated by the red arrow. The RSN-related map illustrates a visual activation. Artefactual activations are indicated by orange arrows.

Figure 2.

BOLD maps of patients from the group I (frequent IEDs). A) The epilepsy-related maps found by 2dTCA (p (FWE) <0.05 and cluster threshold of 5 voxels), and B) the epilepsy-related maps found by classic EEG -fMRI (p (uncorrected) <0.001 and cluster threshold of 5 voxels). The cluster matching the concordance criteria is indicated by the red arrow. For each patient, the signals + or - indicate whether the map was resultant from a positive or a negative histogram, respectively. The surgery location is described for each patient. For patients #3 and #4 the maps are overlaid on their postsurgical anatomical image.

Figure 3.

BOLD maps of patients from the group II (infrequent IEDs). A) The epilepsy-related maps found by 2dTCA ($p(\text{FWE}) < 0.05$ and cluster threshold of 5 voxels), and B) the epilepsy-related maps found by classic EEG-fMRI ($p(\text{uncorrected}) < 0.001$ and cluster threshold of 5 voxels). The cluster matching the concordance criteria is indicated by the red arrow. For each patient, the signals + or – indicate whether the map was resultant from a positive or a negative histogram, respectively. The surgery location is described for each patient. For patients #11 and #12 the maps are overlaid on their postsurgical anatomical image.

Figure 4.

2dTCA BOLD maps of patients from the group III (No IEDs visually detected) ($p(\text{FWE}) < 0.05$ and cluster threshold of 5 voxels). The cluster matching the criteria is indicated by the red arrow (1st global maximum in all patients). For each patient, the signals + or - indicate whether the map was resultant from a positive or a negative histogram, respectively. The surgery location is described for each patient.

Figure 5.

Example of Resting State Networks found in healthy subjects (HS) ($p(\text{FWE}) < 0.05$ and cluster threshold of 5 voxels). The top panels from the left to the right present respectively the RSN related to visual, default mode network and language. The bottom panels from the left to the right present respectively the RSN motor-visual, PCC/MPFC and a dorsal attention process.

Table 1

Patient information

Patient	MRI findings	Engel score	Video EEG localization	Surgery Location	#of IEDs on EEG-fMRI	
Frequent IEDs (Group I)						
1	LHA	I b	L Parietal	LCH	60L	82L
2	RMTS	I b	R Temporal	RTL	19L	10L 6R
3	LDW_LFG	I a	L Frontal	LFL	22L	-
4	RMTS	I a	R Temporal	RTL	104R	84R
5	LMTS	II	L Temporal	LTL	42L	54L 10R
6	RMTS	I b	R Temporal	RTL	23R	30R
7	RMTS	I a	R Temporal	RTL	-	16R
Infrequent IEDs (Group II)						
8	LMTS	I a	L Temporal	LTL	7L	5L
9	RMTS	II	R Temporal	RTL	1L 1R	1L 2R
10	CA	I a	R Temporal	RTL	1R	7R
11	LMTS	I a	L Temporal	LTL	1L	3L
12	RMTS	I a	R Temporal	RTL	7R	-
No IEDs visually detected (Group III)						
13	LMTS	I b	L Temporal	LTL		0
14	RFGN	I a	R Frontal	RFL		0
15	LMTS	I a	L Temporal	LTL		0
16	RMTS	I d	R Temporal	RTL		0
17	RMTS	I a	R Temporal	RTL		0
18	RMTS	I a	R Temporal	RTL		0

IEDs – interictal epileptic discharges during EEG-fMRI (2 runs per patient), R -Right, L - Left, FL - Frontal Lesionectomy, LCH-Left Central Hemisphere, TL -Temporal Lesionectomy, MTS -Mesial Temporal Sclerosis, CA -Cavernous Angioma, LDWG_LFG - Low differentiation between white and gray matter in left frontal gyrus, RFGN -Right frontal glial neoplasia. HA – Hemispheric Atrophy. The “-” indicates fMRI run excluded due to excessive head movement. The Engel score was assessed at 18 months post-surgery.

Table 2

Number of concordant maps for different thresholds

	2dTCA (N=18)												
	<i>p(unc)<0.001</i>						<i>p(FWE)<0.05</i>						
k-threshold	5	10	15	30	60		5	10	15	30	60		
#patients	13	13	13	14	10		13	11	10	8	6		
1 st max	9	9	9	8	6		8	8	6	5	4		
2 nd max	1	1	1	1	2		1	1	2	2	1		
3 rd max	3	3	3	6	2		4	2	2	1	1		
EEG-fMRI (N=12)													
#patients	5	2	2	1	0		0	1	1	1	1		
1 st max	2	1	1	0	0		0	0	0	0	0		
2 nd max	1	1	1	1	0		0	1	1	1	1		
3 rd max	2	0	0	0	0		0	0	0	0	0		

N is the number of patients in which each analysis method was applied. Bold indicates threshold with best performance used for method comparison.

Table 3

Number of maps classified into the different categories

<i>2aTCA (maps thresholded at $p(FWE)<0.05$ and $k>5$)</i>						
Patient	# of maps	# of concordant maps	# of discordant maps	# of RSN-related maps	# of artefact-related maps	# not informative/sensitive map
Frequent IEDs (Group I)						
#1	8 (3N)	1	2	0	3 (2N)	2 (1N)
#2	16 (10N)	3 (1N)	7 (1*) (4N)	0	0	6 (3N)
#3	3 (1N)	1 (1N)	1	0	1	0
#4	15 (8N)	1	2 (2N)	4 (2N)	3 (3N)	5 (1N)
#5	9 (4N)	1 (1N)	0	0	1 (1N)	7 (3N)
#6	13 (6N)	2 (1N)	2 (1N)	0	0	9 (4N)
#7	3 (2N)	0	2 (2N)	0	0	1
Infrequent IEDs (Group I)						
#8	12 (6N)	1 (1N)	1*	1	4 (3N)	5 (2N)
#9	11 (6N)	0	3 (2N)	0	2 (1N)	6 (3N)
#10	13 (8N)	2 (1N)	2 (1N)	5 (2N)	4 (4N)	0
#11	13 (6N)	1 (1N)	3 (1*)	3 (1N)	3 (2N)	3 (2N)
#12	11 (6N)	1 (1N)	0	4 (1N)	1	5 (4N)
No IEDs visually detected (Group III)						
#13	5 (3N)	1 (1N)	0	0	0	4 (2N)
#14	8 (3N)	0	1	3 (2N)	2 (1N)	2
#15	12 (5N)	0	2 (1N)	3 (2N)	5 (2N)	2
#16	4 (2N)	1 (1N)	1 (1N)	0	0	2
#17	11 (5N)	1 (1N)	2	3 (1N)	3 (3N)	2
#18	10 (4N)	0	1**	0	4 (3N)	5 (1N)
<i>EEG-fMRI (maps thresholded at $p(unc)<0.001$ and $k>5$)</i>						
Frequent IEDs (Group I)						
#1	2	0	0	0	0	2
#2	4	1	2	0	0	1

<i>2dITCA (maps thresholded at $p(FWE)<0.05$ and $k>5$)</i>							
Patient	# of maps	# of concordant maps	# of discordant maps	# of RSN-related maps	# of artefact-related maps	# not informative/sensitive map	
#3	1	0	1	0	0	0	
#4	2	1	1	0	0	0	
#5	4	0	1	0	3	0	
#6	2	1	1	0	0	0	
#7	1	1	0	0	0	0	
Infrequent IEDs (Group I)							
#8	2	0	2	0	0	0	
#9	6	0	4	0	0	2	
#10	2	0	2	0	0	0	
#11	2	0	0	0	0	2	
#12	1	1	0	0	0	0	

N indicates the number of maps resultant from negative histograms;

* indicates maps showing from 1st to 3rd maxima on temporal lobe network structures (e.g. insula and thalamus);

** indicates maps showing from 1st to 3rd maxima on contralateral temporal lobe, for TLE patients.