# IDENTIFICATION AND CHARACTERIZATION OF ETIOLOGY, MECHANISMS OF DAMAGE, NEURONAL DYSFUNCTION, AND MOLECULAR DEFECTS IN MESIAL TEMPORAL LOBE EPILEPSY AND ITS RELATIONSHIP WITH RESPONSE TO TREATMENT

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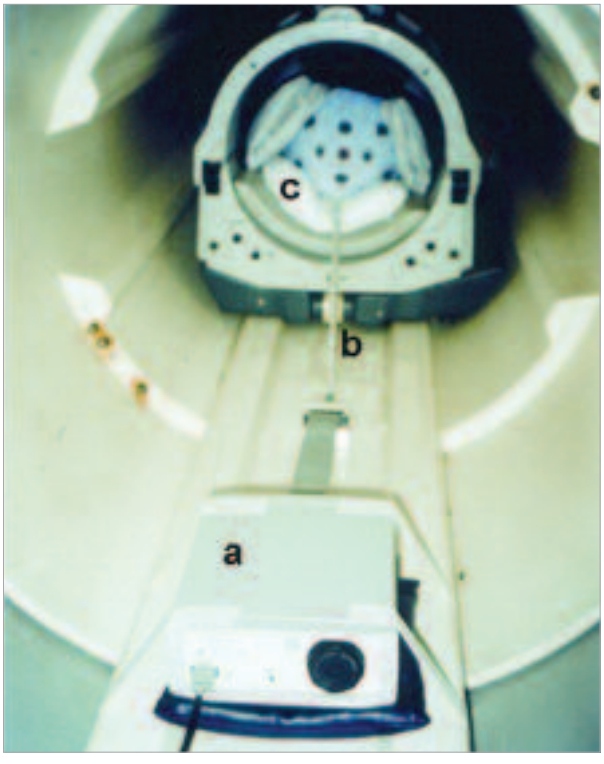
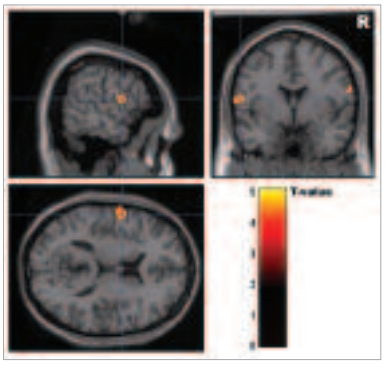



*(a) fMRI Amplifier; (b) EEG electrodes and (c) BOLD*

Epilepsy affects approximately 1-2% of the population and partial epilepsies with complex partial seizures account for approximately 40% of all epilepsies in adults. The most frequent form of partial epilepsy in adults is temporal lobe epilepsy (TLE). Classical histopathological studies and, more recently, different high-resolution neuroimaging modalities identify hippocampal atrophy and other signs of hippocampal sclerosis (HS) as the most prominent pathological substrate in patients with intractable mesial temporal lobe epilepsy (MTLE). Our aim is to perform a longitudinal study in a series of patients with MTLE and other forms of partial epilepsies. We will evaluate and quantify structural and functional brain abnormalities, by using different modalities of magnetic resonance (MR) imaging, and investigate the relationship between these abnormalities and the genetic substrate by using molecular genetic techniques. Specifically, we propose (a) to continue the development of MR techniques for evaluating TLE, including the use of functional MRI with simultaneous EEG recording (EEG-fMRI), (b) to study the relationship between the degree of hippocampal damage determined by MR techniques and anti-epileptic drug (AED) resistance in patients with MTLE, (c) to investigate factors related to prognosis for seizure control in patients submitted to surgical treatment for AED resistant MTLE; (d) to identify and characterize molecular genetic defects in patients with MTLE. We believe that this study will help to better understand the underlying pathogenic mechanisms in MTLE and other forms of partial epilepsies, and consequently, this may allow for a better diagnosis and treatment for these patients.

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

One of the main achievements of the project was the construction of a database of normal controls including over 200 MRI scans of individuals of different ages. This database was used for comparison in prospective studies addressing the recovery of neuronal function accessed by different modalities of MR imaging and fMRI after epilepsy surgery. In addition, we have developed a number of tools for brain imaging segmentation that address specific biologic questions and problems such as description of structures based on different 'signatures' that can be defined by the user (i.e. shape and texture). These analyses are made based on the definition of patterns of asymmetry of each signature and the subsequent comparison between left and right brain hemispheres. These are based on forest-imaging techniques and implemented in a tool named BIA – Brain Image Analyzer. In the fMRI project we were able to establish relationships between patterns of activation in the brain and (i) the epileptogenic activity seen on the EEG of patients and (ii) the structural lesions detected by the different modalities of MRI. One of the major challenges of the project is the simultaneous acquisition of the fMRI signal and EEG recording which was successfully achieved by our group. The genetic studies of families with TLE lead us to conclude that a major locus segregating in an autosomal dominant pattern was involved in the predisposition to the disease. However, the same study also pointed out that minor effect genes are also modifying this effect, and are probably responsible for the clinical variability and differences in severity of the disease seen among patients. A genome wide search using 450 DNA markers was subsequently conducted and identified a major locus for familial MTLE on chromosome 18p in a candidate interval spanning 13 cM.




*(c) BOLD response associated with EEG interictal activity in a patient with left temporal lobe epilepsy*

## MAIN PUBLICATIONS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