Electroencephalography source localization analysis in epileptic children during a visual working-memory task

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Abstract

We localize the sources of brain activity of children with epilepsy based on electroencephalograph (EEG) recordings acquired during a visual discrimination working memory task. For the numerical solution of the inverse problem, with the aid of age-specific MRI scans processed from a publicly available database, we use and compare three regularization numerical methods, namely the standardized low resolution brain electromagnetic tomography (sLORETA), the weighted minimum norm estimation (wMNE) and the dynamic statistical parametric mapping (dSPM). We show that all three methods provide the same spatio-temporal patterns of differences between the groups of epileptic and control children. In particular, our analysis reveals statistically significant differences between the two groups in regions of the parietal cortex indicating that these may serve as "biomarkers" for diagnostic purposes and ultimately localized treatment.

KEYWORDS

children, epilepsy, neuroimaging, numerical analysis, source localization

1 | INTRODUCTION

Epilepsy affects more than 65 million people worldwide while, approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years of their life.¹ Although many children self-heal before adulthood, it has been shown that children with epilepsy confront various cognitive and behavioral problems such as problems in learning, attention and memory capacity.² Thus, the systematic study of the brain (dys)functionalities of children with epilepsy, and ultimately the development of efficient/targeted treatments is one of the most challenging problems in neuroscience and beyond. Towards this aim, non-invasive neuroimaging techniques and in particular electroencephalograph (EEG) recordings are commonly used for clinical assessment.^{3–10}

However, an analysis at the scalp level does not give insight to the malfunctioning of the actual brain regions and/or their connectivity. On the other hand, fMRI analysis can provide a better insight but it is limited by its low-time resolution. Thus, source localization, that is, the identification of the brain region activity from scalp/non-invasive recordings (usually EEG or MEG) has emerged a promising approach that can facilitate the analysis of brain activity as a clinical diagnostic tool.^{11,12} However, source localization is an

ill-defined problem and as such, it poses open questions regarding its robustness and in general the validity of the obtained results.¹³

Comparative studies between the various numerical methods that aspire to solve the source localization problem are critical.^{14,15} Toward this aim, Jatoti et al¹⁶ have compared the standardized low resolution brain electromagnetic tomography (sLORETA) with the exact LORETA (eLORETA) based on EEG recordings of a visual experiment on healthy subjects. Cincotti et al¹⁷ compared two techniques for source localization, namely the surface Laplacian and LORETA using EEG recordings from a group of Alzheimer disease patients and age-matched controls. Yao and Devald¹⁸ compared the performances of several source localization methods on the basis of both synthetic and experimental EEG data of somatosensory evoked potentials. Attal and Schwartz¹⁹ compared the performance of three methods, namely the weighted minimum norm estimation (wMNE), sLORETA and the dynamic statistical parametric mapping (dSPM) for the characterization of distortions in cortical and subcortical regions using a realistic anatomical and electrophysiological model of deep brain activity. Seeland et al²⁰ compared wMNE, sLORETA and dSPM using EEG data taken from eight subjects performing voluntary arm movements.

Regarding epilepsy, the majority of the studies have performed source localization with the aid of EEG-fMRI recordings and/or synthetic data approximating epileptic spatio-temporal patterns such as spikes and discharges. For example, Ioannides et al²¹ assessed the performance of two source localization methods, wMNE and eLORETA using MEG signals of ictal and interictal epileptiform discharges in epilepsy and K-complexes. Chowdhury et al²² compared the performance of the coherent maximum entropy on the mean (cMEM) and the fourth order extended source multiple signal classification (4-ExSo-MUSIC) using MEG and EEG synthetic signals mimicking normal background and epileptic discharges. Hasan et al²³ evaluated four algorithms (dSPM, wMNE, sLORETA and cMEM) using simulated data from a combined biophysical/physiological model used to generate interictal epileptic spikes as well as real EEG data recorded from one epileptic patient who underwent a full presurgical evaluation for drug-resistant focal epilepsy. Moeller et al¹⁵ provide a review of the studies that used EEG-fMRI recordings to assess different types of epileptic form activity, underpinning the necessity for comparing with other methods including EEG source analysis.

Fewer studies have dealt with source-level analysis and compared different source localization methods using EEG clinical data taken by children with epilepsy. Among these studies, Adebimpe et al²⁴ performed source localization using eLORETA to investigate changes in functional connectivity in 11 children with benign rolandic epilepsy (BRE) with centroparietal spikes using resting-state EEG recordings using 12 subjects in the same age range as controls. Groening et al²⁵ combined EEG-fMRI and EEG source analysis to identify epileptogenic foci in six children. Elshoff et al²⁶ examined the efficiency of EEG-fMRI and EEG source analysis to localize the point of seizure onset in nine children with refractory focal epilepsy.

The above studies have focused mainly on the study of brain regions that are activated during seizure periods or before their onset. Several other studies have also aimed at analyzing the emerged patterns during seizure periods. For example, Fergus et al²⁷ used a supervised machine learning approach to classify seizure and non-seizure records using an open dataset of seized EEG signals from both children and adults.

On the other hand, it has been shown that studying epileptic seizure-free EEG recordings is of great importance as such analysis can facilitate the identification of patients at risk of epilepsy and/or forecast forth-coming seizures (for a discussion and review of ictal and interictal activity and their analysis see for example Reference 10).

Here, we perform a source-localization analysis of the brain activity of well-controlled epileptic children (with BRE and idiopathic generalized epilepsy [GE]) during a visual working memory (WM) task⁷. WM is commonly viewed as a functional integration system with limited capacity that is able to store information within a short-term register and simultaneously manipulate it on-line. Thus, WM is one of the most important components of information processing and its dysfunction leads to various problems in several cognitive functions including mental arithmetic,²⁸ reading,^{29,30} decision making³¹ and reasoning.³² Epilepsy affects a lot the WM functioning as it has been shown by many studies.³³⁻³⁷

Here, for the solution of the inverse problem, we use three methods, namely, sLORETA,³⁸ dSPM³⁹ and wMNE.⁴⁰ A statistical comparative analysis between methods and groups (healthy children vs children with epilepsy) revealed the crucial role of the superior parietal lobule (SPL) and inferior parietal lobule (IPL) at WM. Our findings are in line with fMRI studies⁴¹⁻⁴⁴ that have shown that SPL and IPL are being involved in WM processing and thus can serve as a “biomarker” for identifying, monitoring and assessing epilepsy in children.

2 | MATERIALS AND METHODS

2.1 | Experimental procedure

For a detailed description of the procedure please refer to Ref. 7.

2.1.1 | Subjects

In the study group, 21 children with established childhood epilepsy (age 6-16 years old; mean of 11.43 years, $SD \pm 2.3$, 10 boys) were enrolled⁷. These children were diagnosed with one out of two following epilepsy syndromes: BRE ($n = 9$) and idiopathic GE ($n = 12$, including childhood absence epilepsy ($n = 5$) and GE with tonic-clonic seizures ($n = 7$)). All children were admitted to the neurophysiology laboratory of the University Hospital of Leuven for a 24-hours video-EEG monitoring during which the ERP study was done. They had no anti-epileptic treatment ($n = 3$) or were on standard anti-epileptic medication (monotherapy, $n = 15$, duotherapy, $n = 3$), with drug dosages always being within normal ranges. Patients on monotherapy received valproic acid ($n = 7$), carbamazepine ($n = 4$), lamotrigine ($n = 3$) or sulthiame ($n = 1$). Patients on duotherapy received different drug combinations.⁷ None of the patients had structural brain abnormalities; in 18 patients, brain MRI was performed showing normal findings in all cases. Only patients with at least an 8 days seizure-free period preceding the test were included.⁷ Thereby we could avoid an acute effect of epileptic seizures on the child's performance. All children followed mainstream school and none had a history of learning problems.

As a control group, 25 age-matched non-epileptic children (mean age 10.76 years, $SD \pm 3.4$, 17 boys) were selected, who did not have any school problem either. The study protocol was approved by the Ethical Committee of University Hospital of Leuven. For more details about the experimental procedure please see Myatchin et al.⁷

2.1.2 | Design and stimuli

The event-related potentials study was done as part of video-EEG monitoring⁷. A visual one-backmatching working memory task was performed: children observed a continuous stream of seven different figures presented one after the other in pseudorandom order at the middle of a computer monitor, which was located at a distance of 1.0 m from the subject's eyes. Everyday figures were used (horse, wardrobe, jacket, cake, comb, bunch of grapes, hammer), white with a black contour on grey background, size 7.5 cm $\times$ 6.5 cm, visual angle $4^{\circ}18' \times 3^{\circ}02'$. Each stimulus was presented for 1.5 seconds, followed by a delay of 1.0 second, after which the next stimulus was presented. During the delay period a fixation point (dark-grey cross) was shown at the middle of the screen to facilitate eyes fixation. Any figure identical to the one immediately preceding it was defined as a target stimulus (probability .30). Children were asked to respond to all targets by pressing a button with their dominant hand. Both accuracy and speed were stressed. The single experimental block contained 120 trials, 36 of which were targets. The duration of the block was 5 minutes. This is an easy working memory task, which was chosen to ensure a good level of participant's performance.

First, the electrode placement and impedance calibration was performed. After that, the experimental procedure was described to the child. The child was seated comfortably in a dimly lit registration room and was instructed to look at the middle of the computer screen placed in front of him to avoid unnecessary eye movements; a fixation point (dark-grey cross) was shown between figures to facilitate eye fixation. The child was also instructed to avoid movements to reduce muscle artifacts in the EEG signal. The instruction for the task was given directly before the task. During the experiment, no interaction with the experimenter was allowed during the task and the experimenter sat out of sight of the child.

2.1.3 | EEG recordings

Nineteen Ag/AgCl electrodes (Technomed Europe) were placed according to the international 10 to 20 system at Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1 and O2⁷. The placement of additional four EOG electrodes resulted in two EOG channels: horizontal EOG—two electrodes on the outer canthi of eyes, and vertical EOG—

two electrodes above and below one eye. EOG channels allowed us to detect both vertical and horizontal eye movements in order to effectively remove them from EEG recording during subsequent preprocessing of the signal (see below). Two linked mastoid electrodes were used as a reference. EEG was sampled at a frequency of 1000 Hz with 12 bits A/D converter and amplified using a band-pass filter of 0.095 Hz to 70 Hz. Notch filter was off. Registration of the digital EEG was made using the software program Brainlab 4.0 (OSG, Belgium). The impedance of all electrodes was monitored for each subject prior to recording and was always kept below 5 k Ω .

2.1.4 | Data pre-processing

Data pre-processing was performed offline using the EEGLAB v.5.02 toolbox (Matlab 7.0.4 platform).⁴⁵ The ECG channel was factored out. Data were filtered with a 50 Hz digital low pass filter. Eye movement artifacts were marked and removed from the continuous signal without affecting the signal itself using an ICA-based algorithm.⁷ EEG fragments containing movement artifacts as well as any epileptic activity were removed based on visual inspection of the data. This resulted in an EEG signal clean from (eye) movement artifacts and epileptic activity, which was then used for further analysis. Afterwards, the continuous EEG signal was epoched according to the type of stimulus (target and non-target), with 200 ms pre-stimulus (delay period) and 400 ms poststimulus (presentation period of the second stimulus, where the motor responses had not yet taken place). Omitted target trials (ie, trials without correct motor response) and committed non-target trials (ie, trials with a wrong motor response) were excluded from the analysis. We then performed a down-sampling at 500 Hz and we applied a baseline correction by subtracting the mean value of the 200 ms of the pre-stimulus period. Overall, we ended up with 92 datasets (21 epileptic $\times$ 2 trial types + 25 control $\times$ 2 trial types) of 19 multi time series, which were divided into four group types (epileptic-target [ET], epileptic-non-target [ENT], control target [CT], control non-target [CNT]); a further subdivision into benign rolandic target (BRE)T, idiopathic generalized epilepsy target (GE)T and benign rolandic non-target (BRE)NT, idiopathic generalized epilepsy non-target (GE)NT was also considered for investigating any differences between the two epileptic types.

2.2 | Numerical solution of the source localization problem

Source localization aims at identifying the (unknown) sources of the brain from data taken usually from noninvasive electromagnetic recording (here: EEG recordings). Its solution involves a forward and an inverse problem. The forward problem refers to the calculation of the electric potentials of the electrodes starting from a given electrical source. The solution of the forward problem is related to the construction of a head model. The head model contains both anatomical information and the conductivities of three layers, namely the skull, the cortex and the scalp.⁴⁶ Anatomical images can be obtained experimentally with the aid of MRI scans, while volume conduction models can be constructed using, for example, the BEM⁴⁷ or the FEM.⁴⁸ The head model volume is tessellated into small-sized cubes, the voxels. Sources may be associated to single voxels or clusters of voxels. Here, each voxel is associated to a single source. The relation between the scalp recordings and the discretized head model volume is performed using the linear matrix equation:

$$V = Gx + \epsilon, \quad (1)$$

where V is a known $N \times 1$ matrix which contains the time instances as recorded by each channel (N is the number of channels), x is the unknown $M \times 1$ matrix of the intensities of the M sources (M is the number of voxels).

The matrix G , with dimensions $N \times M$ is the so-called lead field matrix that contains the information of the head geometry and conductivities. G is known (from the solution of the so-called forward problem [see eg, in Reference 49]) and is related with the head model⁵⁰; ϵ reflects the noise in the measurements.

The inverse problem is ill-defined, as there is an infinite number of combinations of positions and intensities that could effectively produce the electric potentials and magnetic fields measured. The general idea behind its solution is to express it as a linear optimization problem with regularization:

$$\hat{x} = \min_x \left(\|V - Gx\|_2^2 + \sum_{i=1}^k \alpha_i \|W_i x\|_p \right). \quad (2)$$

In the above equation, k is the number of regularization constraints (reflecting the a-priori physiological information) (usually $k=1$); the matrix W , of dimension $M \times M$ is a weighted matrix related to the imposed constraints; α_i is the regularization parameter and denotes the importance of every constraint.

For different choices of W , k and p (reflecting the type of the norm), we get different methods.

Here, for our analysis, we used and compared three different²⁰ methods, namely the wMNE, the sLORETA and the dSPM that are described below.

2.2.1 | Weighted minimum norm estimation

For $W = I$ (the identity matrix) and $P = 2$ (the $L - 2$ norm) in Equation (2) we get the minimum norm estimation (MNE).⁵¹ MNE uses the mathematical assumption that the best solution, through the infinite set of solutions, is the one with the minimum norm. Despite the fact that MNE was the first method used to extract a 3D distributed solution, the simplicity of its assumption often leads to inadequate solutions. In particular, it has been shown, that this method fails in identifying deep sources.⁵² Because of the minimum norm constraint, sources that are located in deep regions are moved closer to the cortex.

The wMNE method is a variation of the MNE that improves the problem of the mislocation of the deep sources. wMNE uses instead of the identity matrix, a diagonal matrix W_c of dimension $M \times M$, that contains the weighting factors. From the multiple choices that can be chosen as weighted factors, usually chosen as $W_c = \text{diag}(\|G_i\|_2)$ (for $i = 1, \dots, M$) (i.e. based on the norm of the columns of the matrix G).⁵³ Then, the unique solution is given by:

$$x_{\text{wMNE}} = LV, \quad (3)$$

where $L = (W_c^T W_c)^{-1} G^T (G (W_c^T W_c)^{-1} G^T + a C_e)^{-1}$ is called the inverse operator with dimensions $(M \times N)$.

2.2.2 | The dynamic statistical parametric mapping

The dSPM³⁹ is similar to the wMNE but uses a different regularization. dSPM computes the source estimates of the noise based on the noise covariance matrix $C_e = aH$ and normalizes the rows of the inverse operator.

$H = I_{N \times N} - (11^T / 1^T 1)$ is the $N \times N$ centering matrix and plays the role of the identity matrix in the measurement space; $1 \in \mathbb{R}^{N \times 1}$ is a vector of ones. Then, from Equation (3), the source estimates of the noise form a diagonal matrix:

$$C_{\hat{x}} = L C_e L^T. \quad (4)$$

Thus, the dSPM solution is given by:

$$x_{\text{dSPM}} = L_{\text{dSPM}} V, \quad (5)$$

where $L_{\text{dSPM}} = W_{\text{dSPM}} L$, where W_{dSPM} is a diagonal matrix with elements derived by $C_{\hat{x}}$

2.2.3 | Standardized low resolution brain electromagnetic tomography

sLORETA considers another source of variance, except from the covariance of the measurement noise C_e , the covariance of the actual sources $C_x = I_{N \times N}$. Assuming that the activity of the actual sources and the noise of the measurements are uncorrelated and based on the linear relation of Equation (1), we have³⁸:

$$C_V = GC_x G^T + C_e = GG^T + \alpha H. \quad (6)$$

Substituting Equation (6) in (3), setting $W_c = I_{M \times M}$, we can estimate the variation of the estimated sources as:

$$C_{\hat{x}} = LC_V L^T = L(GG^T + \alpha H)L^T = G^T(GG^T + \alpha H)^{-1}G. \quad (7)$$

The covariance of the estimated sources is equivalent to the Backus and Gilbert resolution matrix,⁵⁴ which is given by plugging Equation (1) into (3) and substituting the inverse operator to get³⁸:

$$x_{sLORETA} = G^T(GG^T + \alpha H)^{-1}V = Ax = C_{\hat{x}}x, \quad (8)$$

where $A = LG$ is the resolution matrix.

2.2.4 | Head models for children

In our study, we did not have individual MRI scans for each child that participated to the experiment. Thus, in the absence of such specific information, we used age-specific MRI templates for children acquired from the “Neurodevelopmental MRI database”.^{55–58} The goal of this database is to provide for research purposes, exactly in the absence of specific MRI scans, a series of age-appropriate average MRI reference templates and related information. Each template was constructed using identical procedures to facilitate comparisons across lifespan. The database consists of average templates (T1W and T2W), segmenting priors, and stereotaxic atlases.⁵⁵ The “Neurodevelopmental MRI Database” is available online (<http://jerlab.psych.sc.edu/NeurodevelopmentalMRIDatabase/>). The database is publicly available to researchers upon request for clinical and experimental studies of normal and pathological brain development. The data is shared under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License (CC BY-NC-ND 3.0; http://creativecommons.org/licenses/by-nc-nd/3.0/deed.en_US).

Using this database, we were able to construct an “average” age-specific head model for each child taking into account its age. For our study, we constructed 11 averaged head models (taking into account the database with head models of children between 6 and 16 years old, that is, one “average” head model per year). In Table 1, we provide information about the total number of MRI scans per age.

Here, for the construction of the head models, as skull conductivities are age-dependent,⁵⁹ we used different conductivities ratios (CR, cortex/skull) for every age-dependent model. The conductivity value for scalp and cortex was set to the standard value of 0.33 S/m.⁶⁰ Table 2 presents analytically the different conductivity ratios for every age.⁶⁰

Age	6	7	8	9	10	11	12	13	14	15	16
1.5 T	27	27	46	46	62	31	37	34	32	32	34
3.0 T	10		19		16		15	11	30		13
Combined	37	27	56	46	72	31	47	34	42	32	44

Note: All 1.5 T MRIs and part of 3.0 T MRIs are included in the “Combined” column as in the original publications.^{55,57}

TABLE 1 Total number of scans per age for 1.5 T, 3.0 T and combined average MRI templates

Age	6	7–8	9–10	11–12	13–14	15–16
CR	15	20	30	40	50	60

Note: The standard conductivity value for scalp and cortex was set to 0.33 S/m.⁶⁰

TABLE 2 Conductivity ratios (cortex/skull) for every age-dependent head model

2.3 | Statistical analysis

After the data pre-processing and the implementation of the source-localization algorithms, as described in the previous section, we get 92 time-series at the source space. Our data have a spatio-temporal structure: number of voxels (spatial dimension) and time points (time dimension).

Here, we sought for statistically significant differences between (a) the groups of BRE and idiopathic GE, (b) the groups of healthy controls (C) and epileptic children (E) in total, and (c) the three different source-localization methods. For the comparisons, we performed two-sample t tests based on three basic assumptions. In particular, in order to perform the t tests, we checked if (a) the amplitude of the source signal at each voxel and at each time instant follows a normal distribution among subjects in a group; (b) the variances of the amplitude of the source signal at each voxel and at each time instant of (BRE)T, (GE)T, (BRE)NT, (GE)NT, CT, ET, CNT, ENT are equal; and (c) the amplitudes of the source signal at each voxel and at each time instant are independent for (BRE)T, (GE)T, (BRE)NT, (GE)NT, CT, ET, CNT, ENT.

For the test of normality, we used the Shapiro-Wilk test.⁶¹ The null hypothesis of the test is that a sample comes from a normal distribution. The test statistic reads:

$$W = \frac{\left(\sum_{i=1}^M \alpha_i x_{(i)}\right)^2}{\sum_{i=1}^M (x_i - \bar{x})^2}, \quad (9)$$

where $x_i, i=1,2,\dots,M$ is the intensity of the source i , $x_{(i)}$ is the i -th order statistic, $\bar{x}$ is the sample mean and coefficients α_i are given by $(\alpha_1, \alpha_2, \dots, \alpha_M) = (m^T C_V^{-1} / C)$. C is a vector norm: $C = \|C_V^{-1} m\|$, $m = (m_1, m_2, \dots, m_M)^T$ are the expected values of the order statistics of independent and identically distributed random variables sampled from the standard normal distribution and C_V is the covariance matrix of those normal order statistics. F tests were performed to validate the second assumption (ie, the equality of the variances of the amplitude values of each voxel between the different group comparisons).

For the comparison between the groups of epileptic syndromes, we considered the pairs (BRE)T vs (GE)T and (BRE)NT vs (GE)NT. For the comparison between the control and epileptic groups, we considered the pairs CT vs ET and ENT vs CNT. Thus, we tested for normality and equality of variances for each voxel and each time sample (ie, we have performed a total of $5.148 \times 600 = 3.088.800$ t tests). The level of significance was set to $P < .05$, meaning that the risk of taking a false positive is 5% of the cases. Here, in order to deal with the multicomparison problem, we used the FDR correction.⁶² The null hypothesis H_0 for all comparisons was that the two different groups have equal means regarding the emerged spatio-temporal activation at the source level. Based on the above, the H_0 hypothesis could not be rejected. Similarly, the F tests validated also the second assumption. The independence is reasonably assumed to hold true. Having guaranteed that the t test can be applied, we proceeded with the comparisons between the different groups and methods.

Thus, we performed $3.E^6$ simultaneous two-sample t tests with $P < .05$ level of significance. FDR was used to deal with the multicomparison problem. Another constraint that we added to avoid spurious and random effects was the one of the minimum duration of the activations. Thus, we excluded all the signals that were statistically significantly for time intervals less than 50 ms.

In order to detect statistically significant differences between the three methods at the source level, we also performed paired t tests taking the absolute difference between the signals at the source level. Again, in order to deal with the multicomparison problem the FDR correction was used. This processing was performed to detect possible different brain areas induced by the different inverse algorithms and not by the original brain activity. We excluded all the signals that were statistically significantly for time intervals less than 50 ms as before. Furthermore, we also applied a space constraint (of 30 voxels) in order to exclude sparse voxels (or small-size groups of voxels) that do not represent a coherent brain area.

3 | RESULTS

For our analysis, we used the BrainStorm toolbox for Matlab.⁶³ The source-reconstructed time series were obtained by combining the EEG recordings with the appropriate (respect to the age of the subject) constructed MRI templates. From each template, we extracted three layers (scalp, inner skull, outer skull) and the source space (cortical surface). The

number of vertices for each layer were set to 2562 vertices for each surface. Then, the volume conduction models were constructed in openMEEG software⁶⁴ which uses the BEM. The space resolution for the source model was set to 5124 voxels with fixed orientation perpendicular to the cortex surface.

Thus, the time series at the source level were reconstructed using wMNE, dSPM and sLORETA. The noise was computed from the raw EEG data using the pre-stimulus period for baseline correction and then the noise covariance matrix was calculated. A parameter that has to be determined is the “signal to noise ratio” (SNR). In Brainstorm, the computation of SNR is performed as in the original MNE software of Hamalainen.⁶⁵ The signal covariance matrix is “whitened” by the noise covariance matrix and the square root of the mean of its spectrum yields the average amplitude of SNR. The default value in Brainstorm is set to 3.

For our illustrations, we have split the time period to three main intervals: the pre-stimulus period [−200 ms 0 ms), the period exactly after the stimulus [0 ms-199 ms] and the post-stimulus period [200 ms-400 ms).

Following the statistical analysis described in the methodology, the comparison between the epileptic group of BRE and that of GE revealed no significant differences at the source-level.

At the next step we considered the comparison between the group of control and the group of epileptic (BRE and GE). The main results of the source localization procedure for these groups are presented analytically in Table 3.

In Table 4, we also provide the numerical residuals for each method (the L2-norm ($\text{res} = \|V - G\hat{x}\|_2$, where G is the forward operator and $\hat{x}$ the estimated amplitudes), as well as the corresponding values of the regularization terms.

The statistical analysis between the groups (normal vs epileptic) revealed that all methods gave relatively similar results. The pair t test between ENT and CNT revealed a statistically significant difference in the time-range of 170 ms to 230 ms.

TABLE 3 Group averaged sources as obtained by the three methods: wMNE, dSPM and sLORETA

Time period	Method	CT	CNT	ET	ENT
Pro-stimulus (−200- −1 ms)	wMNE	Right occipital lobe (~140 voxels)	Occipital lobe (~100 voxels)	Right occipital lobe (~90 voxels)	Occipital lobe (~80 voxels)
	dSPM	Right occipital lobe (~220 voxels)	Right occipital lobe (~150 voxels)	Right occipital lobe (~160 voxels)	Occipital lobe (~190 voxels)
	sLORETA	Right occipital lobe (~530 voxels)	Occipital lobe (~230 voxels)	Right occipital lobe (~290 voxels)	Right occipital lobe (~270 voxels)
Exactly after stimulus (0-199 ms)			Left parietal lobe (~150 voxels)		
	wMNE	Occipital lobe (~120 voxels)	Right occipital lobe (~100 voxels)	Occipital lobe (~90 voxels)	Superior parietal lobe (~50 voxels)
					Occipital lobe (~110 voxels)
	dSPM	Right occipital lobe (~330 voxels)	Right occipital lobe (~310 voxels)	Occipital lobe (~240 voxels)	Superior parietal lobe (~100 voxels)
					Right occipital lobe (~330 voxels)
	sLORETA	Right occipital lobe (~590 voxels)	Occipital lobe (~510 voxels)	Occipital lobe (~450 voxels)	Superior parietal lobe (~240 voxels)
Post-stimulus (200-399 ms)					Occipital lobe (~500 voxels)
	wMNE	Parietal lobe (~70 voxels)	Right parietal lobe (~60 voxels)	Right parietal lobe (~60 voxels)	Right parietal lobe (~80 voxels)
	dSPM	Parietal lobe (~180 voxels)	Parietal lobe (~110 voxels)	Right parietal lobe (~200 voxels)	Parietal lobe (~190 voxels)
	sLORETA	Parietal lobe (~390 voxels)	Parietal lobe (~360 voxels)	Right parietal lobe (~470 voxels)	Parietal lobe (~500 voxels)

Abbreviations: CNT, control non-target; CT, control target; ENT, epileptic non-target; ET, epileptic target.

TABLE 4 Mean and SD values for the L2-norm residuals and the regularization term for each method and each group

Method	Group	Residuals (μV)	Regularization term (nA-m)
wMNE	CT	4.53 ± 0.94	13.2 ± 2.14
	ET	5.34 ± 1.02	15.41 ± 3.23
	CNT	3.63 ± 1.25	13.13 ± 3.42
	ENT	6.42 ± 1.76	16.31 ± 3.67
dSPM	CT	3.92 ± 0.71	12.78 ± 3.12
	ET	5.21 ± 1.18	15.91 ± 3.54
	CNT	4.11 ± 1.37	14.34 ± 4.15
	ENT	7.08 ± 1.58	17.37 ± 4.52
sLORETA	CT	3.12 ± 0.59	10.91 ± 3.19
	ET	4.04 ± 0.86	11.46 ± 2.84
	CNT	2.98 ± 0.43	11.51 ± 2.9
	ENT	3.45 ± 0.73	12.43 ± 3.57

Abbreviations: CNT, control non-target; CT, control target; ENT, epileptic non-target; ET, epileptic target.

FIGURE 1 ENT vs CNT: The SPL (superior parietal lobule) mainly of the right hemisphere is activated more for the ENT group at the time interval from 170 ms to 230 ms. (A) wMNE, (B) dSPM, (C) sLORETA

FIGURE 2 ET vs CT: The IPL (inferior parietal lobule) of the right hemisphere is activated more for the ET group at the time interval from 160 ms to 360 ms. (A) wMNE, (B) dSPM, (C) sLORETA

TABLE 5 Analytical presentation of the statistically significant differences for ET vs CT and ENT vs CNT

Comparison	Time period (ms)	Group activated more	Brain region	Brodmann area	Number of voxels	Comments
ENT vs CNT	170-230	ENT	SPL	7	~80	Only at the right hemisphere
ET vs CT	160-360	ET	IPL	22, 39-40	~170	Only at the right hemisphere

Abbreviations: CNT, control non-target; CT, control target; ENT, epileptic non-target; ET, epileptic target; IPL, inferior parietal lobule; SPL, superior parietal lobule.

In this time-range, the SPL was activated more in the ENT group; the activation of the SPL was mostly at the right hemisphere (Figure 1). The pair *t* test between ET and CT revealed a statistically significant difference in the time-range of 160 ms to 360 ms. In this time-range, the IPL was activated more in the ET group (only at the right hemisphere) (Figure 2).

The above findings are summarized in Table 5.

Finally, regarding the comparison between methods, the statistical analysis revealed no significant differences between the three methods with respect to the voxels that were identified as statistically significant based on the contrast analysis between the groups and tasks. In particular, there were no specific areas (over 50 voxels) with significant different activation for more than 50 ms duration. Of course, this may be due to the low number of EEG recordings used for the source-localization analysis. We discuss this issue next.

4 | CONCLUSIONS

Sensor-level analysis does not provide information about the actual sources that are involved in brain activity. From a mathematical point of view, the problem of source localization from scalp recordings is an inverse ill-defined problem and as such, different types of regularization approaches may in principle result to different solutions. Thus, especially for clinical assessment of brain neurological disorders such as epilepsy, there is a need for comparing and assessing the robustness of such methods.

This is the first study to perform a comparative analysis of three numerical methods, namely the sLORETA, wMNE and dSPM to identify differences at the source level between healthy children and children with well-controlled epilepsy (ie, in the absence of seizures) during a working memory task. In the absence of anatomical MRI scans, we used the publicly available “Neurodevelopmental MRI database” that provides age-specific average MRI templates.

In particular, we studied the localization of the sources of brain activity of children with BRE and idiopathic GE (including childhood absence epilepsy and GE with tonic-clonic seizures). These types of epilepsy are traditionally seen as distinct clinical entities: however, this difference appears to be much less pronounced. For example, Verrotti et al^{66,67} showed that BRE and childhood absence epilepsy may be pathophysiologically related, and the two epileptic phenotypes may indicate a neurobiological continuum. In another study, it was found that “children with BRE may have slightly lower verbal IQs than normal controls, but similar verbal deficiencies to children with idiopathic GE”.⁶⁸ Furthermore, as the interim analysis in the work of Myatchin et al⁷ showed, there were no statistically significant differences between those two epilepsy subgroups in terms of the brain activity recorded by EEG. Importantly, the source analysis that we conducted in the current work, showed that there were no statistically significant differences between the two types of epilepsy for the specific working memory task.

To avoid an acute effect of epileptic seizures on the child's performance, only patients with at least an 8 days seizure-free period preceding the test were included. Tromp et al⁶⁹ found no significant decline in cognitive testing performance in children with frequent seizures (>1/week) comparing to children with sporadic seizures (<1/week). In the study of Bailet and Turk⁷⁰ in children with epilepsy and normal IQ, no difference in performance on neurocognitive tests was found between patients with one or more (up to five) seizures in 1 month preceding the testing vs patients with no seizures in the last month. Therefore, 8 days of being seizure-free is a long enough period to avoid an acute effect of seizures on neurocognitive performance. Next, the majority of children in our study had much longer seizure-free period: median seizure-free period of 8 months with only two patients being seizure free for 3 weeks (for details see Myatchin et al⁷).

Our analysis shows that all three methods yield essentially the same results, thus providing adequate confidence for our findings. More specifically, our analysis revealed consistent differences between the two groups in the parietal lobes. Importantly, our findings are in line with other studies investigating abnormalities of the brain function due to epilepsy with the use of anatomical MRI, fMRI and EEG recordings.⁷¹⁻⁸⁰ More specifically, regarding children with epilepsy, Besenyei et al⁸⁰ used anatomical MRI and resting state EEG recordings to identify the abnormal brain activity in children with benign rolandic epilepsy. Using LORETA, they found an increase activity, compared to controls, in the temporal and inferior parietal lobule. Other studies that have investigated the abnormal activity in children with epilepsy in the presence of seizures have also pinpointed the importance of these areas. Clemens et al⁸¹ find increased activity in the superior parietal lobe children with benign childhood epilepsy with rolandic spikes, using MRI scans and resting state EEG recordings. For the source localization analysis they used LORETA.

Importantly, our study and findings reveal also the importance and potential that originates from the use of publicly available scientific resources such as the “Neurodevelopmental MRI” database, which allow to the researchers to re-analyze available neuroimaging data and investigate questions beyond the scope of the original studies. This carries, in principle, the potential to gain new insights without the need to perform new from scratch, time-consuming and expensive experiments.

We are aware of the low number of participants that contained 21 epileptic children and a similar size of healthy children that served as a control group. However, other relevant studies have used even smaller number of subjects, yet leading to consistent results.²⁴⁻²⁶ Thus, our findings can serve as a basis for future studies that will consider a bigger number of subjects.

Finally, we would like to comment on the small number of electrodes that were used. The EEG signals have been recorded for the purposes of a clinical study using 19 electrodes with 4 additional EOG electrodes that may result to a blurred source localization in specific areas such as the temporal lobe.⁸² However, this does not mean that a low spatial sampling precludes source localization. For example, as it has been shown in a comparative study for epileptic source-localization in children using EEGs recorded from 19 to 29 scalp electrodes, valuable insight about the underlying sources could be also extracted with the use of 19 electrodes.⁸² In our study, despite the small number of electrodes, the source analysis revealed differences between the two groups which are consistent with what has been found in other studies as discussed above.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest in this paper.

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