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## Source localization in magnetoencephalography to identify epileptogenic foci

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*Keywords:* Magnetoencephalography; Epilepsy; Single dipole method; Time frequency analysis; Short-time Fourier transform analysis

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## **Abstract**

*Rationale:* Magnetoencephalography (MEG) is useful to localize epileptic foci in epilepsy as MEG has higher spatio-temporal resolution than conventional diagnostic imaging studies; positron emission computed tomography, single photon emission computed tomography and magnetic resonance imaging (MRI).

*Methods:* We use 204-channel helmet-shaped MEG with an sampling rate of 600 Hz. A single dipole method calculates equivalent current dipoles to localize epileptic sources. The equivalent current dipoles are superimposed onto MRI as magnetic source imaging (MSI). Ictal MEG data are analyzed using time frequency analysis. The power spectrum density is calculated using short-time Fourier transform and superimposed onto MRI results.

*Results:* Clustered equivalent current dipoles represent epileptogenic zones in patients with localization-related epilepsy. The surgical plan is reliably developed from source localizations of dipoles and power spectrum of interictal spike discharges, and ictal frequency.

*Conclusion:* MEG is indispensable in diagnosis and surgical resection for epilepsy to accurately localize the epileptogenic zone.

## **1. Introduction**

Magnetoencephalography (MEG) arose originally from investigations into superconductivity and its subsequent practical application in the measurement of weak electric fields. The technique is now used clinically [1, 2]. Magnetoencephalography is particularly useful in studying epileptic disorders, as it provides better spatial and temporal resolution than electroencephalography (EEG) for the localization of pathological brain activity or lesions.

Many reports describe the application of MEG in the clinical investigation of epileptic patients [3-9]. Magnetoencephalography also currently has an important role in defining epileptogenic lesions in epilepsy surgery candidates, especially those with neocortical epileptic lesions [10-14]. In the present study, we report the efficiency of MEG in the diagnosis of two epileptic syndromes.

## **2. Methods**

### *2.1. MEG data acquisition*

MEG data were recorded using 204-channel helmet-shaped gradiometers (Vector View, Elekta, Stockholm, Sweden) at a 600 Hz sampling rate. The MEG data were digitally filtered with a band-pass from 3 to 30 Hz for offline analysis. Segments containing abnormal paroxysms were identified manually.

### *2.2. Equivalent current dipole*

Individual spikes were aligned on the basis of the peak latency and analyzed. The distribution of brain activity generating the spikes was determined using a source estimation approach; the equivalent current dipole (ECD) model. This model is appropriate when the underlying brain activity is focal, i.e. restricted to a relatively small region of the brain.

Equivalent current dipoles were calculated with xfit software (Elekta Neuromag Ltd) using the single dipole model. The conductivity geometry of the head was assumed to be spherical and symmetrical. Dipoles were calculated for each time point measurement (every 2.5 ms) within 100 ms of each MEG spike. Results from all sensors were analyzed, with no regions of interest selected. The initial location for the

iterative ECD fit was assumed to be under the sensor with the largest signal, and the ECD with the best goodness of fit (GOF) was selected as being representative of that particular MEG spike. The GOF is a measure of how well the ECD model explains the measured signals. A dipole fit was accepted when the GOF was greater than 70%. To visualize anatomical locations, the ECDs were superimposed on the MRI generated for each patient.

### *2.3. Short-time Fourier transform analysis*

Short-time Fourier transform (STFT) analysis may be used to reveal the distribution of MEG polyspikes [15]. The MATLAB (MathWorks, Natick, USA) program was used to execute the STFT for the MEG signals. Each signal was divided into small sequential frames, and fast Fourier transformation (FFT) applied to each frame.

In the present study, the STFT was implemented using a 256-point window. The duration of each window was 426.7 ms (i.e.  $256 \text{ points} \times 1000 \text{ ms} / 600 \text{ Hz}$ ). The window was shifted every four points, corresponding to 6.7 ms (i.e.,  $1000 \text{ ms} / 600 \text{ Hz} \times 4 \text{ points}$ ). The fast Fourier transform method was applied to each window. This process was repeated for all representative signals. The time-frequency distributions were displayed as graphs.

Fast Fourier transform was performed for frequencies in the ranges of 3-30 Hz, 30-50 Hz, and 50-100 Hz. A signal's spectrum was considered to be aberrant when it was isolated from the background frequency spectrum in the graph. Such aberrant frequency spectra were superimposed onto the 3D magnetic resonance imaging (MRI) reconstruction.

### **3. Case reports**

#### *3.1. Case 1*

A 13-year-old boy whose seizures first occurred at the age of 10 years, and began with focal motor seizures in the left leg and foot. His seizures evolved until, by the age of 13 years, they developed into a form of continuous focal seizure or epilepsy partialis continua. Sometimes these focal seizures progressed into secondary generalized tonic-clonic seizures. Electroencephalography (EEG) demonstrated intermittent spikes in recordings from the Cz and Fz electrodes, and MEG showed corresponding spikes at the top of the left frontal lobe (Fig. 1A). Equivalent current dipoles were located at the top of primary motor area in the left frontal lobe (Fig. 1B and C). A MEG-guided MRI scan showed a T2WI high intensity area at the top of left frontal lobe that corresponded to the clustered ECDs calculated following analysis of MEG data (Fig. 1D).

Antiepileptic drugs were administered to control the patient's seizures; however cortical resection is planned as he still has daily seizures.

#### *3.2. Case 2*

An 11-year-old girl had, immediately following her birth, been presented with right

hemiplegia. A computed tomography (CT) scan showed a stroke lesion due to congenital thrombosis of the left middle cerebral artery (Fig. 2A). Her seizures initially occurred at the age of 3 years. These seizures were postural, and resolved on decumbency. The seizures were described as involving extension of the patient's right arm and leg and contraction of the left arm and leg, and upward eye deviation.

Her interictal EEG showed spikes, as well as spikes with slow waves in the F3, Fp1, and F7 electrode data. MEG demonstrated epileptic spikes in the left frontal lobe, and ECDs localized near to the infarct in the left frontal lobe (Fig. 2B).

Ictal EEG showed slow waves in the left frontal recording, followed by left frontal dominant polyspikes. Ictal MEG data 4.0 seconds prior to ictal motion artifact was analyzed using STFT, and demonstrated left frontal dominant, rhythmic magnetological activity of 7-12 Hz (Fig. 3). These areas of high magnitude activity were located in the left superior frontal gyrus on 3D MRI (Fig. 4), which was consistent with the spike sources estimated using the single dipole method (SDM) (Fig. 5).

After noninvasive presurgical evaluation, the patient underwent long-term intracranial EEG monitoring using subdural electrodes. Electrical stimulation near the left premotor area induced her usual seizure. She underwent frontal lobectomy, including areas where high magnitude activity in ictal MEG data had been recorded (Fig.

5). She has been seizure free for the year following surgery, and has no mental or motor deficits.

#### **4. Discussion**

MEG has become an indispensable diagnostic tool for patient evaluation prior to neocortical epileptic surgery. This was demonstrated by the accurate localization of epileptogenic lesions in our two case studies. In patient 1, the MEG data also demonstrated a strong epileptogenic region and predicted a cortical lesion in the left frontal lobe. Hence, the high spatial resolution of MEG provided valuable information in the diagnosis of the epileptic syndrome in this case. The MEG data from patient 2 demonstrated a restricted and clustered epileptogenic focus resulting from a widespread cortical lesion, resulting from a congenital stroke in the cerebral cortex. MEG thus indicated the site of the cortical resection required for successful treatment of this patient.

This study has also shown the usefulness of MEG in identifying the ictogenic area in patients through investigations into epileptic rhythmic activity. Recently, Sueda et al. and Yagyu et al. described the clinical value of MEG oscillation analysis, and confirmed the efficacy of this method for pre and postoperative evaluation of epileptic patients [16, 17].

The location of an ECD can be calculated only when a 3 cm<sup>2</sup> or wider area of

cerebral cortex is synchronously activated [18]. Therefore, to obtain a suitable ECD, the activated areas of the cortex should be restricted in the analysis. This allows SDM to be applied to signals which have a good signal to noise ratio in comparison to background cortical activity. The SDM uses an inverse problem formula based on the hypothesis that the spike is generated from a localized area. Hence, SDM has limitations in its use in the evaluation of epileptic paroxysmal discharges, and is not applicable in cases with widespread cortical activity and propagated ictal activity with low amplitude recruiting of rhythmic activity. In contrast, time-frequency analysis has an advantage over the single dipole method, as there is no need to solve the inverse problem and define a region of interest for evaluation of these discharges.

Ictal rhythmic activity specifically shows the epileptogenic focus, especially using electrocorticography (ECoG). However in this study, MEG showed equivalent diagnostic usefulness for definition of the ictal onset zone, and unlike ECoG, is a noninvasive technique [19, 20]. Thus, MEG potentially has an advantage over ECoG in pediatric patients, in whom long-term invasive monitoring is not possible. Further, MEG can simultaneously detect whole cortical activity, while investigation of the region of interest is limited in ECoG to the area of the craniotomy.

This study has confirmed MEG analysis is an invaluable tool in the diagnosis of

epileptic syndromes and in presurgical evaluation.

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## Figure legends

Fig. 1. EEG, MEG and MRI of Case 1 (A) EEG showed interictal spikes on readings from Fz and Cz electrodes (white arrows) (B) MEG showed spikes in the right frontal area (C) Equivalent current dipoles from MEG were localized to the top of the primary motor area in the right frontal lobe (red dots) (D) FLAIR MRI image showed high signal region at the top of the primary motor area in the right frontal lobe (yellow arrows).

Fig. 2. MRI, MEG, PET and SPECT of Case 2 (A) Axial and sagittal MR images demonstrated a congenital middle cerebral artery stroke in the left hemisphere (B) Equivalent current dipoles from MEG study with clustered spike source localization near a stroke lesion in the left frontal lobe (green dots) (C) [18F]-fluorodeoxyglucose (FDG) positron emission CT (PET) showed hypofunctional glucose metabolism in the left frontal lobe (D) [11C]-flumazenil (FMZ) PET showed reduction of the benzodiazepine receptor binding in the left frontal lobe (E) 99m-Tc ethylcysteinate dimer (ECD) single photon emission CT (SPECT) showed hypoperfusion in the left frontal lobe.

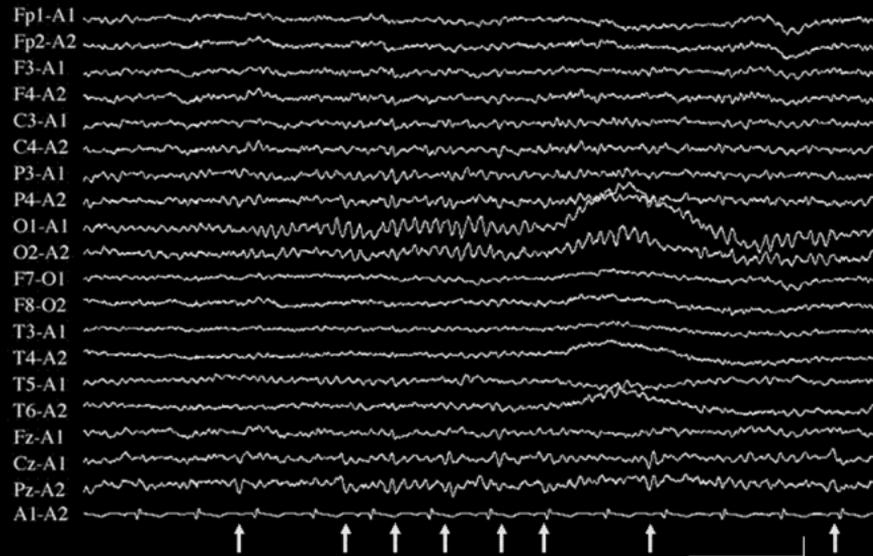
Fig. 3. STFT analysis in Case 2. STFT showed aberrant magnetological oscillation in the left occipital and temporal and frontal areas at 7-12 Hz (surrounded by red lines).

Fig. 4. MEG signal combined with the 3D MRI image in Case 2. Aberrant oscillation generated from the top of the encephalomalacic areas at 105 ms with maximum power spectrum at 314 ms.

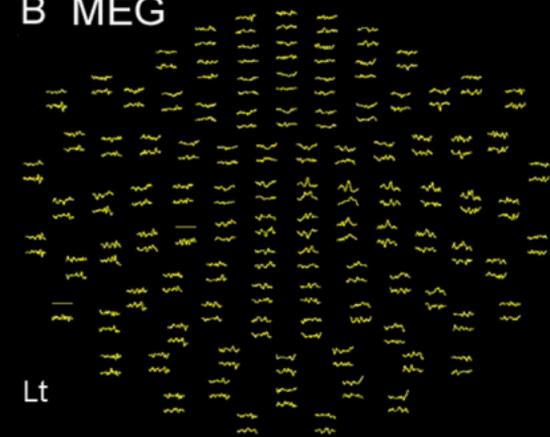
Fig. 5. MEG spike sources, maximum power spectrum of STFT and resected area in Case 2 (A) MEG spike sources (green dots) were located in the middle frontal gyrus near to the encephalomalacic region (pink area) (B) The maximum power spectrum of the STFT analysis was located in the comparable area to that from which MEG spike sources (red area) were mapped (C) Area of the cortical resection of the left frontal lobe (yellow area) which excluded the precentral gyrus

# A Case 1

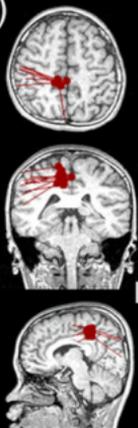
## EEG



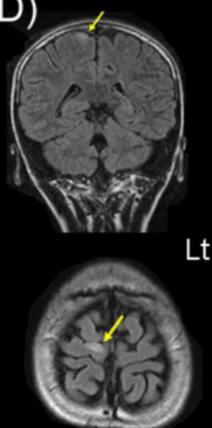
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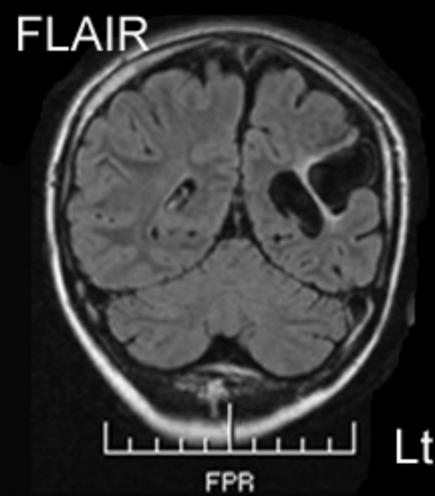
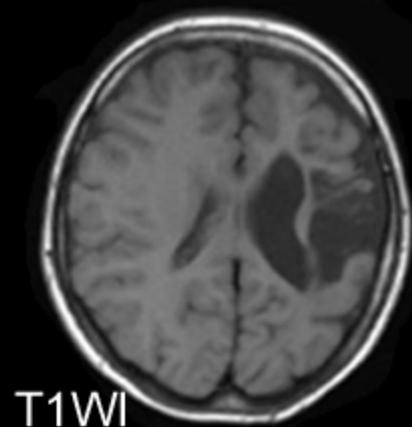
## (C)



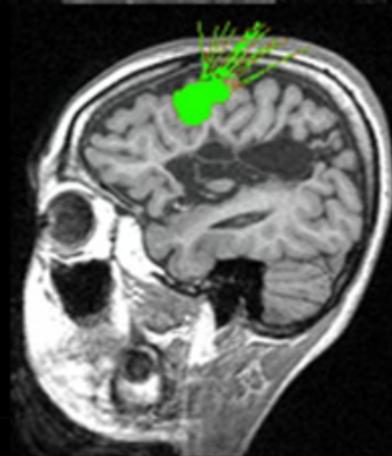
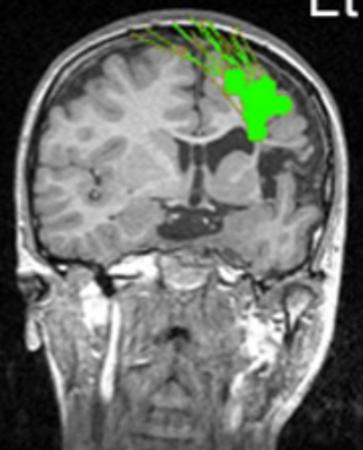
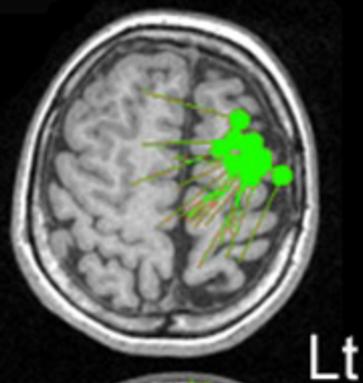
## (D)



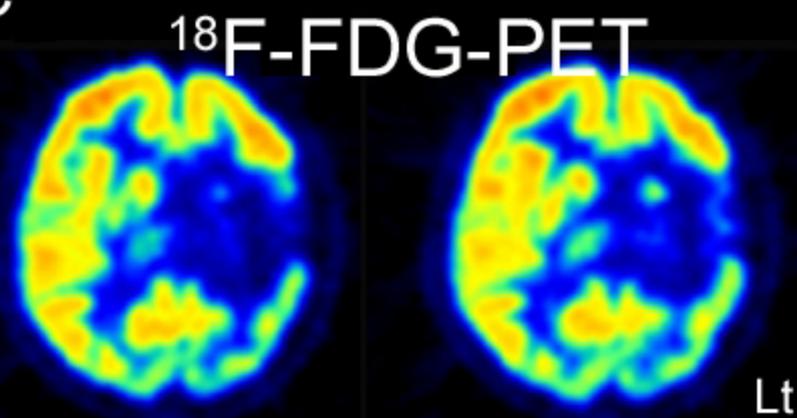
A Case 2



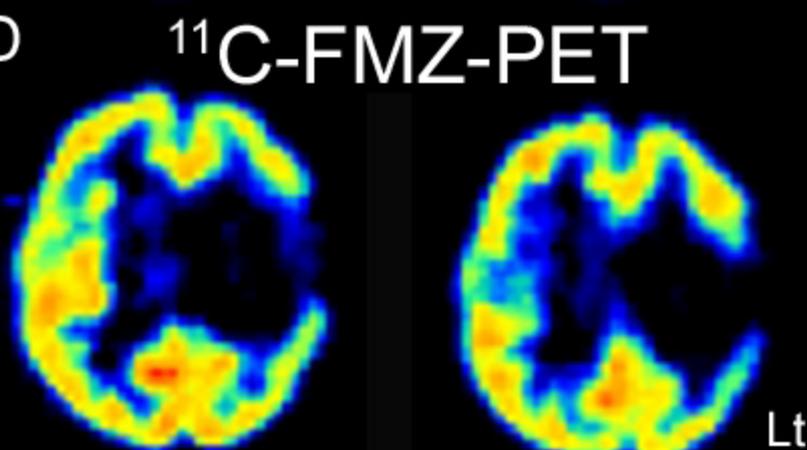
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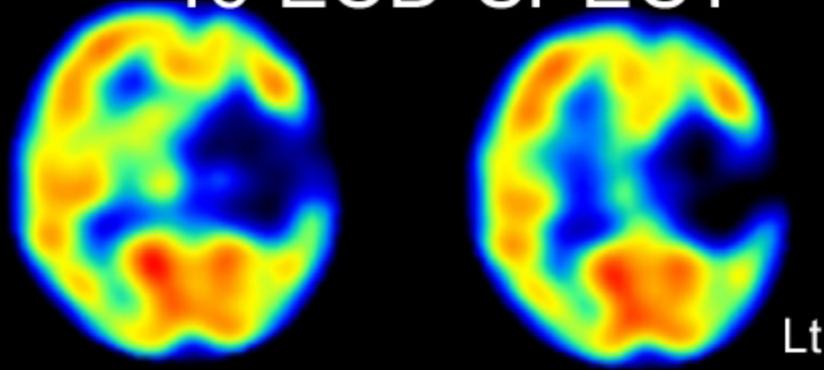
C



D

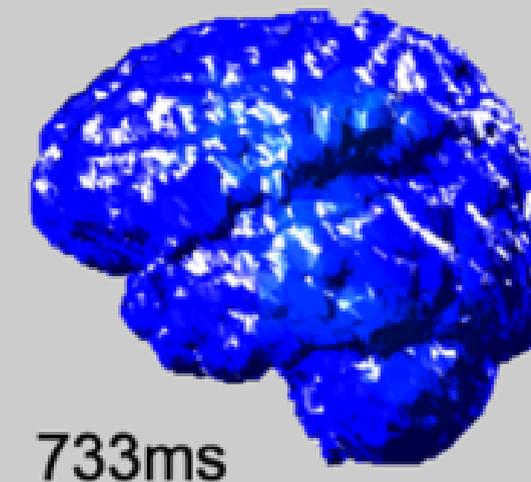
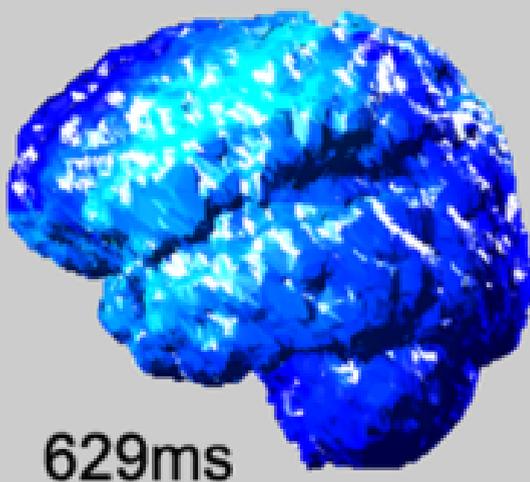
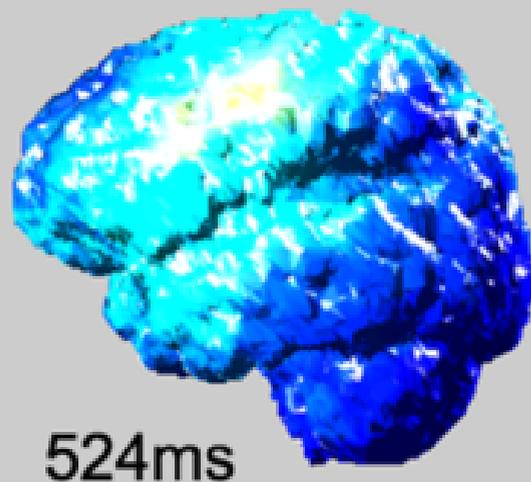
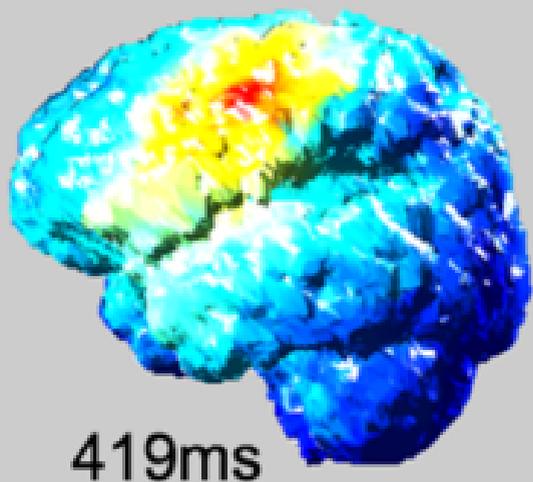
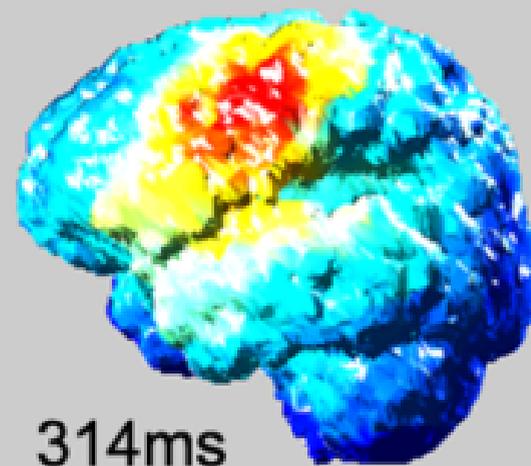
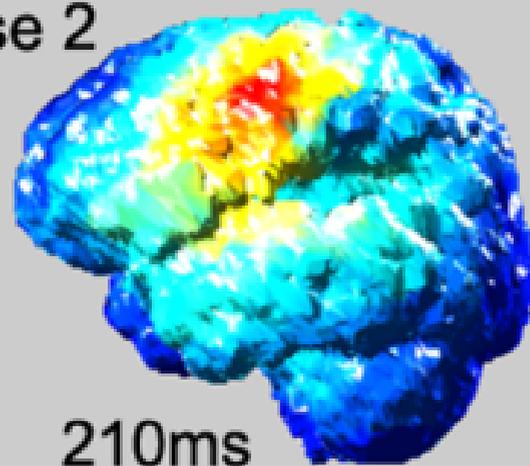
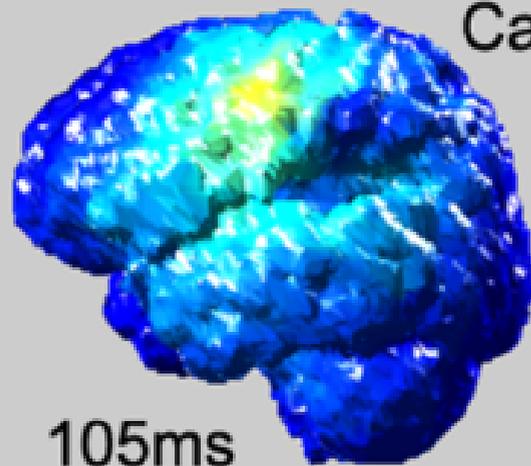
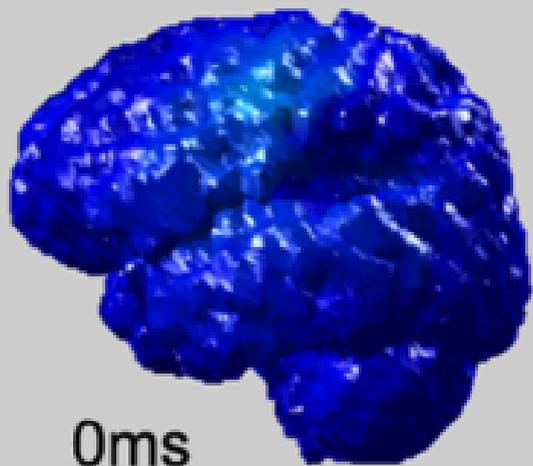


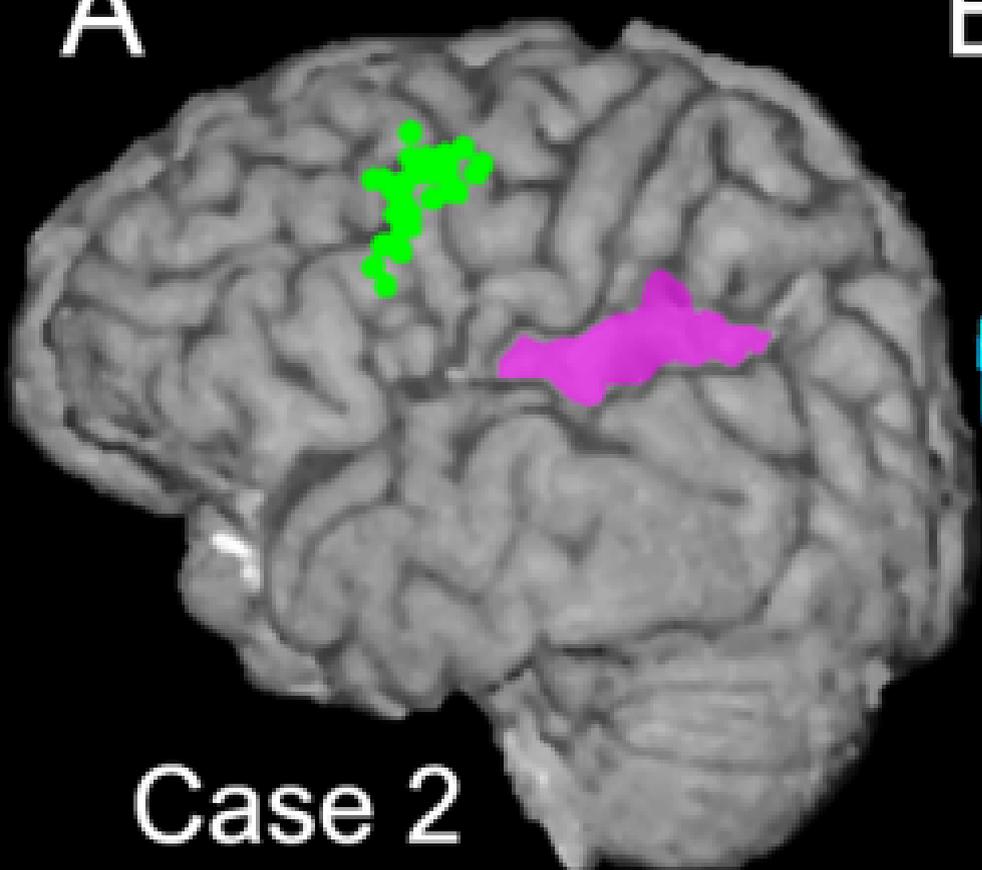
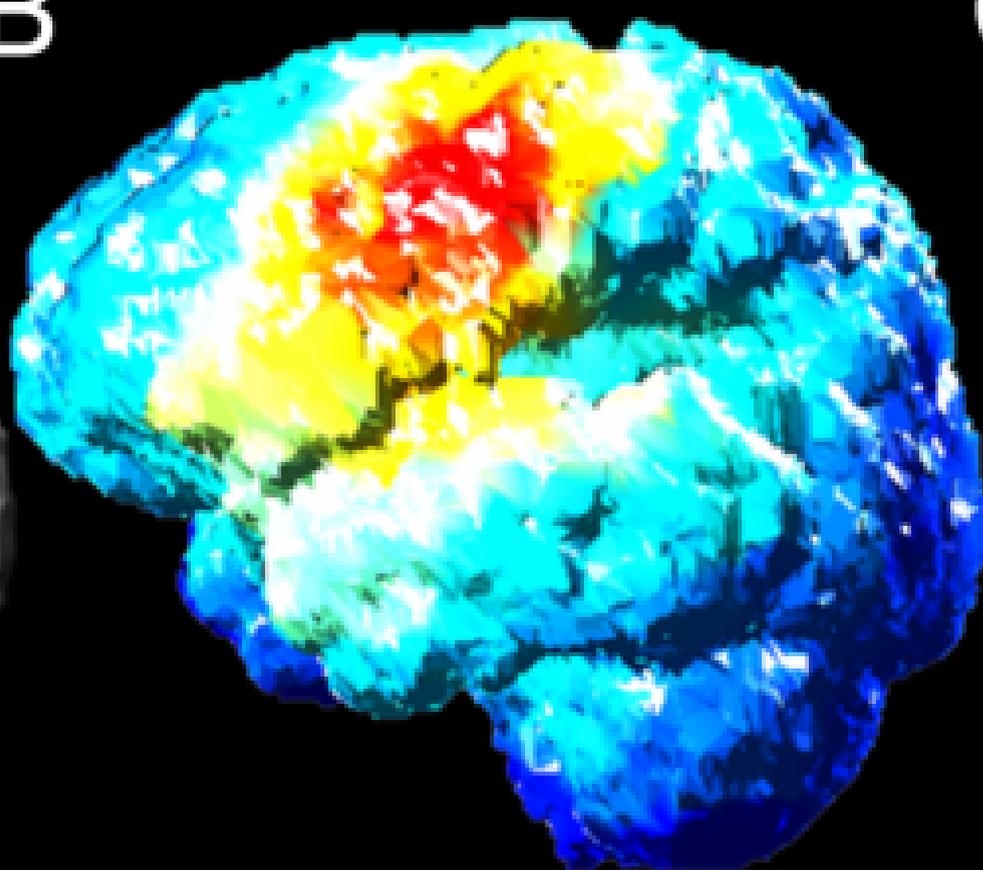
E  $^{99\text{m}}\text{Tc}$ -ECD-SPECT





Case 2



**A****B****C**