PRACTICAL ASPECTS OF FUNCTIONAL MRI IN CLINICAL EXAMINATIONS

Recebido em: 17/05/2023
Aceito em: 22/06/2023
DOI: 10.25110/arqsaude.v27i6.2023-053

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ABSTRACT: The eloquent cerebral cortices are involved in movement, sensation, speech, vision, and higher cortical functions. Functional magnetic resonance imaging (fMRI) allows the evaluation of brain function, aiding in neurosurgical planning by mapping eloquent cortical areas. Considering the high cost of the hardware involved, the purpose of this work is to present a more affordable, in-house alternative for these studies that can provide adequate results in a clinical setting. We also present some practical information on how to perform these exams. We describe an affordable in-house hardware solution used by an imaging center, and examples of fMRI paradigms used to evaluate motor and language tasks. The fMRI studies show robust activations in eloquent areas consistent with the tasks performed on the exam. Images of post-processed studies illustrate clinical cases. The fMRI have well-established applications, mapping eloquent cortical areas in patients with brain lesions. In the case of surgical planning, it allows the surgeon to maximize the resection area while minimizing sequelae. More affordable hardware can reduce the cost of these exams, making them more accessible to the general public.
KEYWORDS: Functional MRI (fMRI); BOLD Effect; Cortical Brain Mapping; fMRI Hardware; Language fMRI Paradigms.

ASPECTOS PRÁTICOS DE RM FUNCIONAL EM EXAMES CLÍNICOS

RESUMO: O córtex cerebral eloquente está envolvido nas atividades motora, sensação, fala, visão e funções corticais superiores. A ressonância magnética funcional (RMf) permite a avaliação da função cerebral, ajudando no planejamento neurocirúrgico através do mapeamento de áreas corticais eloquentes. Considerando o elevado custo do hardware envolvido, o objetivo deste trabalho é apresentar uma alternativa mais acessível para estes estudos, que possa fornecer resultados adequados em um ambiente clínico. Também apresentamos algumas informações práticas sobre a realização destes exames. Descrevemos uma solução de hardware acessível utilizada por um centro de imagens, e

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exemplos de paradigmas de RMf usados para avaliar tarefas motoras e relacionadas à fala. Os estudos de RMf mostram ativações em áreas eloquentes, consistentes com as tarefas realizadas no exame com imagens de estudos pós-processados ilustrando casos clínicos. A RMf tem aplicações bem estabelecidas, mapeando áreas corticais eloquentes em pacientes com lesões cerebrais. No caso do planejamento cirúrgico, permite que o cirurgião maximize a área de ressecção enquanto minimiza potenciais sequelas. Equipamentos mais acessíveis podem reduzir o custo destes exames, podendo aumentar a disponibilização ao público em geral.
PALAVRAS-CHAVE: Ressonância Magnética Funcional (RMf); Efeito BOLD Mapeamento Cortical do Cérebro por RM; Hardware RMf; Paradigmas de Linguagem RMf.

ASPECTOS PRÁCTICOS DE LA RM FUNCIONAL EN LOS EXÁMENES CLÍNICOS

RESUMEN: La corteza cerebral elocuente está implicada en las actividades motoras, la sensibilidad, el habla, la visión y las funciones corticales superiores. La resonancia magnética funcional (RMf) permite la evaluación de la función cerebral, ayudando en la planificación neuroquirúrgica mediante el mapeo de las áreas corticales elocuentes. Teniendo en cuenta el elevado coste del hardware implicado, el objetivo de este artículo es presentar una alternativa más asequible para estos estudios que pueda proporcionar resultados adecuados en un entorno clínico. También presentamos información práctica sobre cómo realizar estos exámenes. Describimos una solución de hardware asequible utilizada por un centro de diagnóstico por imagen, y ejemplos de paradigmas de RMf utilizados para evaluar tareas motoras y relacionadas con el habla. Los estudios de RMf muestran activaciones en áreas elocuentes, coherentes con las tareas realizadas en el examen, con imágenes de estudios postprocesados que ilustran casos clínicos. La RMf tiene aplicaciones bien establecidas en el mapeo de áreas corticales elocuentes en pacientes con lesiones cerebrales. En el caso de la planificación quirúrgica, permite al cirujano maximizar el área de resección minimizando las posibles secuelas. Un equipo más asequible puede reducir el coste de estas exploraciones, aumentando potencialmente su disponibilidad para el público en general.
PALABRAS CLAVE: Resonancia Magnética Funcional (fMRI); Efecto BOLD Mapeo cerebral cortical por RMN; Hardware de RMNf; Paradigmas lingüísticos de RMNf.

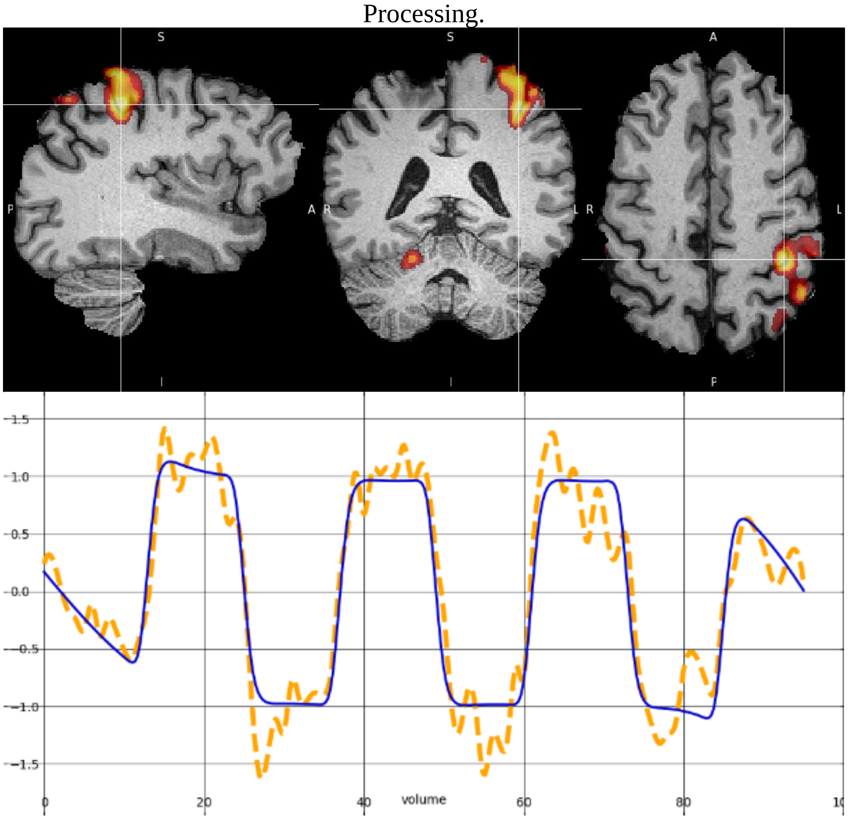
1. INTRODUCTION

The functional magnetic resonance imaging (fMRI) technique is used for the localization of eloquent areas in the cerebral cortex, related to motor and language activities, hearing, and vision, with an important role in pre-surgical planning (SOPICH; HOLODNY, 2021). In this paper, we highlight theoretical aspects in the introduction and practical aspects in the methods section. We present an affordable hardware in-house solution, allowing better interaction with the patient with visual instructions instead of auditory ones, and with the possibility of response collection in tests involving decisions.

Blood oxygenation level-dependent (BOLD) is the sequence used for fMRI acquisition, sensitive to changes in the oxygenation state of hemoglobin. Hemoglobin saturated with oxygen (oxyhemoglobin) is diamagnetic and deoxyhemoglobin is paramagnetic. Voxels with a high concentration of oxyhemoglobin have increased signals compared to areas with lower concentrations. fMRI is based on the neurovascular coupling mechanism (SMITS et al., 2006) whereupon the occurrence of neuronal activity we have a hemodynamic response, with increased blood flow accompanied by an increase in the oxy-deoxyhemoglobin ratio and a consequent increase in signal. If the stimulus for neuronal activity is maintained the signal reaches a plateau and upon cessation of the stimulus, the signal returns to baseline (SOPICH; HOLODNY, 2021). When performing tasks in a paradigm, changing moments of control or rest and moments of activity we will have variations in signal due to variations in the oxy/deoxyhemoglobin ratio. Voxels showing signal variation correlated with the paradigm model are then considered paradigm-related activations. The signal variation of the BOLD effect is directly proportional to the magnetic field strength, being between 1 and 5% in 1.5T systems and between 2 and 10% in a 3T magnet. This is the reason for choosing high magnetic field equipment to perform these examinations (AMARO; BARKER, 2006). Figure 1 illustrates aspects discussed in this paragraph.

The BOLD sequence is based on gradient-echo echo-planar imaging (GRE-EPI), which is most sensitive to magnetic susceptibility effects. This sequence has a low spatial resolution, requiring an anatomical acquisition for co-registration, usually a T1-weighted 3D volume. Problems of misregistration of the functional sequence in the anatomical sequence, i.e., activations shifted to nearby but not expected areas, must be carefully analyzed, and one of the causes may be the phase or frequency encoding direction (HOLODNY et al., 2013).

Figure 1. Example of a right-hand motor task with activation in the posterior cortical of the left precentral gyrus, in the region of the inverted omega. Also, note the activation in the superior portion of the right cerebellar hemisphere. The graph corresponding to the location indicated by the intersection of the white lines shows the signal changes in percent, ranging in this case from -1.5 to +1.5%. The curve in blue corresponds to the fitted model of the signal and the dashed curve in orange shows the signal acquired in the task, showing a strong correlation between the paradigm and the task performed. FSL-FEAT Processing.



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Taking into consideration the examination environment, the tasks should be as simple as possible, allowing patients with varying degrees of difficulty to perform them, while also sufficiently challenging to evoke the activations of interest (SMITS et al., 2006).

The most used motor paradigms are the assessment of hand finger movements, with apposition of the fingers to the thumb, and foot movements with plantar or toe dorsiflexion. Although simple, these tasks can present varying degrees of difficulty in patients with lesions in the corresponding cortical areas in the precentral gyrus or corticospinal tracts.

Language paradigms are used to determine the dominant cerebral hemisphere for language, which is left-lateralized in 95% of right-handed people and 70% of left-handed people (SMITS et al., 2006). The classical model of language processing consists of an area of expression or productive speech, Broca's area, and a center of language reception or receptive speech, Wernicke's area (SMITS et al., 2006; MORENO; HOLODNY, 2021). Broca's area is located in the pars opercularis and the posterior portion of the pars triangularis of the inferior frontal gyrus. Wernicke's area is less well defined, involving parts of the supramarginal gyrus, angular gyrus, and the superior and middle temporal gyri. Currently, this model is considered simplistic given the highly complex function of language. A more recent hypothesis, proposed by Hicklock and Poeppel considers the presence of dorsal and ventral language streams (JONES; SELVARAJ; HO, 2020) related to production and comprehension, respectively. The dorsal stream is lateralized to the left cerebral hemisphere in right-handed patients and includes the receptive speech area (Wernicke) and the expressive speech area (Broca). Lesions located in the frontal and temporal lobes, in the classical language areas, can cause language disorders (aphasia). Brain hemisphere dominance can be quantified by a laterality index (MORENO; HOLODNY, 2021), but in clinical practice, visual inspection is more commonly used, with a strong correlation with laterality indexes (SMITS et al., 2006). Several language paradigms can be run, and three were selected, two for verbal fluency assessment (phonological and semantic) and one for semantic decision, explained in the methods section.

The workflow of an fMRI scan consists of analyzing the patient's clinical data and previous imaging studies, choosing the most appropriate paradigms related to the areas of interest in or near the lesion; explaining the scan procedure to the patient with a simulation to familiarize the patient with the tasks they will be requested to perform in the examination room; carefully observation of the execution of the tasks during the scan, direct patient monitoring, and analyzing fMRI images in real time; post-processing and reporting the relationship of the lesion to the eloquent areas studied. The details of the fMRI examination are described in the methods section.

2. METHODS

2.1 MR System and fMRI Parameters

As earlier mentioned, the higher the magnetic field strength of the MRI device, the higher the signal will be, favoring the signal-to-noise ratio. We use a 3T system (MAGNETOM Skyra) and a 16 or 32-channel head coil.

The sequence for anatomy co-registration of the fMRI scan is a T1-weighted 3D volume. The BOLD sequence parameters are echo time (TE) of 30ms and repetition time

(TR) of 2,500ms (2.5s), acquisition of 96 volumes in interleaved form, totaling 240s in a 4-minute paradigm.

2.2 fMRI Hardware

Texts with instructions or tasks are projected from a projector positioned in the control room onto the screen in the examination room (Figure 2). The in-house screen solution consists of a transparente acrylic plate with dimensions equivalent to a 40-inch monitor to which a 3M Vikuiti^{TM} rear projection film is applied. The result obtained is sufficient to perform basic fMRI studies. The head coil viewing mirror is mounted onto the head coil, allowing the screen to be seen. Images or pictures can also be projected and Figure 3 is an example of a color projection.

Figure 2. The rear projection display in the examination room is mounted on a foot stand, acting as an in-room viewing device. The head coil viewing mirror can be seen mounted onto the head coil inside the magnet.

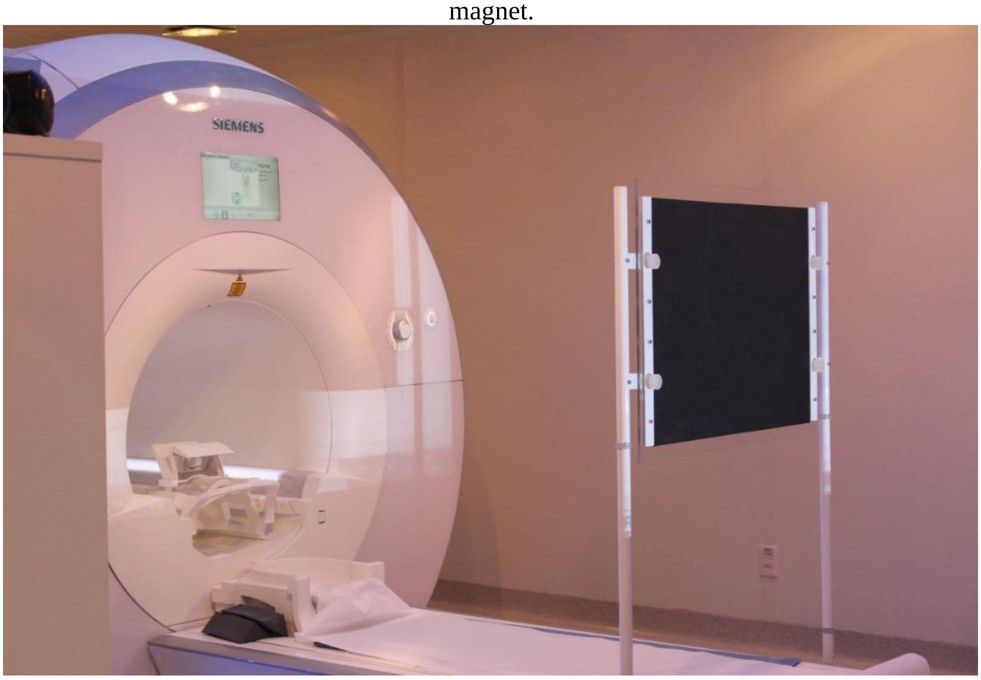

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Figure 3. Example of a color image projection.

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For capturing responses, in the case of decision tests, devices with two pneumatic buttons (Figure 4) were manufactured, thus allowing the application of tests with up to 4 alternatives, considering one device in each hand.

Figure 4. Interaction device with pneumatic buttons for capturing patient responses during the exam.

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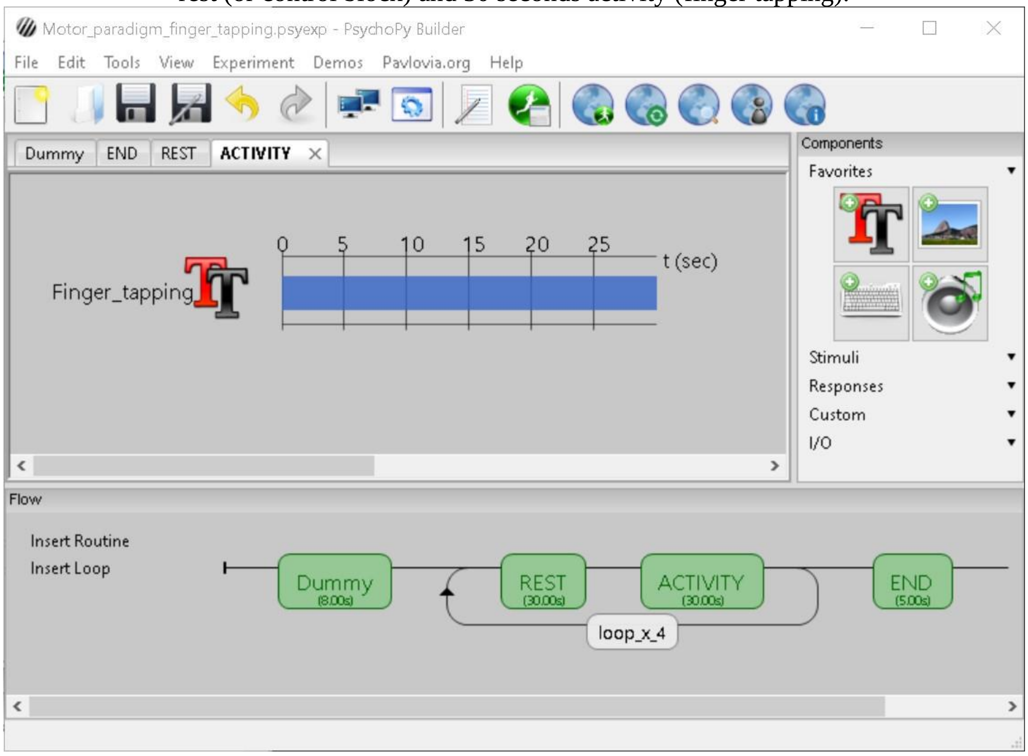
2.3 Paradigm Design

We use the block paradigm design, which is more robust[3] in the statistical analysis applied in post-processing. The number and duration of the blocks vary between imaging centers. The basic design of the paradigms presented consists of 8 blocks, each lasting 30 seconds, alternating between control and activity blocks. In this way, the total duration of the functional study is 4 minutes. The paradigms were programmed in the PsychoPy platform (https://www.psychopy.org/) (PEIRCE et al., 2019), a flexible and user-friendly tool. A sample screenshot of a motor task experiment is illustrated in Figure 5. We explain the fMRI procedure to the patient and make a simulation before the exam. All tasks are presented visually, with instructions on a screen, rather than auditory instructions. The synchronization of the starts of instruction presentation and acquisition is done manually, that is, without a synchronization device and without prejudice to post-processing.

Figure 5. A PsychoPy programming example of a motor paradigm, with 4 loops, each with 30 seconds rest (or control block) and 30 seconds activity (finger tapping).



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2.4 Motor Tasks

Basic motor paradigms consist of the movement of the fingers or dorsiflexion of the feet. In the finger-tapping task, the patient is asked to make the apposition of the fingers to the thumb. The classical location for finger movement activations is in the motor homunculus of the hand, which is usually shaped like an inverted omega, located in the posterior region of the precentral gyrus contralateral to the hand under study (HOLODNY et al., 2013). Another area of activation is the superior portion of the cerebellar hemisphere ipsilateral to the motor task. The motor area of the foot is in the high frontoparietal convexity, in the most medial portion of the precentral gyrus, adjacent to the interhemispheric fissure (MORENO; HOLODNY, 2021).

2.5 Language Tasks

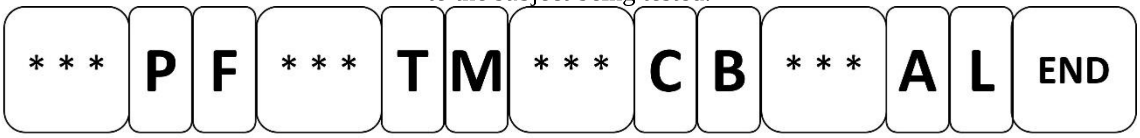
2.5.1 Phonological and semantic verbal fluency tasks

In language assessment, we apply verbal fluency tasks using the silent word generation strategy, minimizing movement artifacts, but with the disadvantage of not being able to monitor performance while performing the task (SMITS et al., 2006). Verbal fluency tasks can be in phonological or semantic form. In the case of phonological verbal fluency, the individual is asked to think in words that begin with a certain letter, for example, words that begin with the letter A (e.g. ant, adult, arch). In the case of semantic verbal fluency, the individual must produce words related to a certain category, for example, colors, fruits, or animals. For example, if presented with the word color, the individual could think of blue, red, yellow, etc.

In phonological verbal fluency tasks, for native English speakers, the letters F, A, and S are considered the easiest for word generation. In the present work, we used a database of letters ranked for Brazilian Portuguese speakers (SENHORINI et al., 2006). We used asterisks in the control block so that the patient would maintain a fixed gaze. In the activity block, letters were exposed for 15 seconds, i.e., 2 letters per activity block. A schematic of the phonological verbal fluency paradigm can be seen in Figure 6, using the letters P, F, T, M, C, B, A, and L.

Typical areas of activation in verbal fluency tasks are in the inferior (SMITS, 2006) and middle (MORENO; HOLODNY, 2021) frontal gyri of the dominant cerebral hemisphere. Activations in the pre-supplementary motor area (pre-SMA), considered the supplementary motor area of language, located in the posteromedial aspect of the superior frontal gyrus, are also observed (MORENO; HOLODNY, 2021).

Figure 6: Phonological verbal fluency paradigm scheme with control blocks displaying asterisks and activity blocks exposing letters. Each control block lasts 30 seconds. Each letter is exposed for 15 seconds to the subject being tested.



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2.5.2 Semantic decision task

Another paradigm for evaluating language lateralization is the semantic decision. The activity block consists of tests with pairs of words. One word represents a higher category (e.g., color) and the other word represents a subordinate category exemplar (e.g., blue). The individual responds with the interaction device with a yes or no answer. The control block corresponds to non-alphanumeric character set pairs and the individual responds whether the shown pairs are identical or not. Figure 7 illustrates examples of word pairs and character set pairs. Each block contains 6 pairs presented every 5 seconds, enough time for the patient to read, interpret and respond (Figure 8). Unlike the silent word generation strategy, with the collection of responses in the semantic decision task, it is possible to evaluate the patient's performance on the test by the number of hits and infer whether there has been adequate recruitment in the activation area of interest. The usual activations are observed in the posterior portion of the temporal lobe (SMITS et al., 2006; MORENO; HOLODNY, 2021) of the dominant cerebral hemisphere. Activations can also be observed in the inferior frontal gyrus.

Figure 7: Example tests with the expected responses on pairs of character sets in the control block and on pairs of words in activity blocks in the semantic decision task. Each test is displayed for 5 seconds.

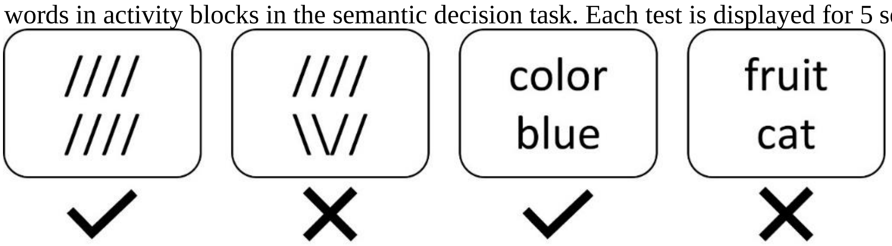

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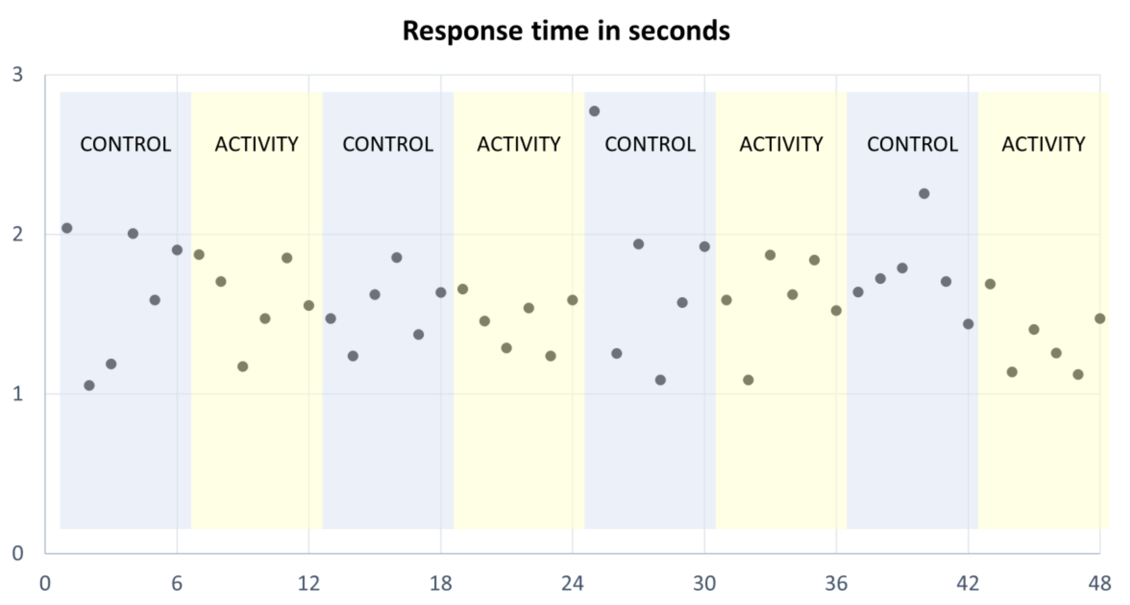
Figure 8: The graph illustrates the response time for each of the 48 tests of pairs of words or character sets presented. For this patient, most of the response time ranged between 1 and 2 seconds.



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2.5.3 Post-processing

Post-processing of the images can be done using programs for research or commercial purposes. An example of software widely used by researchers is the FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL, Functional MRI of the Brain, FMRIB Software Library) (WOOLRICH et al., 2001), a comprehensive library of analysis tools for fMRI, MRI, and DTI brain imaging data. Most of the tools can be run either from the command line or through graphical user interfaces (GUI). At FSL, fMRI processing is done with the FEAT automated tool, taking only a few minutes to process. The equipment manufacturers also offer programs that can be installed on the acquisition system itself or post-processing workstations.

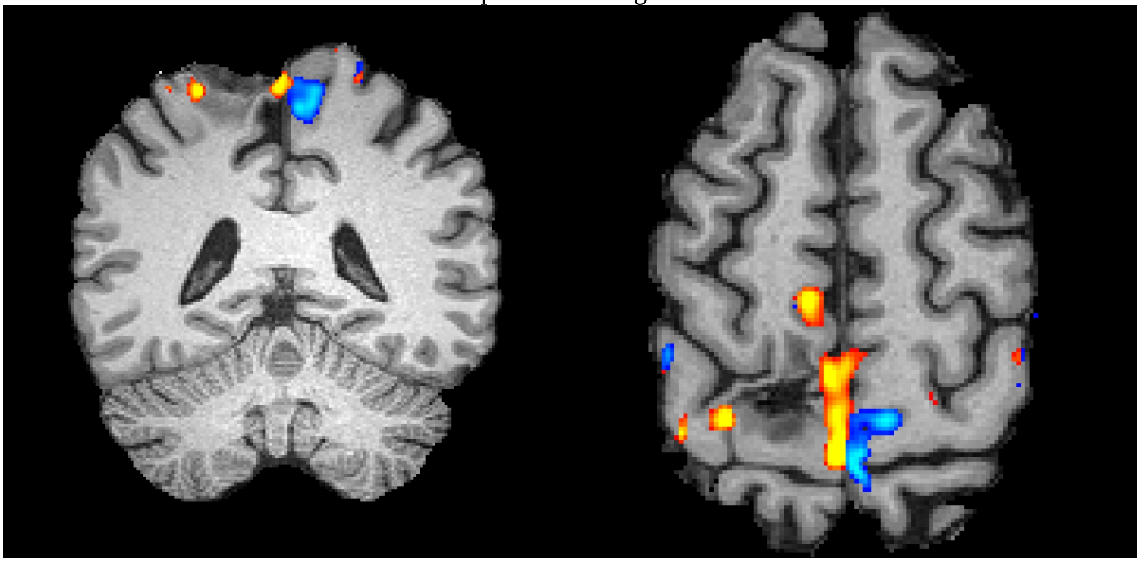
3. RESULTS

The following sequence of figures shows post-processing results using the FSL-FEAT tool. The examples are clinical cases, with observed activations in the areas expected for the applied tests.

3.1 Motor Paradigms

An example of hand motor cortex activation was already presented in the introduction (Figure 1). In the toe dorsiflexion task, we observe activations in the high frontoparietal convexity, in the most medial portion of the precentral gyrus contralateral to the tested foot (Figure 9).

Figure 9. Patient with an operated lesion in the transition between the right superior frontal and precentral gyri. Overlap of motor task activations in the feet. The orange coloration in the right paracentral lobe corresponds to the movement of the left foot and the bluish coloration in the left paracentral lobe corresponds to the right foot.



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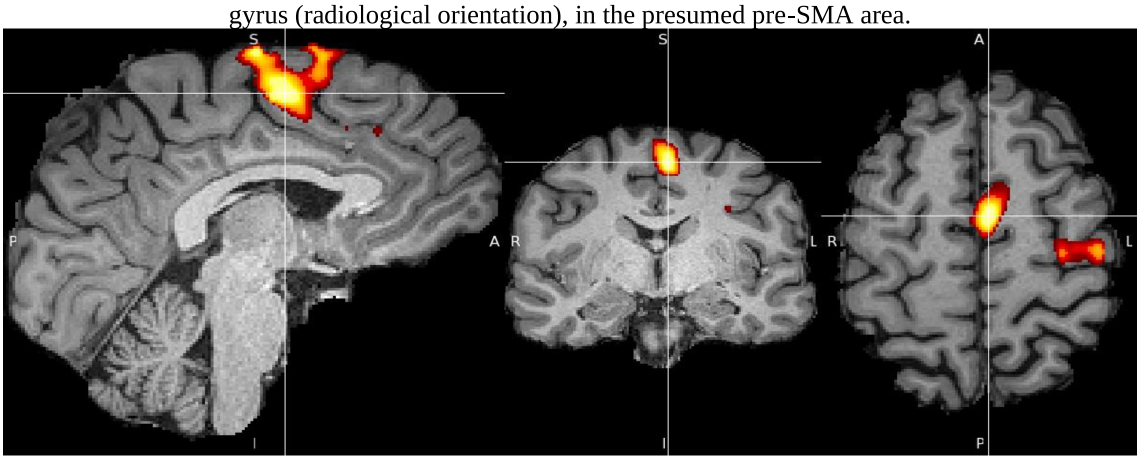
3.2 Language paradigms

In verbal fluency tests, activations can be observed in the presumed pre-SMA area, related to motor speech planning (Figure 10).

Figure 10: Verbal fluency test showing activation in the posteromedial portion of the left superior frontal gyrus (radiological orientation), in the presumed pre-SMA area.



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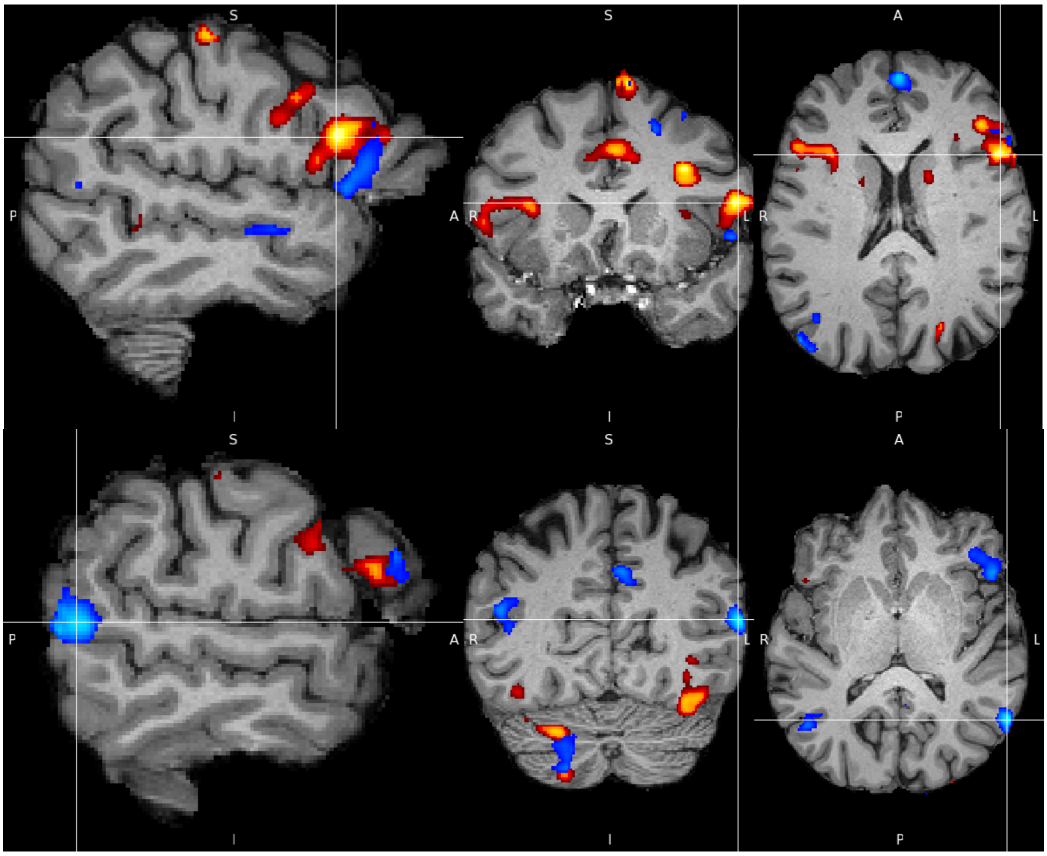
In the semantic decision test, activations are expected in the posterior portion of the temporal lobe. Activations in the inferior frontal gyrus can also be observed (Figure 11).

Figure 11: Overlapping tests of verbal fluency (orange shades) and semantic decision (blue shades). In the upper figure, the position indicated by the intersections of the white lines shows activations in the left inferior frontal gyrus, in the classical Broca's area. In the lower figure, the position indicated by the intersections of the white lines shows activation in the posterior portion of the left temporal lobe, in the classical Wernicke's area.



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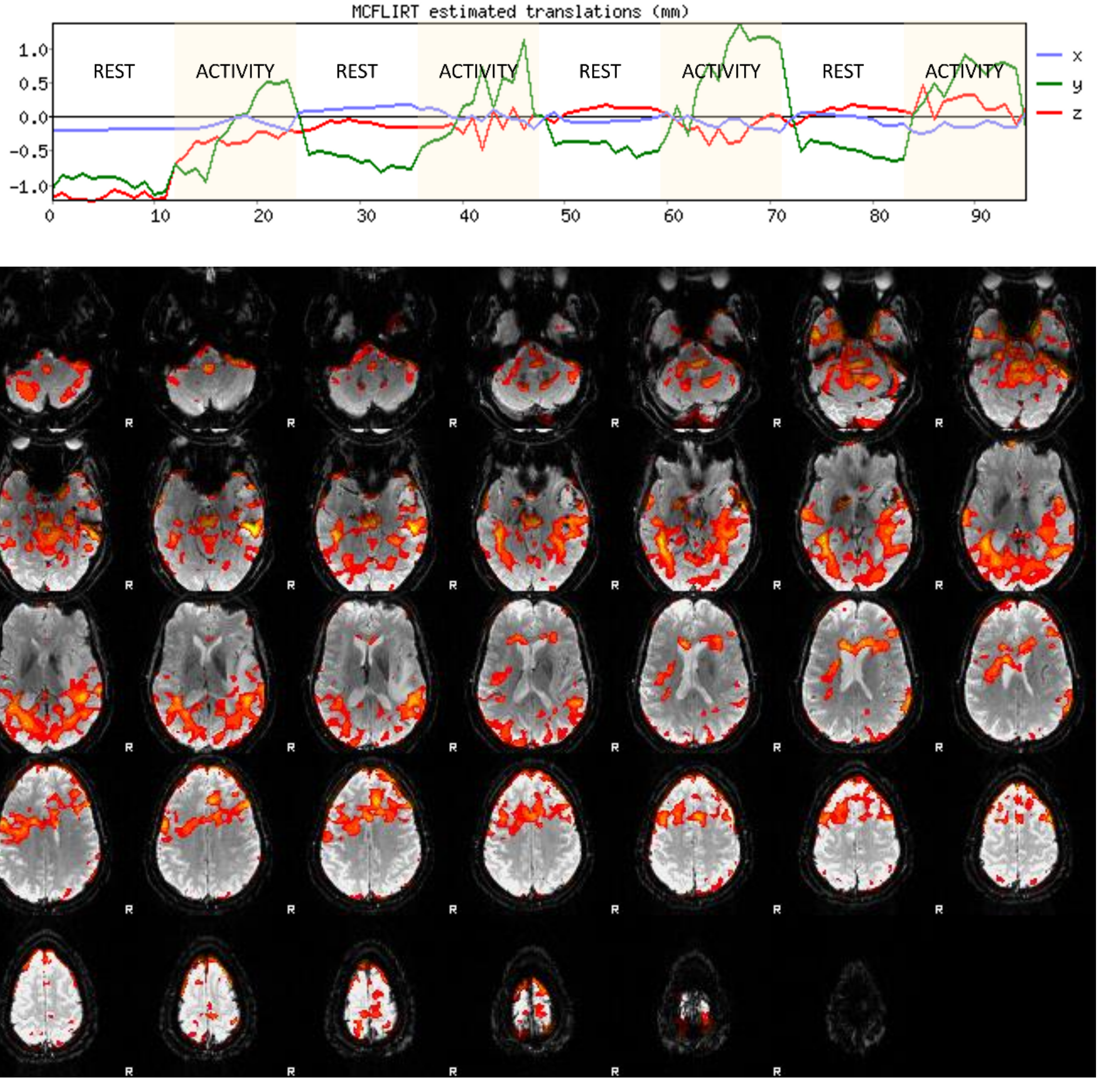
4. DISCUSSION

Some factors can impair the quality of an fMRI examination and care must be taken to minimize potential problems with optimized study planning and continuous attention during the execution of the examination, including in-line real-time monitoring of functional images during the exam and direct observations of patient task execution. To optimize patient time in the MRI scanner, the workflo (SOPICH; HOLODNY, 2021; PECK; CHO; HOLODNY, 2021) includes evaluation of patient clinical data and previous imaging studies of the patient, looking at eloquent areas affected by or near the lesion, and allowing the selection of necessary and sufficient paradigms to aid in the management and preoperative planning. Details that go unnoticed during acquisition may render interpretation impossible or invalid. Preparing the patient before entering the exam room, with proper orientation of the tasks that will be performed, preferably with a brief simulation, can help minimize repetitions due to errors in execution (PECK; CHO; HOLODNY, 2021). The tasks are designed to be the simplest to perform, but considering that many of these exams are pre-operative studies for brain lesions, it is not uncommon that the patient may present deficits that limit or hinder the execution of the requested tasks. Motion artifacts, which can be circumvented in the interpretation of a conventional MRI, can render the interpretation of an fMRI impossible.

Figure 12 illustrates a situation of head movement artifacts coinciding with activity blocks. This may be caused by the vocalization of responses or excessive or large movements in motor tasks, resonating with head movement. The presence of these movement artifacts should be monitored during the examination, and the task should be repeated after the patient has been instructed again. In the case of the phonological and semantic verbal fluency paradigms we opted for silent word generation, without vocalization, not being possible to monitor the patient, but aiming to minimize movement artifacts. Even without monitoring the patient's responses, the evaluation of the images during the examination, with activations in the expected regions can indicate the degree of the patient's cooperation in the examination. Performing the semantic decision task with response collection allows a more objective assessment of whether the patient is interacting and performing the tasks adequately. The joint analysis of the information in the verbal fluency paradigms and the semantic decision tests also helps to assess and infer the quality of the execution of language tasks by the patient.

Considering the aspects presented, the limitations of fMRI are related to the relative complexity of the exam, but they can be overcome with the appropriate training of the team involved and the constant care and attention to all details during the execution of the exam. Another important factor to be considered is related to the patient, who may present some degree of difficulty in adequately executing the requested tasks. In the case of severe motion artifacts, the exam may exceed the time allocated for the exam due to repetitions or even not allowing the interpretation (JONES; SELVARAJ; HO, 2020).

Figure 12: Example of patient movement in the activity block, evidenced by the green (y-axis) trace on the translations graph, resulting in inadequate post-processing for interpretation. FSL-FEAT Processing.



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5. CONCLUSION

The fMRI can assist in the preoperative planning of lesions near or at eloquent areas, helping the surgical team in the best possible approach and minimizing the risk of sequelae. It is an exam with its particularities and complexities, requiring more attention in the execution and also depending on the patient's collaboration in the correct execution of the proposed tasks. Some practical aspects in the execution of the exam were mentioned, and we emphasize that problems or errors in the acquisition can render the interpretation unfeasible or even invalid. Although the technique has been studied for the past three decades, in some places, for different or diverse reasons, the access to this type of examination to the general public may sometimes be limited, and therefore we consider of interest the presentation of an affordable in-house hardware solution that allows the execution of standard clinical examinations for the assessment of motor and language areas.

DECLARATIONS

Conflict of interests: The authors declare no competing interests.

Term of free and informed consent: Consent forms for the publication of the images were obtained from the patients.

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