Journal of Epilepsy and Clinical Neurophysiology

Editor convidado:
ANDRÉ PALMINI

J Epilepsy Clin Neurophysiol 2005; 11(1):39-44

Caso 03/2005

Functional MRI Memory Mapping for Epilepsy Surgery Planning: A Case Report

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ABSTRACT

Introduction: Functional evaluation of memory lateralization can have an impact on planning of epilepsy surgery for mesial temporal lobe (MTL) epilepsy. Functional MRI (fMRI) may provide non-invasive method to assist in the determinations of memory dominance. FMRI based memory mapping, however, is still not straightforward and determining lateralization can be difficult for a number of reasons. One outstanding question relates to the influence of material type on MTL activation. **Objectives:** To improve pre-operative memory lateralization evaluation using an event-related fMRI paradigm. This approach was designed to take into account successful encoding and material type. **Methods:** We describe here the case of a patient with MTL epilepsy who underwent memory mapping using this new functional MRI design. For each stimulus modality, we generated maps and calculated the lateralization of the activations. **Results:** The patterns encoding task was associated with the most right-lateralized MTL activity, whereas word encoding was the most left-lateralized. **Conclusions:** We found that it is possible to achieve a strong lateralization in several brain regions for different stimulus modalities that follow the overall pattern found in our previous blocked-design studies. The mapping in this case was concordant with the structural imaging and electrophysiological findings.

Key words: brain mapping, memory encoding, fMRI, epilepsy surgery.

RESUMO

A ressonância funcional da memória para o planejamento da cirurgia da epilepsia do lobo temporal mesial: relato de caso

Introdução: A avaliação functional de lateralização de memória pode ter impacto no planejamento da cirurgia da epilepsia do lobo temporal mesial (LTM). A ressonância funcional (RMf) pode prover um método não invasivo para ajudar a determinar a dominância de memória. O mapeamento de memória baseado por RMf, no entanto, ainda não é simples e determinar lateralização pode ser difícil por uma série de razões. Uma questão importante se refere à influência do tipo de material na ativação do LTM. **Objetivos:** melhorar a avaliação pré-operatória de memória utilizando um paradigma de RMf tipo "event-related". Esta abordagem foi elaborada para levar em consideração a memorização bem sucedida e o tipo de material. **Metodologia:** Nós descrevemos o caso de um paciente com epilepsia do LTM que sofreu um mapeamento de memória utilizando este novo paradigma de RMf. Para cada modalidade de estímulo, nós geramos mapas e calculamos a lateralização das ativações. **Resultados:** A tarefa de memorização de padrões foi associada com a atividade de LTM mais lateralizada para a direita, enquanto que a memorização de palavras lateralizou mais para a esquerda. **Conclusões:** Nós encontramos que é possível obter uma forte lateralização em diversas regiões cerebrais para difrentes modalidades de estímulo que segue aproximadamente o mesmo padrão encontrado em nossos estudos, em bloco, prévios. O mapeamento, neste caso, foi concordante com a imagem estrutural e com os achados eletrofisiológicos.

Unitermos: mapeamento cerebral, memorização, ressonância funcional, cirurgia da epilepsia.

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Received Dec 10, 2004; accepted Jan 10, 2005.

INTRODUCTION

Memory is likely one of the most complex cognitive functions. Rather than a single depository from where we obtain the information we need in our daily lives, it is a very dynamic process that constantly incorporates new data, selects and retrieves the specific information needed for a certain moment, deletes unnecessary information, and subserves other more explicit brain functions. One, for instance, needs memory to speak in order to retrieve what must be said (contents of speech), and to select the best words and grammatical structure to transmit that information. One also needs memory to ride a bike (he or she needs to *remember* how to ride a bike every time it does it). Also, there are aspects of memory that cannot be consciously controlled. For example, one can consciously try to encode new information, learn a new skill, or remember a past event, but the process of consolidation and forgetting of these information is greatly unconscious.

There are basically two types of memory: *declarative* (or *explicit*) and *procedural* (or *implicit*) (Izquierdo, 2002). Declarative memories can be volitionally retrieved and verbally transmitted (or "declared"). Procedural memories, on the other hand, are made up of information the brain uses to execute tasks (like riding a bike). The declarative memories can be split up into *episodic* and *semantic* memories (Portuguez, 1998; Cummings et al., 2003). Episodic memories are related to facts and events that occurred in a specific point in the past. Semantic memories represent knowledge acquired through life and generally does not include when or where it was obtained. Episodic memory might contain, for example, information about your last trip do Athens (if you're lucky), but it is semantic memory that retains the information that Athens is the capital of Greece.

Episodic memory is likely the most fragile, and can be affected by several medical conditions. It also is the most prone to impairment after medial temporal lobe (MTL) resection, as this region has been demonstrated to be critical in the acquisition of new declarative memories (Scoville, 1957). Therefore, memory evaluation prior to surgery is an important part of the surgical planning, and is aimed at determining to what extent each hippocampus is involved with memory encoding. Currently, the gold standard technique for the evaluation of memory lateralization is the intracarotid amytal (IAT or Wada) test. The Wada test consists of intracarotid administration of amytal, a barbiturate drug that causes transient anesthesia of the hemisphere of interest. This procedure, however, is invasive and not without risks, and it is difficult to repeat for confirmation of findings. Additionally, the short duration of anesthesia is often not enough for an adequate neuropsychological evaluation, which can also be affected by behavioral effects of the drug. And in the specific case of memory evaluation (the Wada test is also used for language lateralization), another important drawback is the sparing of the posterior two thirds of the hippocampus, which is supplied mostly by the posterior circulation of the brain. It is understood that the memory disruption that occurs during the Wada test is the result of disconnection of the hippocampus from the afferent inputs. Although there is the possibility of selectively injecting the posterior cerebral artery (Jack et al., 1989), it carries even a greater risk for the patient (Rausch, 1993).

Perhaps, as epilepsy surgery gets more precise and demands more detailed information, one of the main drawbacks of the Wada test is the fact that it has poor spatial resolution precluding memory localization and at best can only assess memory lateralization. More recently, functional magnetic resonance imaging (fMRI) has been used as a research tool to map cerebral areas involved with both encoding and retrieval stages of memory. At first, these fMRI studies assessed encoding lateralization of just one material type (Tulving et al., 1994; Nyberg et al., 1996). But subsequent studies started to address the impact of material type and material verbalizability (i.e., how much the material is encoded in a verbal or descriptive way) (Kelley et al., 1998; Wagner et al., 1998; McDermott et al., 1999; Golby et al., 2001).

We have previously shown that fMRI is a valid tool for assessing memory lateralization in patients with MTL epilepsy (Golby et al., 2002). In that study, subjects performed a block design. Blocks with novel pictures were alternated with blocks containing the same two pictures repeated throughout the run. A total of four runs were performed for each subject, each containing a single stimulus category (words, faces, scenes, and patterns). Mappings were produced with the contrast "novel > repeat", which showed areas that were more activated during the novel blocks than during the repeat blocks. In eight of nine subjects, lateralization of MTL activations by fMRI was concordant with that obtained from the Wada test. Moreover, group-level analysis demonstrated greater activation in the MTL contralateral to the seizure focus such that in the left MTL group, verbal encoding engaged the right MTL, whereas in the right MTL epilepsy group, nonverbal encoding engaged the left MTL.

Here, we describe the findings from a similar procedure in a single patient. This time, however, we used an event-related paradigm with 5 stimulus categories.

METHODOLOGY

Subject

We scanned a 40 year-old, male, with bilateral temporal lobe epilepsy, no hippocampal atrophy, scalp EEG with no lateralization for epileptogenic activity, and intracranial EEG with seizures coming from left MTL. His Wada test did not provide any clear lateralization. Seizures had started two years earlier, and has been presenting up to two partial complex seizures a day, despite concomitant use of correct doses of three antiepileptic drugs.

Functional paradigm

The patient underwent 5 encoding runs, one for each modality. The modalities were Snodgrass pictures, scenes, patterns, faces, and words, presented in this order (which were randomly generated). Stimuli were presented visually using a magnet-compatible goggle system (Resonance Technology, Inc., Chicago, IL) for 2000 m, with an inter-stimulus interval ranging randomly from 1000 to 1500 m. During each run, 44 novel and 44 instances of two familiar (repeated) stimuli were presented. The presentation order of the 88 stimuli within each run was also randomized. Stimulus display parameters and response collection was controlled by a custom-developed python program running on the Linux operating system; of which the code was based on the Python Experimental Psychology Library (Computational Memory Lab, University of Pennsylvania).

Task

For each delivered stimulus, the patient performed a two-choice decision task (encoding runs), depending upon the subcategory in each modality. For words, subcategories were concrete (e.g., "house") and abstract (e.g., "friendship"); for faces, male and female; for scenes, outdoor and indoor, and for Snodgrass pictures, living things (e.g., animal, vegetable, plant, fruit, or part of the body), and non-living objects (e.g., candle, bed, bag). Faces were color photographs extracted from the Color Feret Facial Image Database (National Institute of Standards and Technology, USA). Scenes were obtained from a Corel database (Corel, Ottawa, Canada), and patterns were collected from the Internet.

Recognition memory was tested for each stimulus type in five additional runs consisting of previously presented stimuli or foils. (Although recognition runs were scanned, imaging data are not discussed here.) For each image, the patient was instructed to distinguish between pictures he recognized as previously presented stimuli, and those that were novel stimuli. Recognition runs were performed immediately after each encoding run.

Image acquisition

Subject was scanned using a 3.0T GE Signa MRI system. Whole-brain functional imaging was performed using a single-interleave gradient echo pulse sequence, with 29 contiguous axial slices at 2000 ms per image volume. There were no gaps in between volumes. A T2 weighted 29-slice volume was also acquired in the exact same orientation as the functional images. Matrices were 512 × 512 for the T2 and 64 × 64 for the functional images. Before pre-processing, functional data were coregistered to the T2 volume for optimal anatomical overlaying in the analysis software. A volumetric T1 weighted MPRAGE (Magnetization Prepared RApid Gradient Echo) acquisition was also acquired for posterior overlaying with the functional activations (matrix = 256 × 256).

Data analysis

Stimulus onset vectors for novel, repeated, remembered and forgotten stimuli were generated for event-related analysis. Following image reconstructions, motion correction was performed using the SPM2 (Statistical Parametric Mapping) software package (Wellcome Department of Imaging Neuroscience, London, U.K.). Both smoothed (Full-Width Half-Maximum set to 8) and unsmoothed images were independently processed. Smoothed images improve the signal-to-noise ratio, producing clearer activations; whereas unsmoothed images have better spatial resolution, and can detect smaller activations, but can be compromised by false-positive findings. SPM2 was also used to process the statistical General Linear Model (GLM). Slice timing was not performed as a TR of 2000 m can be considered short enough to avoid loss of signal due to temporal misalignment of slices within a volume. Time and dispersion derivatives were applied to the hemodynamic response function. Since the initial presentations of the two repeated stimuli worked as novel images, we applied an exponentially decaying covariate to account for the novel effect of the three first instances of each repeated stimulus.

Constrasts

In order to examine the effect of novelty, we used contrasts that compared novel and repeated stimuli. To assess the effect of the posterior recognition of the encoded stimuli, we also used contrasts that involved either forgotten or remembered stimuli. The following contrasts were applied in our analysis: "remembered >> repeated", "remembered >> forgotten", "novel >> repeated", and "forgotten >> repeated".

RESULTS

Behavior

The most remembered modality was Snodgrass pictures (42 out of 44). The patient remembered 32 of the 44 words, 29 scenes, 28 patterns, and 26 faces.

Words

The word encoding task, when examined with the "remembered >> repeated" contrast produced a strong activation in Broca area (Fig. 1), with a strong overall lateralization to the left, including pre-motor areas (Fig. 2).

The left temporal angular gyrus and temporal superior sulcus, corresponding to Wernicke area, were also activated (Fig. 2). Fig. 1 also depicts left lateralized occipito-parietal activation. For "Novel >> Repeated" (which could also be expressed as "remembered + forgotten – repeated"), these same areas were activated, and others as well, including the left collateral sulcus, the right temporal pole, and the inferior temporal sulcus (Fig. 3). The right middle temporal gyrus was also activated, but to a much lesser extent as compared to the left. "Remembered >> Forgotten" interestingly produced a much weaker activation in Broca area, with no Wernicke activation, but a strong occipitoparietal activation, suggesting that this region might be intimately related to the successful encoding of verbal information (compare Fig. 4 to Fig. 1). Moreover, the map for "forgotten >> repeated" (Fig. 5) produced a discrete, but contra-lateral activation in this region.

Although we could not find any hippocampal activations for words, the left collateral activation might be an indicator of left hippocampal involvement. The strong left activation on language suggests that this memory paradigm may be an alternative way to perform language memory and could actually replace standard

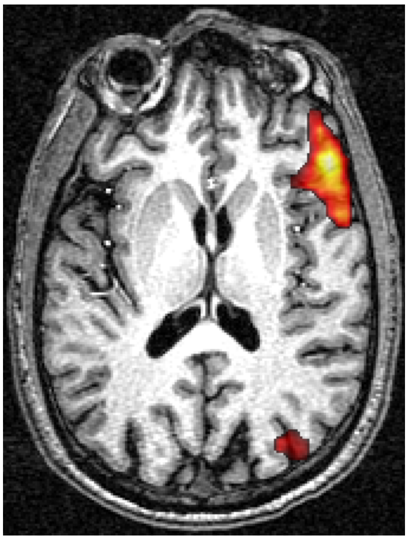

Figure 1. Activation in Broca area for contrast "remembered >> repeated" during memorization of words (from smoothed functional images).

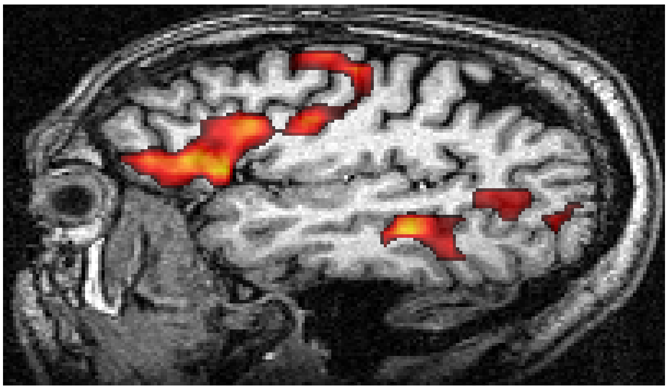

Figure 2. Activation in Broca and Wernicke areas for contrast "remembered >> repeated" during memorization of words (from smoothed functional images).

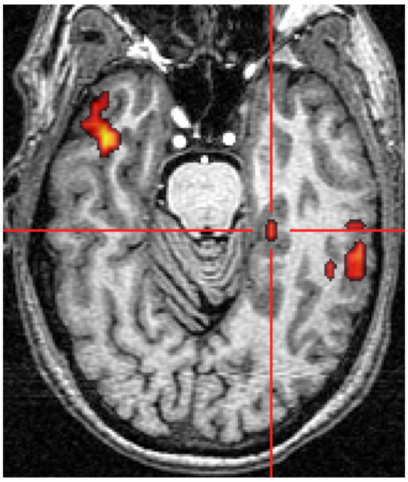

Figure 3. Activation in left collateral sulcus (bars) and right temporal lobe for contrast "novel >> repeated" during memorization of words (from smoothed functional images).

Figure 4. Activation in left occipito-parietal area persisted for "remembered >> forgotten" whereas the activation in Broca area was almost completely gone during memorization of words (from smoothed functional images of word encoding).

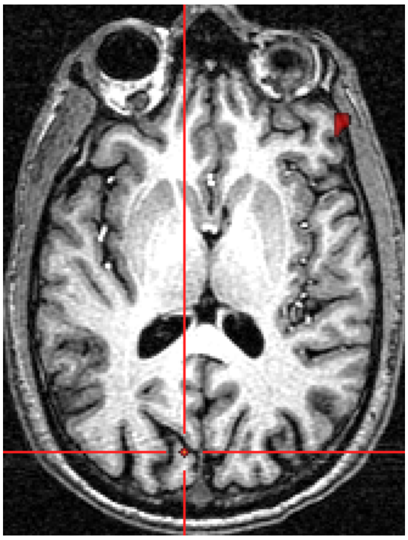

Figure 5. Right activation in right occipito-parietal area for "forgotten >> repeated" during memorization of words (from smoothed functional images of word encoding).

language mapping for a combined, shorter, language/ memory task. The exact function of the superior occipital (cuneus) and intraparietal sulcus is not yet exactly understood, but its activation has been found in previous blocked-design fMRI studies (Wagner, 1998), where it was consistent with remembered but not forgotten stimuli.

Scenes

For scenes, "remembered >> forgotten" strongly activated the right superior frontal gyrus (SFG), but also Broca region (and its right counterpart), Wernicke area, the cingulate gyrus bilaterally (but mostly on the left), and the left collateral sulcus. It is important to note, however, that the activations in language areas were much weaker when compared to the word encoding task. With a "remembered >> repeated" contrast, activations were concentrated on the collateral gyrus, but strongly lateralized to the right. Right occipital activation was also present, as were activations on the left cingulate gyrus and right parietal lobe. The same results occurred with "novel >> repeated", but for this contrast the cingulate activation was absent and there was a new right inferior frontal gyrus (IFG) activation. "Forgotten >> repeated" activated primarily a right frontal and right parietal area. The frontal area, as in "remembered >> forgotten", was in the SFG, but more anteriorly. The parietal area, if compared to "remembered >> repeated", was located more superiorly.

The findings for scenes suggest that successful encoding was related to a verbal strategy used by the patient, as we only found Broca and Wernicke activations using the "remembered >> forgotten" contrast. On the other hand, "remembered >> repeated" strongly involved the right middle temporal lobe (bilateral collateral sulcus activation lateralized to the right), suggesting that a visuospatial strategy was also used. We previously demonstrated that both scenes and faces do not lateralize substantially (Golby, 2001 and 2002); a dual strategy for scenes may be the reason for the bilateral findings. The left cingulate gyrus appears to be also strongly related with successful encoding, since it is present for both "remembered >> forgotten" and "remembered >> repeated". The right parietal lobe was involved with both successful and unsuccessful encoding.

Snodgrass pictures

For Snodgrass pictures, contrasts that incorporated forgotten stimuli did not produce very useful information as the "forgotten" pictures were well remembered, and the vectors contained only two data points. "Remembered >> repeated", however, produced very clear bilateral hippocampal activation, with lateralization to the right (Fig. 6). This contrast also produced bilateral activations of the collateral and lateral occipitotemporal sulci, with lateralization to the left. As with scenes, there also was a right occipital activation, but stronger than with scenes. Left occipital (cuneal) and right parietal activations were also present, and in Broca area as well.

Again as with scenes, Snodgrass pictures (which one can easily name) involved bilateral regions, but it is likely that a dual encoding had been performed by the patient. Right parietal lobe and right occipital activations are also consistent with scenes. And anterior middle temporal lobe activations lateralized to the right, whereas posterior middle temporal lobe activations prevailed on the left.

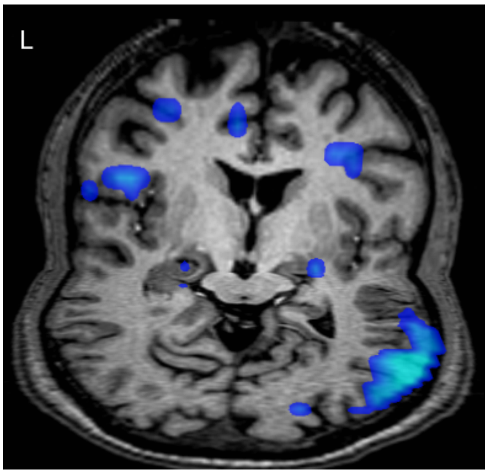

Figure 6. 3-D posterior view. Bilateral hippocampal activation for Snodgrass pictures encoding, but lateralized to the right (at the intersection of the axial and the coronal slices), using a "remember >> repeated" contrast (from smoothed functional images). Also note the strong right occipital activation.

Faces

Activations related to "remembered >> forgotten" were present in the right parietal lobe and left SFG (whereas scenes activated the right SFG). IFGs were activated bilaterally. For "remembered >> repeated", the very same part of the left SFG was activated, the parietal activation was absent, and the IFG was present only on the left (Broca). For "novel >> repeated", the bilateral angular gyri were activated. And for "forgotten >> repeated", a bilateral medial parietal activation was present.

For faces, successful encoding was strongly related with right SFG activations, and right parietal and the IFG also appeared to be implicated as well.

Patterns

Finally, "remembered >> forgotten" for patterns produced strong activation on the right IFG, and a weak activation in the right occipital lobe. "Remembered >> repeated" produced bilateral activation on the collateral sulci, with lateralization to the right (Fig. 7), and a strong occipital activation. Right parietal regions, again, were strongly activated. As for "novel >> repeated" activations were more restricted to right occipital lobe and right collateral sulcus. "Forgotten >> repeated" was basically confined to the right collateral sulcus.

Successful encoding for patterns was related to the right IFG, whereas both successful and unsuccessful encoding were related to the right collateral sulcus.

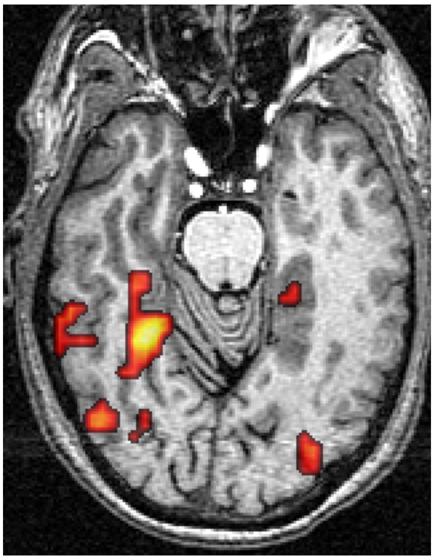

Figure 7. Strong lateralization on the collateral sulcus during encoding of patterns using a "remembered >> repeated" contrast (from smoothed functional images).

DISCUSSION

Although the lateralization of medial temporal lobe activations has been previously demonstrated for most stimulus modalities we used in this work, the physiological relevance of parietal, frontal and even occipital lateralizations is still not clear. In this patient, we did not observe a substantial amount of anterior hippocampal activation. We believe this may be related to signal artifacts that obscure the anterior tip of the medial temporal lobe. An echo-planar spiral sequence has been recently used in our lab with normal subjects, and we have obtained better results in terms of anterior hippocampal activation. Nevertheless, because this is a difficult region to acquire, we believe that future efforts should be directed at finding positive correlations between the anterior middle temporal lobe activations and activations of other brain regions, so one could rely on other specific findings for surgical planning, even if the anterior hippocampi are not visualized.

Additionally, we also believe that an event-related paradigm that allows the calculation of different complementary contrasts can produce a more detailed evaluation of the brain regions involved in memory encoding. Several more patients and normal subjects should undergo the experiment we described here for a better understanding of how memory areas are connected and which discrete locations in the brain are activated by each contrast.

As for this specific case, a gross comparison of the patient's findings with other normal subjects scanned in our lab, using the same methodology, suggests that his overall pattern of activations across the several modalities follows the same pattern we have been finding in healthy individuals. Although the fMRI results were not very useful for his surgical planning, they were consistent with the structural image and electroencephalographic findings.

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