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A functional MRI and magneto/electro source imaging procedure for cognitive and pre-surgical evaluation

Jafri Abdullah*[a,b], Zamzuri Idris[a,b], Jose M. Sanchez-Bornot[b,c], Pedro A. Valdes-Sosa[b,c]

[a] *Center for Neuroscience Services and Research Universiti Sains Malaysia,* [b] *Department of Neurosciences School Of Medical Sciences/Hospital Universiti Sains Malaysia, Universiti Sains Malaysia, Kubang Kerian, Kota Bharu,16150 Kelantan, Malaysia*
[c] *Neuroinformatics Department, Cuban Neuroscience Center, Cubanacan, Playa 10600, La Habana, Cuba*

Abstract

Analysis of normal/pathological brain activity using neuroimaging methods is necessary to avoid operation risks, and the outcome serves as prior information for surgical neuronavigation. We present an fMRI/MEG/EEG-based methodology for tasks demanding mainly sensorimotor and visual/cognitive responses. This consists of carefully selected/designed stimulation paradigms and statistical parametric mapping methods that demonstrate the practicability of these techniques for clinical applications. The results replicate known findings in the brain-imaging field, with the improvement that our analyses are restricted to grey matter tissue. The latter enhance computations, which is advantageous for the massive data analyses that are typical of clinical and radiological functional brain "checkup" services.

Keywords: brain checkup; clinical applications; SPM; fMRI; MEG; EEG; source imaging; multimodal analysis

1. Introduction

The availability of brain checkup services based on fMRI, MEG, and EEG data is essential for the intention to exhaustively evaluate brain activity before neurological, psychiatric, or neurosurgical interventions. The success of the surgical treatment in pathologies such as brain tumours and epilepsy basically depends upon removing as much pathological brain tissue as possible without affecting the eloquent brain functions. Currently, functional neurosurgery conducted with the help of new technologies to map the brain both prior to surgery and intraoperatively is growing in popularity, as it saves destroying the eloquent motor and sensory areas, as well as the cognitive areas of the frontal and temporal lobes [1, 2, 3, 4]. Shimamura et al. [5] demonstrated the efficacy of the MEG technique for mapping the central sulcus using sensory and motor tasks, and reported the displacement of functional regions from the motor cortex in a patient with arteriovenous malformation (AVM). Functional MRI has also been successful tested for mapping brain activation in tasks such as motor, language, and visual areas, mainly for neurosurgical interventions of brain tumour patients [1].The use of fMRI for hemispheric cognitive mapping in

* Corresponding author Tel: +6097676300; fax: +6097673833
E-mail address: brainsciences@gmail.com

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medically intractable epilepsies provides important information during the surgical intervention [6]. In the latter, accurate identification of the focus of the epilepsy and the involved networks in foci propagation is necessary, but these problems can hardly be solved with the standard techniques and the current state of brain imaging research. However, even in these situations, a priori explorations with fMRI/MEG make the labelling and functional evaluation of the target and surrounding areas easier [7]. In general, our previous experiences have indicated that cognitive, motor, and sensory findings should be corroborated during awake neurosurgical procedures [8].

Functional MRI is a useful non-invasive tool for mapping brain dominance by the determination of the usually lateralised Wernicke's and Broca's areas [1]. The standard technique for brain dominance mapping is the intracarotid amytal, or Wada, test [9], but this is a highly invasive procedure, and thus, is only recommended for critical interventions. Invasive tests such as the Wada, which was popular 20 years ago, have now been replaced by others that are non-invasive [10]. For mapping language areas, picture naming and verb generation have been used as standard paradigms, and the response is usually expected to be lateralised in agreement with the findings that language areas are located in the dominant hemisphere. However, the combined use of these paradigms with fMRI or MEG/EEG recordings produces, in the best case, a close approximation to the localisation of functional areas, given that these techniques are indirect measurements of neuronal activity and the complexity of language processing in the brain [3]. Ojeman et al. [11] directly explored the plausible language areas using intracortical stimulation during a picture-naming task. Their sample consists of 117 epilepsy patients with left-hemisphere dominant brain, 99 of them determined by the Wada test. They evaluated a verbal intelligence quotient intraoperatively for each subject, for better control of intra-individual differences. As a result, they created a left hemisphere map with the percentage of subjects who presented picture-naming errors when a particular area was stimulated (see Figure 8 in [11]). On the basis of their study, we can affirm that (i) there is great variability in language areas also being important in some areas that are distant from the well-known Broca's and Wernicke's (B&W) areas, and (ii) most of these language centres are highly localised, with much less extension than the B&W areas.

With these foregoing discussions, a conclusion could be made that it is not reliable to trust the identification of language based exclusively on prior knowledge. It is necessary to proceed to do a careful exploration for each individual. However, in the previous work, the authors did not control the timing of electrical stimuli with respect to the cognitive task, and logically, if a language region was not perturbed at its critical processing time, the electrical stimulation might have shown little or no impact over the behaviour. In a recent study, Schulmann et al. [12] supported this idea by using chronometric TMS stimulation during a picture-naming task. The TMS-induced current was applied 150, 225, 300, 400, and 525 ms after picture presentation over regions corresponding to the superior temporal gyrus (STG), identified as the locus of Wernicke's area; at a supposed central point of Broca's area located in the inferior frontal gyrus (IFG); and in the central part of the left middle frontal gyrus (MFG) (see Figure 3 in [12] that shows TMS targets for B&W and MFG locations for all subjects). These areas were selected according to the neurocognitive model for language-speech generation [13]. In summary, Schulmann et al. [12] found that subjects presented a significant delayed response when the TMS pulse was applied 300 ms after stimulus presentation at Broca's point, or after 400 ms at Wernicke's point; when using MFG, they found that the critical times had an apparently bimodal distribution, with peaks around 225 and 400 ms. They concluded with some remarks about the causality implications of their study, taking into account the temporal relationship between this timing and cognitive findings on language processing [13]. It is worth noting that they recognised that their study had limitations with respect to the spatial resolution of TMS stimulation [14] and the accurate selection of TMS targets (see discussion in [12] and also [15]). Edwards et al. [16] highlighted a need for further revisions of the neurocognitive models by using intracortical recordings for epileptic subjects.

As part of the brain checkup services at the Hospital Universiti Sains Malaysia (HUSM), we created retinotopy and auditory maps based on fMRI. The results for patients with brain tumours near these important regions will be published in another manuscript. It is important to mention that not all paradigms have the same effectiveness. For example, verb generation and verb conjugation are more useful than picture naming for mapping language areas and predicting brain dominance; however, at the same time, those tasks are more complex [1]. Thus, it is recommended that a psychological test (e.g. WAIS, D-KEFS, WRAT) be applied to assess the patient's verbal fluency prior to the imaging sessions, and thereafter, select the most appropriate paradigm.

2. Materials and Methods

The functional MRI data for HUSM brain checkup services was collected with a 3-T Philips MR Achieva scanner (Philips Electronics, The Netherlands), using a standard whole-head coil and T_2^*-weighted gradient-echo EPI sequence (TR = 2 sec, TE = 30 msec, flip angle = 90°, field of view FOV = 192 mm, matrix = 64 x 64 mm^2). In order to cover the whole brain-cerebellum space, 35–38 interleave slices with 3 x 3 x 3.5 mm^3 voxel resolution were acquired. Prior to the functional session, a high-resolution anatomical image was acquired. For every case, the selected stimulation paradigm differed according to the location of the tumour or pathology, as well as the subject functionality that needed to be explored. During sensorimotor tasks, we alternated 16 sec of right finger movement with 16 sec on the left side and followed the same protocol for foot movement. For movement of the lips, we used the same temporal sequence, but alternating with resting periods. For object and verbal localising, the paradigm was basically blocks of 16 sec for images and scrambled images, 20 images randomly presented (300 msec each one) with interspersed resting/fixation images (500 msec), alternated with 16 sec of resting periods. There were other paradigms used as part of the HUSM brain checkup services, but only those used for the reported results are mentioned herein. In all cases, the subjects were instructed to stare at the centre of the screen, indicated by a fixation cross-hair, during the resting periods; for object and verbal localising, they were to silently read or name the stimulus content, always avoiding movement of the head or jaw. All runs were completed in less than 10 minutes.

For MEG/EEG analyses, the data was collected using an Elekta Neuromag 306-channel MEG system (102 magnetometers and 204 gradiometers) (Elekta Neuromag, Helsinki, Finland) located within a magnetically shielded room. In order to measure the head position with respect to the MEG sensors array, (i) 100–150 points were digitised closely and around the head using a 3D position monitoring system (Polhemus, Colchester, VT), (ii) they also were digitised according to the standard fiducial points (nasion and left/right preauricular references), and (iii) four electromagnetic head position indicator (HPI) coils were used to assess the head position at the beginning of the measurement process. In the case presented in this manuscript, we only measured MEG data. The MEG time series were filtered at 0.1–300 Hz and subsampled at 1 KHz using the standard Neuromag software.

The analyses were conducted using home-made MATLAB-based pipelines based on popular toolboxes (SPM and FieldTrip [17,18]). They were intended to provide a straightforward use of the most standard tools used in neuroscience data analysis, such as (i) analysis of regions of interest with the concomitant detection of significant active regions that respond to external stimuli, (ii) inverse solutions for EEG/MEG data for time domain and spectral analysis, and (iii) functional and effective connectivity estimation for time and frequency domain. In our pipelines, we reproduced some SPM analyses, such as estimation of the generalised linear model (GLM) and computation of contrasts and other statistics. The main advantages are that when computations are restricted to grey matter, the fMRI time series can be kept in memory and computations are faster; although some internal computations could be conveniently performed by considering the white matter information. Furthermore, whether or not subjects' individual anatomical images are provided, the results are shown in the canonical MNI space, which allows symmetric and asymmetric comparisons amongst modalities. In addition, the implemented pipelines and visualisation tools allow the use of anatomical/functional region-based atlases, making it easy to compare the obtained significant regions with known results reported for the corresponding paradigms.

Surgical Techniques: The fMRI-MEG-guided neurosurgery was performed by co-registering the activation maps onto a 3D MRI data set in the Laboratory for Magnetoencephalography and Event Related Potential at HUSM. Targets and areas determined to be at risk were segmented and made visible for the surgeon via the image-guided system. Image-guided neurosurgical support was provided by the StealthStation® neuronavigation system (Medtronic Sofamor Danek, Memphis, TN). A mobile floor-mounted camera was used to monitor the positions of the operating OPMI Pentero surgical microscope (Zeiss, Oberkochen, Germany). For registration, adhesive skin fiducial markers were placed on the head surface prior to imaging and registered with a pointer after their positions were defined in the 3D functional data acquired preoperatively from MEG and fMRI images. Repeated landmark checks were performed to ensure accuracy. After a rigid registration of the pre- and intraoperative images, the data was transferred to the Medtronic navigation system, and the initial patient registration file was restored and used for surgery, as well as integration with the microscope and surgical instruments [8] (see Figure 1).

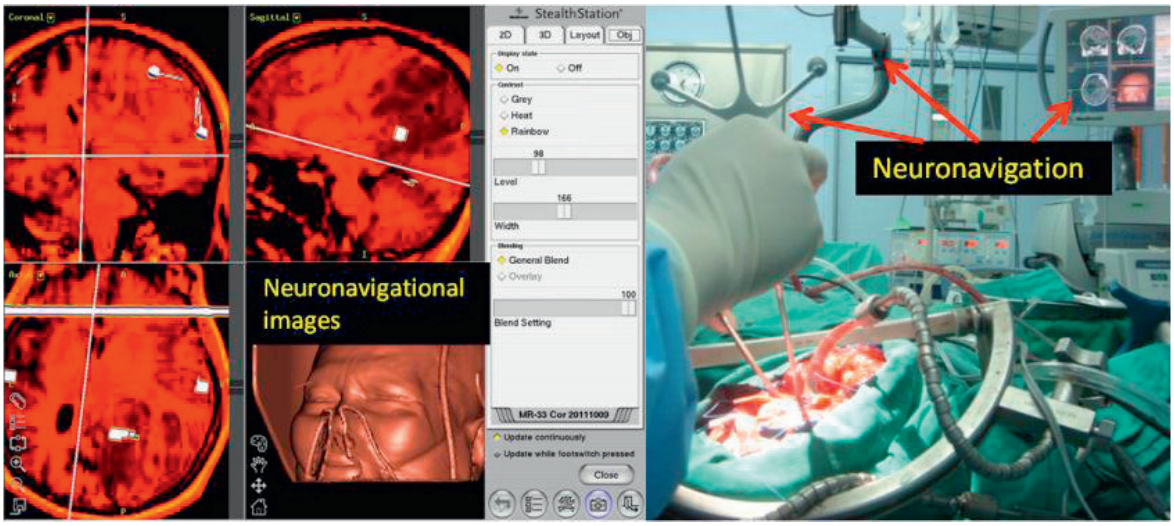

Figure 1: Image-guided neuronavigation used to assist the neurosurgeon to avoid important and relevant eloquent and cognitive areas.

3. Results and Discussion

In this section, we present results from the MEG/EEG and fMRI database samples of HUSM's patients. Our sample consisted of two subjects, designated C1 (with fMRI and MEG data) and C2 (fMRI); C1 had a brain tumour (fMRI) and C2 had an arteriovenous malformation (fMRI). This was an initial effort to standardise a methodology that was oriented to clinical applications, mainly for fMRI, MEG/EEG, and ECG data, and that could be used to perform analysis for pre- and post-surgical interventions, as well as for cognitive evaluations. This methodology will continue to evolve in parallel with the designs and implementations of new brain checkup services and the inclusion of new statistical and visualisation methods.

Figure 2 shows the mapping for the object localiser paradigm contrasting objects versus scrambled objects: most significant active areas were located in the lateral and ventral occipital cortex, known as the lateral occipital complex (LOC). There were significant bilateral activations in the putamen, insula, IFG, MFG, and STG. LOC activations have been reported to be associated with the processing of objects independent of their characteristics and familiarity [19, 20], while the other activations could be explained as part of the process of recovering the internal representation of the objects, including the silently naming behaviour (see also [13]). The figure also shows the segmentation of an atlas of 71 regions used previously in the IBASPM toolbox [21].

Figure 3 shows the significant activations during a verbal localiser task used to map the language areas. The activations corresponded to T-contrast between the verb reading condition and the control conditions represented by scrambled versions of the verbs. The purpose of this contrast was to remove the stimulus visual component; after that, an automatic threshold was established using family-wise error (FWE) statistics. In this case, the subject was a right-handed person, and the expectation is that 63–96% of the right-handed population exhibit left-hemisphere brain dominancy [22]. However, as shown in the figure, activations were bilateral, and the maximum were located in the right hemisphere. Bilaterality of the language functions in tumour cases could be explained as the reorganisation of brain functions due to the tumour lesion and its collateral consequences. In Figure 4, results are shown for the same paradigm, but for a normal right-handed case (C2). Notice that even when some functions were symmetric, the maximum and the majority of the significant activations were located in the left hemisphere

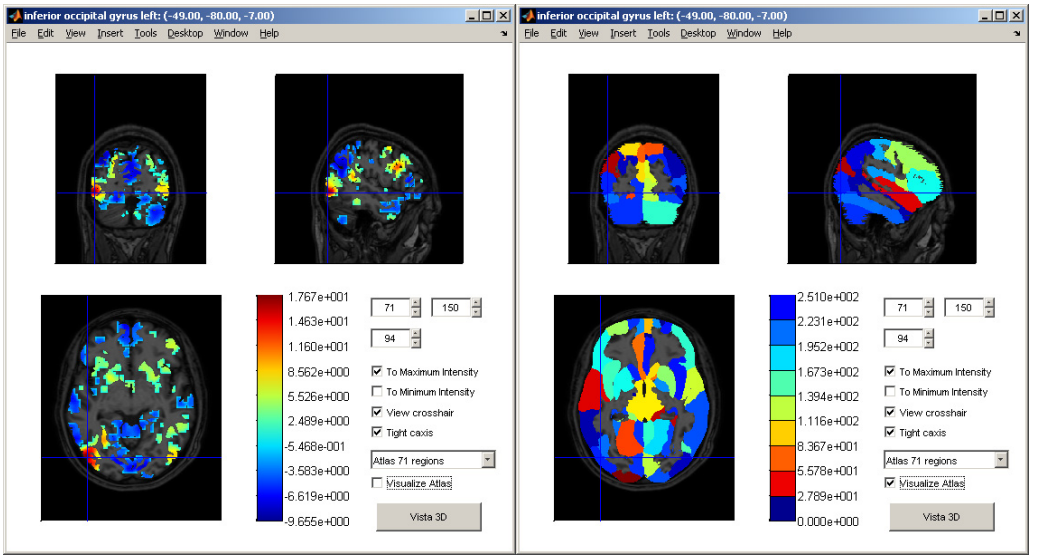

Figure 2: Result, shown in a home-made MATLAB-based interface, for subject C1 for the object vs. scrambled paradigm. Left: significant activations using FWE for correcting for multiple statistical tests and restricting the analysis to grey matter. The cross-hair intersection denotes the voxel of maximum activation. Right: overlay with IBASPM 71 regions atlas; notice that maximum activation is located in the inferior occipital gyrus (left).

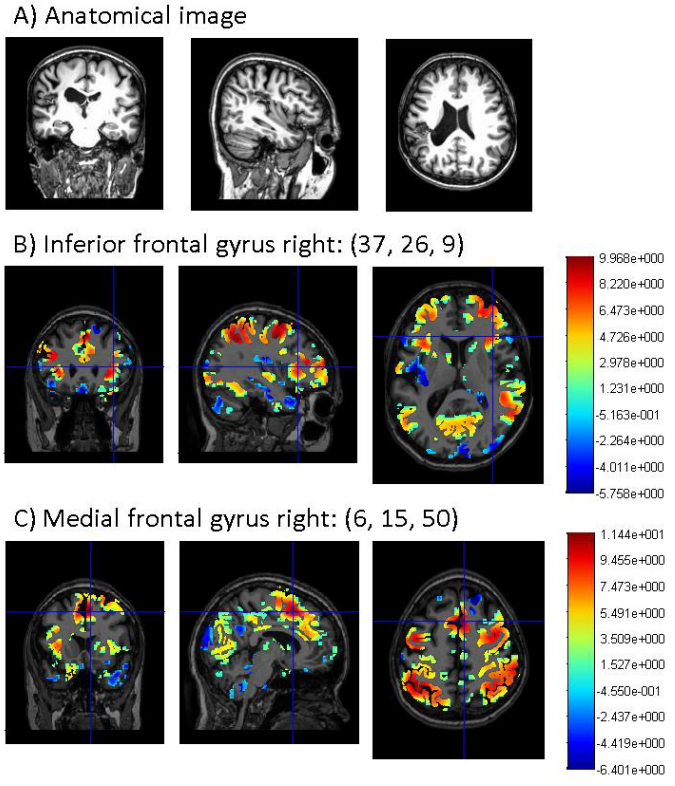

Figure 3: Mapping language areas for a subject with a brain tumour in the left hemisphere, as shown in anatomical image A). The paradigm used corresponds to a verbal localiser using scrambled verbal images as a control. B) Bilateral response in the functional region corresponding to Broca's area. C) Regions of maximum activation. All the active regions are significant. The T-contrast color-coded values are shown on the right.

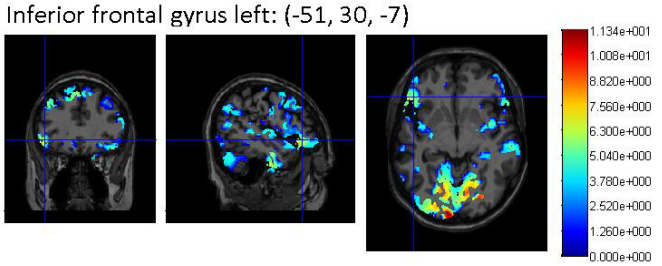

Figure 4: Mapping language areas for subject C2 . The significant activations in Broca's area are mainly lateralised to the left hemisphere, which is the dominant hemisphere for around 63–96% of right-handed persons, according to estimates [22].

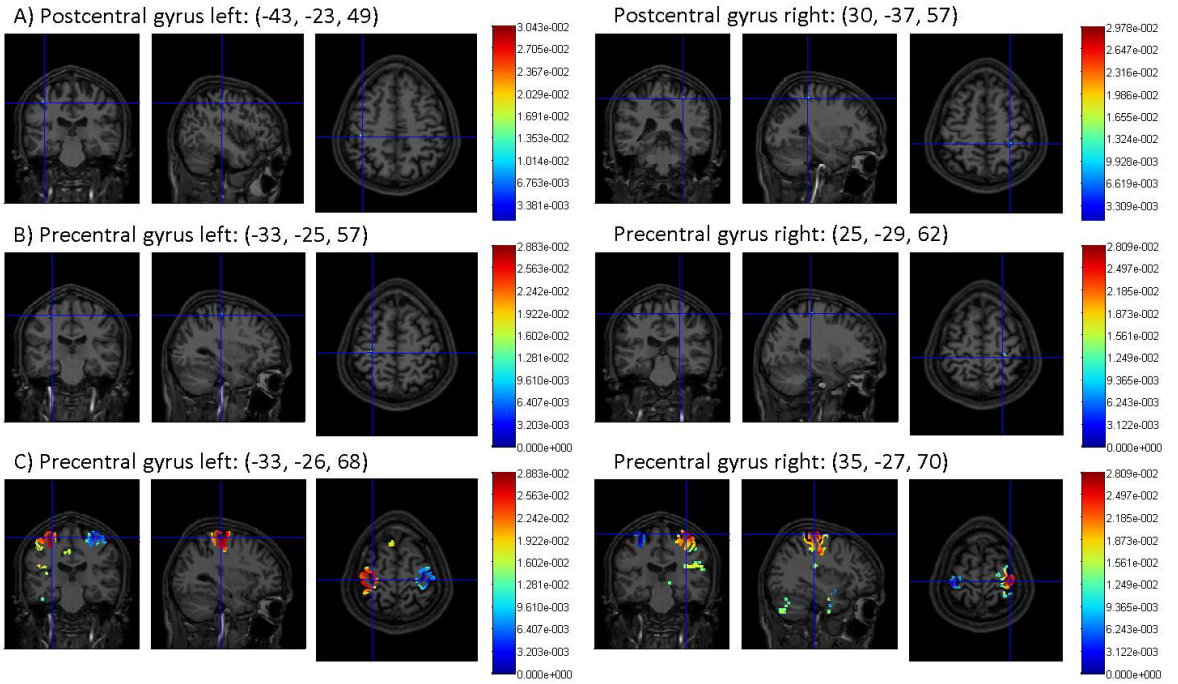

Figure 5: Analysis of sensorimotor activity for C1 using A) median nerve electrical stimulation on the right and left wrists for recording MEG data; right/left finger movement paradigm for B) recording MEG data; and C) the haemodynamic response function (fMRI BOLD signal). In A and B, the results are dipolar solutions, while C represents significant activations obtaining in classical SPM analysis, but restricted to grey matter. The left column shows results for stimuli applied on the right side; the right column shows results for stimuli applied on the left side.

In Figure 5, we present the results of mapping sensorimotor areas in subject C1 using MEG and fMRI analyses (see figure captions). The solutions were contralateral, and for MEG motor and sensory data, dipolar solutions occurred at both sides of the central sulcus, as expected. In addition, there was a high level of correspondence between the MEG and fMRI solutions.

Figures 6 and 7 show the results of right/left finger and lip movement tasks in a patient with AVM in the left cingulate region (6A). The results were consistent with the expected activations, except for the changes provoked by the AVM. As expected, the maximum activations in subplots 6D and 7A occurred contralaterally, but activations in the left hemisphere were not significant (6F), probably because this was near the AVM site and the blood flow changed with the concomitant functional reorganization that the AVM produced ([5]). The results of the lip movement task, presented in 7B, provide further evidence of the latter: only the activations in the right hemisphere were positively significant and accurate (compared against central sulcus homunculus). In the most affected hemisphere, there were several scattered regions that show deactivations. We also presented the brain grey/white matter segmentations in subplots 6B and 6C. Even when these were affected by the AVM condition, they covered

regions surrounding the lesion site, which means that our results were not biased by the choice of restricting solutions to the grey matter.

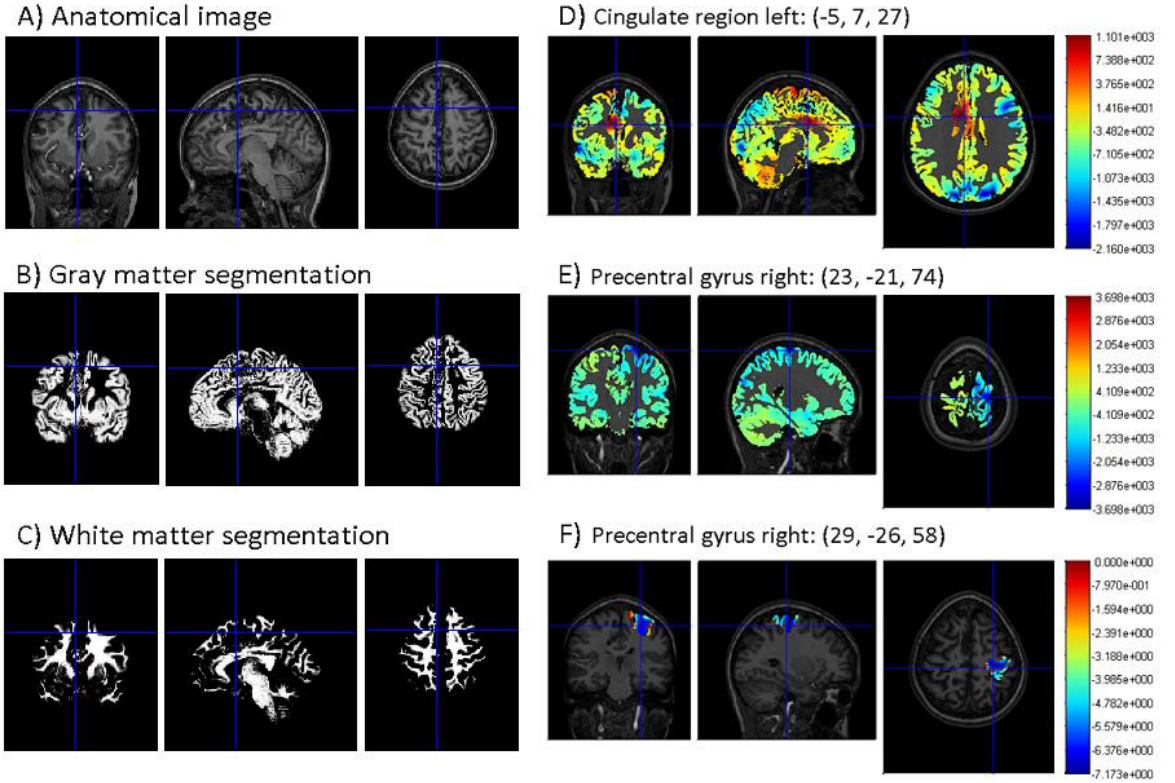

Figure 6: In subplots A, B, and C, anatomical images and their corresponding segmentations for a patient with AVM are represented. In subplots D, E, and F, the maximum activations, minimum activations, and T-contrast for significant active/deactivated regions, respectively, are represented for a right-hand finger movement task. Only deactivations are significant in the ipsilateral primary motor cortex.

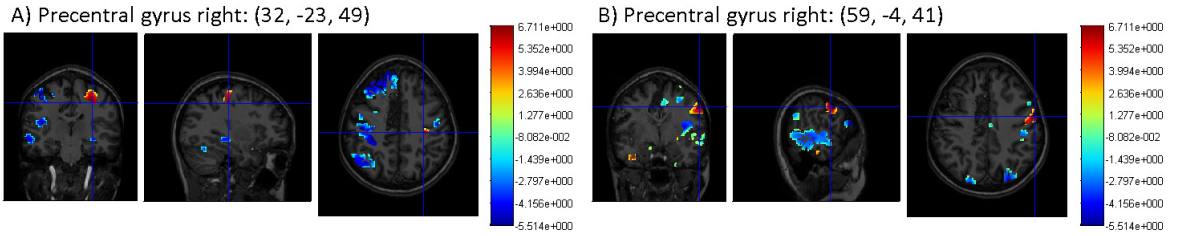

Figure 7: Regions of more significant activation during A) left finger movement and B) lip movement tasks.

4. Conclusions

We have presented a methodology for symmetric/asymmetric fMRI and MEG/EEG studies, and have shown some of the advantages of the evaluation of normal and pathological brain activity. The main purpose was to provide HUSM brain "checkup" services with a robust tool for functional analyses, so that the outcome could be used as prior information during surgical navigation. We also discussed that estimating solutions restricted to grey matter could be computationally advantageous, and these were consistent with expected results in neuroimaging research.

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