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Original article**Hippocampal intracerebral evoked potentials as a marker of its functionality in drug-resistant epilepsy**

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Short running title: MTL-P300 amplitude as a measure of hippocampal functionality

MTL-P300 amplitude as a measure of hippocampal functionality

Abstract

Objectives: To assess hippocampal function during stereoelectroencephalography (SEEG) investigations through the study of the medial temporal lobe event-related potential (ERP) MTL-P300.

Methods: We recorded the MTL-P300 during a visual oddball task, using hippocampal electrodes implanted for SEEG in 71 patients, in a preoperative epilepsy investigation. The presence of an MTL-P300 and its amplitude were correlated with hippocampal involvement during seizures and memory function.

Results: Analysis using ROC curves revealed that an MTL-P300 amplitude below $-46 \mu\text{V}$, has a specificity of 93.3% in detecting the epileptogenic zone, and absence of the MTL-P300 in the left hippocampus of patients with typical language organization was associated with marked alteration of verbal memory scores. There was a significant correlation between performance in non-verbal memory tests and the amplitude of the MTL-P300 in the right hippocampus of patients with left hemispheric seizures (immediate visual recall: $r=0.67$, $p=0.005$; delayed visual recall: $r=0.56$, $p=0.025$). Using a linear regression, we confirmed that the absence of the MTL-P300 in the left hippocampus, the involvement of the left hippocampus during seizures, and the duration of epilepsy were predictors of verbal memory deficits.

Conclusion: Analysis of the MTL-P300 during SEEG recording provides relevant information for the analysis of hippocampal functionality and can help to localize the epileptogenic zone.

Keywords: event-related potentials, iEEG, marker, MTL-P300, oddball, temporal lobe epilepsy

INTRODUCTION

Temporal Lobe Epilepsy (TLE) is the most frequent anatomical form of pharmaco-resistant epilepsy. Surgical treatment may be proposed after a pre-surgical assessment, which may include invasive recordings [19].

Invasive recordings are increasingly based on stereoelectroencephalography (SEEG), which consists of recording different brain regions through the implantation of depth electrodes [28]. In TLE, these recordings have revealed several types of anatomical epileptogenic zones (EZ) (mesial temporal, lateral, mesiolateral and perisylvian) whose size and location help to guide surgery [3]. However, surgery may induce a decline in memory function. This is reported in more than 30% of patients undergoing temporal lobe surgery [5], with a particular risk of verbal memory decline after left (dominant) hemisphere surgery.

Moreover, it is known that the outcome of epilepsy surgery is less favorable in the absence of a detectable MRI anomaly, such as hippocampal sclerosis, and may increase the risk of memory decline after surgery [16]. Event-Related Potentials (ERPs) such as the MTL-P300 have been proposed in order to evaluate the cognitive risk after surgery [16]. The P300 (P3b or classic P3) is elicited for visual, auditory and somatosensory stimulus modalities during the detection of task-relevant infrequent events (Oddball task). The amplitude of the MTL-P300 elicited by an unpredicted rare (target) stimulus is larger than for frequently occurring. This hippocampal component has been specifically named MTL-P300 to indicate the location where it is generated, in the medial temporal lobe [6, 11, 12, 23]. The MTL-P300 has been used for functional mapping of hippocampal regions to help to delimit the epileptogenic zone. It has been reported that a unilateral absence of hippocampal electrophysiological ERPs in intractable TLE is strongly correlated with the side of the seizure-onset zone [25, 27] and hippocampal sclerosis [14].

In this study we have analyzed hippocampal responses in the context of SEEG exploration. Firstly, we explored the amplitudes of neural responses to target stimuli and classified them as absent or present in relation to the response to frequent stimuli. This allowed us to assess whether the MTL-P300 is an accurate marker of the epileptogenic zone. Secondly, we studied to what extent the presence or absence of the MTL-P300 is related to memory function as assessed by a memory task.

METHODS

Ethics Statement

All subjects were fully informed about the aim of the investigation before giving consent. This study was approved in accordance with the Declaration of Helsinki by the Institutional Review Board of the French Institute of Health (IRB00003888).

Study design

We retrospectively studied 81 patients who had been evaluated between June 2010 and June 2020 in a preoperative epilepsy investigation at the Hôpital de la Timone (Marseille) for focal drug-resistant epilepsy. We selected patients investigated by SEEG, with at least one electrode implanted unilaterally or bilaterally in the anterior part of hippocampus (head and body), who underwent visual oddball tasks while waiting for the recording of spontaneous seizures.

The following exclusion criteria were applied: poorly positioned electrodes (5 patients); low signal-to-noise ratio (SNR) in the studied electrode (3 patients); and inadequate performance in the execution of the visual oddball task, having achieved a score below 40, on a scale of 0-50 (2 patients). The task has 50 targets. It is assumed that a patient who can remain focused well enough to perform the task will detect more than 40 targets. After applying these criteria, the final sample consisted of 71 patients. Out of this sample of 71 patients, we performed the analysis on 105 of 108 hippocampal recordings after removing the data of 3 hippocampi due to low SNR.

Patients were classified according to the presence of hippocampal sclerosis or another structural abnormality of the hippocampus. Hippocampal sclerosis was considered when the magnetic resonance imaging (MRI) showed (i) visual atrophy or loss of digitation of the head of the hippocampus and (ii) signal change in a T2-weighted sequence or 3D fluid-attenuated inversion-recovery sequences.

Fifty-seven patients underwent a neuropsychological exam. Age-appropriate Wechsler Intelligence Scales were used at baseline with follow-up assessments. Patients between 6 and 16 years old were assessed by the Wechsler Intelligence Scale for Children, Fourth Edition, WISC IV [30]. Patients older than 16, were assessed using the Wechsler Adult Intelligence Scale, Third Edition, WAIS-III [29] and the Wechsler Memory Scale- MEM III [31]. The various indexes of Wechsler Intelligence Scale and of Wechsler Memory Scale are age-corrected data. These standard scores have a mean of 100 and a SD of 15, in the normal population. MEM III was used to assess memory abilities with verbal and/or visual components. The pre and postoperative cognitive assessment included the Full-Scale IQ (FSIQ), Verbal Comprehension Index (VCI) and

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Perceptual Reasoning Index (PRI) and 4 verbal and visual (non-verbal) summary scores derived from the Wechsler Memory Scale-III: immediate verbal recall, immediate visual recall, verbal delayed recall and visual delayed recall. For each patient, hemispheric specialization of language functions was determined based on several clinical assessments. These included i) the correlation of language deficits during seizure and postictal periods, ii) functional mapping of the regions associated with language impairment using direct electrical stimulations, and iii) functional mapping of the regions producing gamma (>40Hz) activity during a picture naming task [10]. Additionally, functional MRI, handedness, neuropsychological data, and, if necessary, a Wada test were available to determine the hemispheric lateralization of language functions. Forty-eight patients had a typical left organization and 9 had atypical organization.

Stereoencephalogram (SEEG) recordings

The choice of electrode location was based on phase 1 noninvasive work-up and hypothesis about the EZ [18]. All patients had from 6 to 17 intracerebral electrodes implanted orthogonally to the brain midline. Each electrode had a diameter of 0.8 mm and was 33.5 to 51 mm long. The electrodes contained from 10 to 15 contacts, each 2 mm long and separated by 1.5 mm (Alcis, Besançon, France). Signals were recorded on a 128 or 256 channel BrainAmp system and sampled at 512 or 1024Hz. Verification of accurate electrode positioning was done by using coregistered images of computerized tomography scans with pre-operative MRI.

Epileptogenic Zone localization

Each patient had between 1 and 3 spontaneous seizures recorded by SEEG investigation. A correlation was made between semiology at the start of clinical signs and the neural networks implicated early and during the propagation phase of ictal activity in EEG recordings. The epileptogenicity index (EI) [19] was then used as a tool to delimit the distribution of areas participating in the EZ.

The EI combines an analysis of spectral and temporal parameters of intracranial EEG (iEEG) signals, taking into account fast discharges and the time for this area to generate and become involved in the seizure [2]. Each hippocampus was classified with respect to its role in the seizure network dynamics: (i) early participation, that is, being part of the epileptogenic zone (EZ); (ii) late participation, that is, being part of the propagation zone (PZ), and (iii) no participation in the seizures (NIZ).

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Visual Oddball Task

The MTL-P300 was elicited using a visual oddball task. In this task, two different abstract images, which are difficult to verbalize, are presented in a random series. A target image is presented between a series of nontarget images. Thus, patients are required to distinguish between the two stimuli by responding to the target (pressing a button while mentally counting the number of targets) and to refrain from responding to the other images. The visual oddball task consisted of 250 trials, the target stimulus was presented on 20% of the trials (50 trials), while the nontarget was presented on 80% (standard stimulus, 200 trials). The presentation software used for the oddball visual task was Eprime, which synchronizes the stimuli with the EEG signal. The images were presented to the patients before the beginning of the paradigm. They were instructed to fix the cross in the center of the monitor. At 2 s before the presentation of each stimulus item, a fixation character (x) was presented in the center of the video monitor. The duration of the presentation of each stimulus was 400 ms, and the interstimulus interval (ISI) varied between 1000 and 1600 ms.

The SEEG was recorded in a soundproof Faraday cage using a BrainAmp amplifier (Brain Products GmbH, Munich, Germany). SEEG signals were recorded at 1000 Hz, then filtered (bandpass 0.5-70 Hz, 12 dB/octave) and down sampled at 256Hz. An initial analysis of the results was done using BrainVision Analyzer® software (Brain Products GmbH, Munich, Germany). To obtain the evoked potentials, the continuous EEG was epoched using a 200-ms pre-stimulus interval and a 1200-ms post-stimulus interval. Baseline correction (zero-mean normalization of the pre-stimulus interval, -200-0 ms) was performed on separate epochs and contacts for each patient. EEG trials were visually inspected and epochs with artifacts and epileptic spikes were discarded. MTL-P300 was recorded from each hippocampus using a monopolar montage versus a reference extradural lead or a white matter lead selected for its relative electrical inactivity. Out of all contacts used for investigating the hippocampus, we chose the contact presenting maximum amplitude of the MTL-P300 within the hippocampus, for further analysis. The more medial contacts had maximal negative amplitudes and those outside the hippocampus showed less amplitude or inverted polarity (e.g., contacts 4, 5 and 6 in Fig. 1A).

The signal of the selected hippocampus contact was then processed using EEGLAB [7]. The signals were epoched, time-locked to the stimuli (-200; 1000ms). Epochs were separated for frequent and target stimuli and averaged to compute ERPs for each condition (frequent and target), hippocampal location and patient. Custom matlab scripts were used to detect the peak amplitude and latency of the MTL-P300 to target trials and to assess whether ERPs to target and to frequent trials differed or not

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(two-tail signed-rank, non-parametric testing). The peak amplitude and latency were determined using an automatic procedure (Matlab findpeak function) in the 300-600 ms range. Peak detection was also confirmed by visually exploring individual data (ERPs and peaks). The difference between the target and frequent trials was considered statistically significant when $p < 0.05$ (FDR corrected) at the time point corresponding to the MTL-P300 peak. The MTL-P300 was considered as absent when there was no statistically significant difference between the two curves (see Fig. 1D).

Statistical methodology

We used Pearson's bivariate chi-square test (χ^2) to compare the presence and absence of the MTL-P300 responses between hippocampi participating in the EZ or not (outside the EZ). In addition, we used a t-test on the amplitudes and latencies of MTL-P300 between the group of hippocampi in the EZ of the unilateral TLE and the group of hippocampi in the NIZ. The cut-off point between the amplitude in unilateral EZ and NIZ was calculated using the Youden's index in conjunction with the receiver operating characteristic curve (ROC). The index was defined for all points of an ROC curve, and the maximum value of the index was defined to select the optimal cut-off point providing a numerical result rather than a dichotomous one.

We evaluated the association between age and MTL-P300 amplitude, using Spearman's correlation. To explore the relationship between the hippocampal ERPs and memory performance, we also used a t-test. We compared verbal and non-verbal memory performance between the group of patients in which the left MTL-P300 was absent, in relation to the other patients (in which the right MTL-P300 was absent, or the right and left MTL-P300 were present). The same comparison was performed between the group of patients in which the right MTL-P300 was absent, compared to the other patients.

The Kolmogorov-Smirnov test was performed to verify data normality. To determine whether the amplitude of the left and right MTL-P300 were correlated with the results of verbal and non-verbal memory scores we used Spearman and Pearson's correlation, respectively. Then we analysed the correlations between cognitive performance, and the amplitudes of the MTL-P300 of hippocampi ipsilateral and contralateral to the EZ respectively.

Additionally, a linear regression model was developed to predict memory performance in the group of patients who had unilateral temporal or extratemporal epilepsy. We studied 4 outcome variables that are verbal and visual (non-verbal) summary scores of memory performance. The outcome variables studied through multivariate regressions were delayed verbal recall, immediate verbal recall, delayed

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visual recall, immediate visual recall. For the predictors of verbal (delayed verbal recall, immediate verbal recall) and non-verbal memory score (delayed visual recall, immediate visual recall), we used well-known variables such as intellectual level (FSIQ), the involvement of the hippocampus in the seizure (EZ and PZ) of patients with typical language organization on the left, and the duration of epilepsy. We also included the presence or absence of MTL-P300 in the model among the factors already known. We performed 8 linear regression models, 4 for each side: memory scores = $a \cdot \text{FISQ} + b \cdot \text{duration of epilepsy} + c \cdot \text{AbsentMTL-P300} + d \cdot \text{ZEZPsideTypical}$. For the left side: memory scores = $a \cdot \text{FISQ} + b \cdot \text{duration of epilepsy} + c \cdot \text{AbsentLMTL-P300} + d \cdot \text{ZEZPLsideTypical}$. For the right side: memory scores = $a \cdot \text{FISQ} + b \cdot \text{duration of epilepsy} + c \cdot \text{AbsentRMTL-P300} + d \cdot \text{ZEZPRsideTypical}$. The variable ZEZPLsideTypical corresponds to patients with typical language organization on the left with EZ or PZ on the left, and ZEZPRsideTypical corresponds to patients with typical language organization on the left and EZ or PZ on the right. In all tests, p values <0.05 were considered significant. The results of the application are presented below, as previously detailed. Statistical analysis was performed using the computational environment R-project v4.0.4.

RESULTS

The 71 patients studied were 33 men and 38 women with a mean age of 31.5 ± 12.5 years. In this study 57 patients (80.3%) of the population were adults over 19 years of age. We did not find an association between age and MTL-P300 amplitude in the left ($r = -0.218$, $p = 0.092$) or the right ($r = -0.137$, $p = 0.505$) hippocampus. Ten had hippocampal sclerosis, with the hippocampus in the epileptogenic zone. The other patients did not have any hippocampal lesions on MRI.

Thirty-seven (52.1%) patients were investigated by hippocampal electrodes inserted unilaterally and 34 (47.9%) bilaterally, with a total of 105 hippocampi in our sample (Supplementary Table 1). Of the 105 MTL-P300 responses obtained, 90.5% had negative polarity (Supplementary Table 2). Nine (12.7%) patients had bitemporal epilepsy, 13 (18.3%) extratemporal epilepsy and 49 (69.0%) unilateral temporal epilepsy. Of the patients with unilateral temporal seizures, 15 (30.6%) had TLE on the right and 34 (69.4%) on the left. Of the patients with extratemporal epilepsy, 6 (46.2%) had seizures on the right and 7 (53.8%) on the left.

We studied the MTL-P300 responses obtained in the hippocampus with the objective of correlating this response to hippocampal epileptogenicity and cognitive performance.

MTL P300 and Hippocampal involvement during seizure

Remembering that the MTL-P300 response was considered absent when there was no statistically significant difference between the target and frequent trials curves, absence of MTL-P300 was significantly associated with hippocampal involvement in the EZ ($p=0.001$). However, when the hippocampus was included in the EZ, absence of the MTL-P300 was observed only in 29/56 cases, and it remained present in 27/56 cases in the EZ (Table 1). Thus, in about 48% of cases, presence of the MTL-P300 did not exclude epileptogenicity of the hippocampus. The sensitivity was 52% and the specificity 80% for the absence of an MTL-P300 response in the identification of the EZ. The positive predictive value was 0.74 and the negative predictive value 0.59.

Analyzing the MTL-P300 response of hippocampi in the propagation zone (PZ) versus those not involved in seizures (NIZ), we found no significant difference ($p=0.145$). In the sample of 9 patients with bitemporal seizures, only one patient had MTL-P300 bilaterally absent. Of the 13 patients with extratemporal epilepsy, only 3 had an absent MTL-P300. Of the 49 patients with unilateral TLE, only 6 patients had an MTL-P300 absent in the propagation zone (PZ), showing that a low proportion of hippocampi in the PZ have an absent MTL-P300.

We separately evaluated the amplitude and the latencies of MTL-P300 in patients with unilateral TLE, a sample of 39 hippocampi. We found that when an MTL-P300 was recorded in the hippocampus in the EZ, the mean amplitude was significantly smaller - 57 μV (95% CI: -77.69; - 37.06) than in the 15 hippocampi in the NIZ -131 μV (95% CI - 171.4; - 90.6; $p= 0.001$). In addition, comparison of the average latencies of the MTL-P300 showed a statistically significant difference (t-test, $p=0.037$) between the EZ at 404 ms (95% CI: 378.93; 429.99) and the NIZ at 456 ms (95% CI: 410.83; 501.84). The maximum value of the index for selecting the optimum cut-off point between them was - 46 μV , with amplitudes above this normal value, for a specificity of 93.3% and sensitivity of 61.5%. If we aim for a higher sensitivity such as 71.8% and a slightly lower specificity than 73.3%, our cut-off rises to -86.6 μV (Supplementary Table 3.)

In this group of patients with unilateral temporal epilepsy, we found a significant association between absence of MTL-P300 and involvement of the hippocampus in the epileptogenic zone ($p=0.001$), with a sensitivity of 63.4% and specificity of 79.3%. Taking into account whether or not the hippocampus was involved in the seizure, the right and left hippocampi did not differ in terms of sensitivity to the task ($p=1$), showing that the proportion of absent MTL-P300 was equivalent in both hemispheres. In addition, we found the same association between absence of the MTL-P300 and involvement of the hippocampus in the EZ in the group of patients with structurally normal hippocampi on

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MRI (we excluded 8 patients with hippocampal sclerosis), with a specificity of 80% ($p=0.007$).

MTL-P300 and Memory function

Of the 71 patients, 57 underwent a neuropsychological examination. We analyzed the data of 51 of these patients that had unilateral temporal (42 patients) or extratemporal (9 patients) epilepsy. Six patients with bitemporal epilepsy were not included in this analysis.

Of these 51 patients, 43 patients had language organization in the left hemisphere and 8 had atypical representation. Patients were separated into those with right ($n=15$) and left ($n=36$) epileptogenic zones (Supplementary Table 4). The different variables that we tested (FSIQ, duration of epilepsy, verbal and non-verbal tests) did not show a significant difference between these 2 groups (Supplementary Table 5).

Correlation between left MTL-P300 amplitude and memory performance

We then analyzed the correlation between performance in the memory tests and the amplitudes of the left hippocampal MTL-P300 response.

Fig. 2A and 2B plot the amplitude values obtained between 300 and 600 ms for all left hippocampi ($n=40$), including values considered to be MTL-P300 absent represented in red dots ($n=21$). We observed a clear significant correlation between amplitude and performance in verbal memory (immediate verbal recall, $r=0.59$, $p<0.001$; and delayed verbal recall, $r=0.60$, $p<0.001$). In contrast there was no significant correlation between the amplitude of the left MTL-P300 and performance in non-verbal memory (immediate visual recall, $p=0.146$; and delayed visual recall, $p=0.228$). However, we did not find this correlation when we restricted the analysis to the presence of an MTL-P300, removing the absent MTL-P300 responses from the analysis (immediate verbal recall, $p=0.959$; and delayed verbal recall, $p=0.397$).

When we focused on analysis of left MTL-P300 amplitude in 36 patients who had seizures on the left, we found a significant correlation for tests of verbal memory (immediate verbal recall, $r=0.58$, $p=0.001$; and delayed verbal recall, $r=0.57$, $p=0.001$). We also found a significant correlation for a test of non-verbal memory (immediate visual recall, $p=0.026$), but no correlation for delayed visual recall ($p=0.075$). If we remove the amplitude of the absent MTL-P300 responses then the correlations do not hold: immediate verbal recall, $p=0.924$; delayed verbal recall, $p=0.123$, immediate verbal recall, $p=0.659$; and delayed verbal recall, $p=0.208$.

The amplitude of the MTL-P300 in patients who had seizures on the right could not be analyzed because of the small number of patients ($n=4$).

Correlation between right MTL-P300 amplitude and memory performance

If we consider all the amplitude values between 300 and 600 ms in right hippocampi, we do not see a significant correlation between amplitudes of responses and results in non-verbal and verbal memory tests. After removing the absent MTL-P300 responses from the analysis, there was a positive correlation between the right MTL P300 amplitude and immediate visual recall ($r= 0.47$, $p=0.022$, see Fig.3A). However, no correlation was seen for delayed visual recall. (Fig. 3B).

When we focused on the analysis of patients who had seizures on the right, excluding the absent MTL-P300 responses from the analysis, we did not find a significant correlation between amplitude and either immediate or delayed visual recall tests (Fig. 3C; 3D), or verbal memory tests (immediate or delayed verbal recall).

We analyzed the amplitude of the MTL-P300 response in the right hippocampi of patients who had seizures on the left, and we found a positive correlation with performance in the tests of immediate visual recall, $r=0.67$, $p=0.005$ and delayed visual recall, $r=0.56$, $p=0.025$. There was no significant correlation between the right MTL-P300 amplitudes and verbal memory tests (immediate verbal recall, $p=0.231$; and delayed verbal recall, $p=0.192$). There were no absent responses in this group.

Correlation between absent MTL P300 and memory performance

We studied the relationship between memory performance and the absence of MTL-P300. The comparison between the mean performance in verbal and non-verbal memory scores and the absence of the MTL-P300 response, showed a significantly worse verbal memory (delayed verbal recall, immediate verbal recall) in the absence of MTL-P300 in the left hippocampi of patients with typical language organization on the left (Fig. 4). Indeed, the mean performance in verbal memory scores among patients with no MTL-P300 left response versus the others was statistically significant for immediate verbal recall ($p<0.001$) and delayed verbal recall ($p<0.001$) (Fig. 4).

There was no significant correlation between absent left MTL-P300 and non-verbal performance (immediate visual recall: $p=0.155$, or delayed visual recall: $p=0.131$).

There was no significant correlation between mean performance in verbal and non-verbal memory scores and absence of the MTL-P300 response in the right hippocampi: immediate visual recall ($p=0.144$), delayed visual recall ($p=0.393$), immediate verbal recall ($p=0.826$), delayed verbal recall ($p=0.416$).

Predictors of Verbal and Non-verbal memory scores

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We performed linear regression to identify the factors independently associated with performance in verbal and non-verbal memory tests.

The Supplementary Fig. 1 presents the results for the first 4 models, 1 for each of the neuropsychological tests, concerning the implication of the left hippocampus during seizure. Predictive variables of immediate and delayed verbal recall were the absence of MTL-P300 in the left hippocampus, involvement of the left hippocampus during the seizure and longer duration of epilepsy (Supplementary Fig. 1A-1B). As expected, no effect was found on the performance of non-verbal tests (Supplementary Fig. 1C-1D).

Regarding the right hippocampus responses (Supplementary Fig. 2), performance on immediate verbal recall was predicted by FISQ (Supplementary Fig.2A), and delayed verbal recall was predicted by the duration of epilepsy and FISQ (Supplementary Fig. 2B). There were no predictive variables for immediate and delayed visual recall (Supplementary Fig. 2C-2D).

The evolution of memory scores after surgery, and according to the presence or absence of a P300 could only be evaluated in a limited number of cases (11 patients operated on by temporal lobectomy). Results for 11 patients of verbal and non-verbal memory performance before and after mesial temporal lobectomies are show in detail in Table 2.

DISCUSSION

The objective of this research was to analyze if MTL-P300 can be used as a neurophysiological marker of hippocampal functionality, both in terms of its involvement during seizures and in terms of impact on cognitive processes.

MTL-P300 is a high-amplitude potential, easily recognizable, and obtained through a simple paradigm (oddball). It is necessary to check the electrode placement, and to choose the best-positioned contact within the hippocampus, which records the highest responses. In addition to these precautions, to correctly measure the amplitude, it is necessary to be aware of the findings of Kukleta et al. [21]. They found the occurrence of identical ERPs to target and frequent stimuli, in 17% of identified ERPs. The identical and non-identical ERPs to target and frequent stimuli occurred frequently in the same patient and in the same structure.

We found that the absence of an MTL-P300 response has an 80% specificity in identifying the EZ. We observed that 27/56 hippocampi in the EZ (representing false negatives) have large MTL-P300 amplitude illustrating that large amplitudes can be found in hippocampi in the EZ. The same proportion was observed when evaluating only

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the sample of patients with TLE. To characterize this distribution better, we used a Roc curve to calculate the optimal cutoff point for discriminating the normal and abnormal MTL-P300. We observed that as the amplitude increases between the cut off values – 46 μ V and – 86.6 μ V there is a decrease in specificity, ranging from 93.3% to 73.3%.

Our results confirm the fact that the absence of an MTL-P300 is a neurophysiological marker of the EZ for patients with hippocampal sclerosis [25, 27, 12, 24, 26], but also for patients without structural changes in the hippocampus. Grunwald et al. [14] analyzed 84 patients, of which 29 did not have hippocampal sclerosis, and found MTL-P300 amplitudes only significantly reduced on the epileptogenic side in the group of patients with hippocampal sclerosis. However, we found in our study an association between absence of an MTL-P300 and epileptogenicity of the hippocampus (part of the EZ) in the group of 41 patients without hippocampal sclerosis. Our results showed that the absence of MTL-P300 has a high specificity and can be an additional tool for the localization of the epileptogenic zone, even in the absence of hippocampal sclerosis.

In contrast, MTL-P300 did not prove to be a useful marker to analyze the hippocampus contralateral to the EZ. In the group of patients with bitemporal epilepsy, only one had bilaterally absent MTL-P300, showing the ineffectiveness of this method to investigate the less compromised hippocampus. Likewise, in unilateral and extratemporal temporal epilepsies, absence of the MTL-P300 did not prove to be a good marker to assess the propagation zone in the hippocampus.

The low sample size of cases with bilateral absence of MTL-P300 did not allow us to analyze whether the left or right EZ leads to a greater risk of compromise of the contralateral hippocampus. There was no predominance of the absence of MTL-P300 in one of the cerebral hemispheres. In fact, it is likely that both hemispheres show this degree of dysfunction when the EZ is found in the hippocampus, whether in a specialized region for language or not.

In reference to the second question, as to whether MTL P300 is a predictor for cognitive function, we observed that absence of the MTL-P300 in the left hippocampus influenced the preoperative performance in immediate and delayed verbal recall tests and therefore could reflect its functionality. The effect of this variable as a predictor of worse verbal performance was maintained when evaluated in conjunction with other variables already studied in the literature, such as the duration of epilepsy and the presence of the EZ on the left [4, 22].

Verbal scores are considered sensitive to dominant hemisphere dysfunction [22] and we were able to confirm this finding with our results. However, data for lateralization of non-verbal memory in the right hemisphere is not as confirmatory, and the pattern of

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memory change after resection of the right temporal lobe was even less clear. However, a tendency for non-verbal scores to be more sensitive to disturbances in the nondominant (right) hemisphere has been observed.

To find out whether there is a relationship between hippocampal potentials and preoperative performance, memory task scores were correlated with MTL-P300 amplitude values from the left and right hippocampi. We observed a positive correlation between the amplitude of the left MTL-P300 and preoperative verbal memory performance. The correlation between the right MTL-P300 amplitude and performance in a non-verbal task was only evident when there were seizures on the left. Perhaps bilateral hippocampal dysfunction is necessary for non-verbal memory loss, or the visual memory is not as lateralized as verbal memory, and can be more easily compensated for by the functional hippocampus. This result is in line with the link established between the occurrence of spikes in the human hippocampus contralateral to the seizure onset zone and performance in a short-term memory task [20].

We found no significant correlation between performance in non-verbal memory tests and absence of the MTL-P300 response in the right hippocampus, or between the amplitudes of responses in the 33 right hippocampi and non-verbal test performances when there is no seizure in the contralateral (left) hippocampus. Helmstaedter et al. [17], suggests that a well-preserved verbal memory capacity helps to overcome visual learning deficits until the degree of information exceeds its capacity.

The absence of an MTL-P300 in the right hippocampus could not be used to predict preoperative verbal and non-verbal performance. Doss et al. [9] observed a worsening of non-verbal versus verbal scores after a right temporal lobectomy. However, there are no studies demonstrating correlations between ERPs on the right and postoperative non-verbal performance. Our postoperative results did not allow us to correlate the MTL-P300 responses on the right with visual performance. This fact may be due to a greater complexity of the organization of the non-verbal memory system. Nevertheless, the MTL-P300 alone is probably not a good predictive marker of postoperative performance in this case.

Our small sample did not allow us to observe a clear relationship between the presence/absence of the MTL-P300 and a decrease in postoperative verbal performance. Grunwald et al [14] found no correlation between the right and left MTL-P300 and performance of postoperative verbal memory. In this perspective, the AMTL-N400 could be more interesting. Indeed, Grunwald et al. [13] found that the AMTL-N400 amplitude of the right hippocampus after left-sided hippocampectomy, predicted the postoperative verbal recall performance. Few teams have investigated ERPs through iEEG. Some of them have studied the AMTL-N400 and hP600 responses through

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cognitive paradigms [8]. The oddball paradigm is not a verbal memory task with encoding and retrieval, but previous studies suggest that it requires hippocampal function to identify novel events and compare these with previous experiences.

In conclusion, the MTL-P300 is an easily recognizable electrophysiological marker. We found that the MTL-P300 reflects the functional state of the hippocampus, and correlates with memory scores. It would be interesting in the future to combine different markers of the function of temporo-mesial structures such as the hP600 [1] and the AMTL-N400 [8, 15]. In particular, there is no data on correlation of hippocampal verbal memory ERP hP600 and memory performance. This perspective is important because the use of SEEG is increasing and new techniques targeting temporo-mesial structures such as laser interstitial thermal therapy (LITT) will be increasingly used [32].

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Conflict of interest

All authors declare that they have no conflicts of interest.

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Tables

Table 1: Comparison between MTL-P300 responses and hippocampus participation in the epileptic zone and outside the EZ

MTL-P300	EZ		PZ +NIZ		Total	p-value (χ^2)
	n	%	n	%		
Absent	29	51.8	10	20.4	39	0.001*
Present	27	48.2	39	79.6	66	
Total	56	100	49	100	105	

Table note. * $p < 0.05$ for Pearson chi-square test (χ^2). Abbreviations: EZ: epileptogenic zone, PZ: propagation zone, NIZ: not involved in seizures.

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Table 2: Performance results of 11 patients on verbal and non-verbal memory tests before and after mesial temporal lobectomies

Patients	Language	Surgery side	MTL-P300	MTL-P300 Right Absent	MTL-P300 Left Absent	Immediate	Immediate	Delayed	Delayed	Outcome	
						verbal recall	visual recall	verbal recall	visual recall		
						Pre/Post (S)	Pre/Post (S)	Pre/Post (S)	Pre/Post (S)		
P1	Typical	Left	Absent	Absent	Absent	82/89 (7)	94/103 (9)	76/79 (3)	82/100 (18)	Seizure free	
P2	Typical	Left	Absent	NA	Absent	86/76 (-10)	-/115(NA)	84/79 (-5)	-/115 (NA)	Seizure free	
P3	Typical	Left	Absent	Present	Absent	89/94 (5)	82/91 (9)	96/93 (-3)	103/85 (-18)	Seizure free	
P4	Typical	Left	Absent	NA	Absent	82/71 (-11)	85/- (NA)	79/74 (-5)	78/- (NA)	Not seizure free	
P5	Typical	Left	Present	NA	Present	136/132 (-4)	106/129 (23)	110/119 (9)	106/127 (21)	Seizure free	
P6	Typical	Left	Present	NA	Present	94/89 (-5)	103/112 (9)	96/91 (-5)	103/103 (0)	Seizure free	
P7	Typical	Right	Present	Present	Present	140/140 (0)	129/120 (-9)	123/127 (4)	127/118 (-9)	Seizure free	
P8	Atypical	Right	Absent	Absent	Present	105/105 (0)	112/112 (0)	98/119 (21)	100/109 (9)	Seizure free	
P9	Typical	Right	Absent	Absent	Absent	94/86 (-8)	145/88 (-57)	91/82 (-9)	136/91(-45)	Seizure free	
P10	Typical	Right	Present	Present	NA	94/99 (-5)	106/100 (-6)	91/119 (28)	106/100 (-6)	Seizure free	
P11	Typical	Right	Present	Present	NA	102/114 (12)	94/118 (24)	110/110 (0)	91/115 (24)	Seizure free	

Table Note. (P): Patient S: subtraction between performance on post-less preoperative tests; NA: not applicable.

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Figure legends

Figure 1: Electrode position and ERP responses

(A) The blue dot represents the third contact starting from the midline, which presents maximum ERP amplitude.

(B) Patient (n 46); Example of Hippocampal response of a patient, recorded on both sides. Right panel: Left hippocampus involved during seizure in the EZ. The amplitude of the target stimuli response ($-74.17 \mu\text{V}$) is smaller than the contralateral one (Left panel), but a statistically significant difference persists between standard and target stimuli responses ($p < 0.001$).

(B') Left panel: Right hippocampus not involved during seizure. Example of a normal MTL-P300 in the NIZ, with a higher amplitude of target stimuli response (red curves, amplitude: $-333.63 \mu\text{V}$) compared to frequent stimuli response (standard, blue curves), $p < 0.001$.

(C) Patient (n 70); Example of a normal MTL-P300 in the right hippocampus involved in the PZ, with an amplitude of target stimuli responses of $-248.21 \mu\text{V}$ ($p < 0.001$).

(D) Patient (n 47); Example of absence of the MTL-P300 response in the right hippocampus involved in the PZ. No difference was observed between target stimuli response (red curves, amplitude: $-11,67 \mu\text{V}$) and frequent stimuli response ($p = 0.200$).
Abbreviations: ERP: Event-Related Potential, NIZ: does not participate in the seizures, EZ: epileptogenic zone, PZ: propagation zone; ms: millisecond, μV : microvolt.

Figure 2: Correlation between the left MTL-P300 amplitude and the verbal memory performance

(A & B) All left hippocampal responses.

(A) Spearman's correlation between the left MTL-P300 amplitudes and immediate verbal recall.

(B) and correlation between the left MTL-P300 amplitudes and delayed verbal recall.

Figure 3: Correlation between right MTL-P300 amplitude and the non-verbal memory performance removing the absent MTL-P300 responses

(A & B) Right MTL-P300 responses.

(A) The amplitude of the MTL-P300 responses of the right hippocampi, showing a significant correlation to immediate visual recall.

(B) No significant correlation is observed between the right MTL-P300 amplitudes and delayed visual recall score.

(C & D) Responses of the right hippocampus of patients with right seizures

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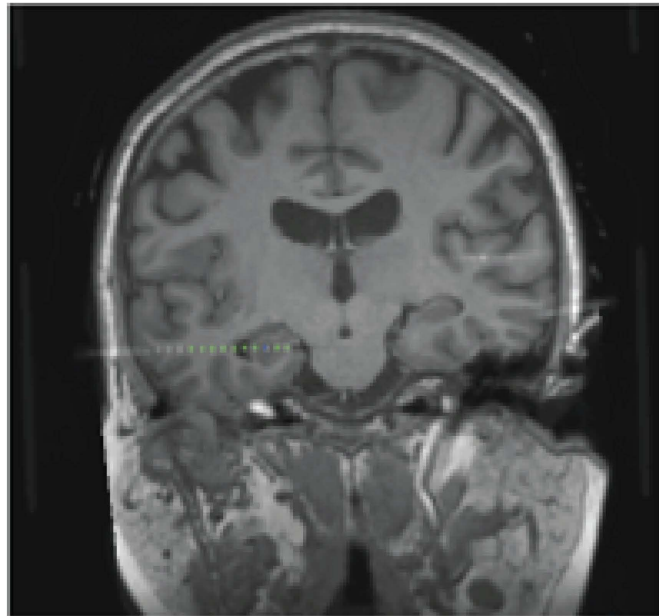
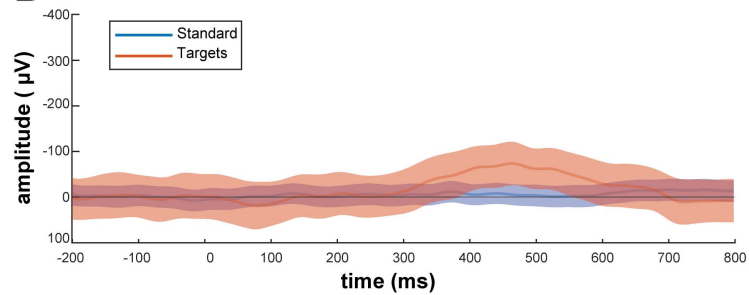
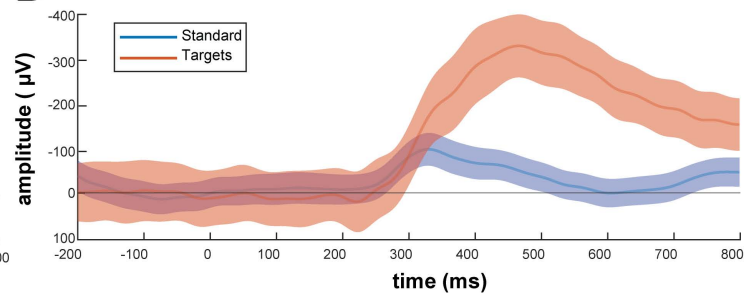
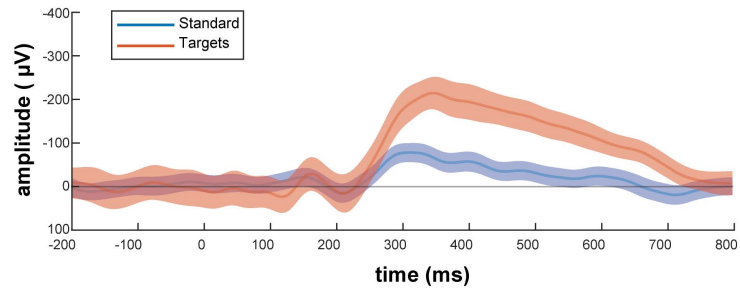
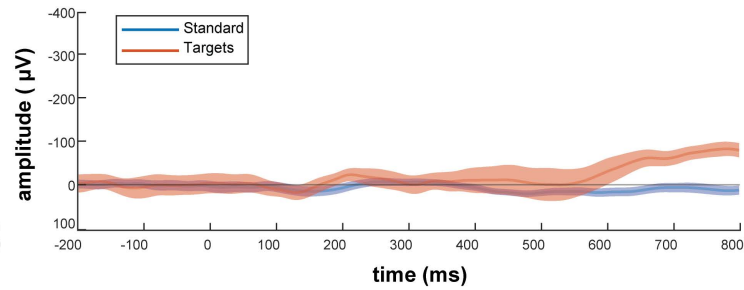
The amplitude of the right MTL-P300 response in patients who had seizures on the right showed no significant correlation with their performance in the non-verbal tests.

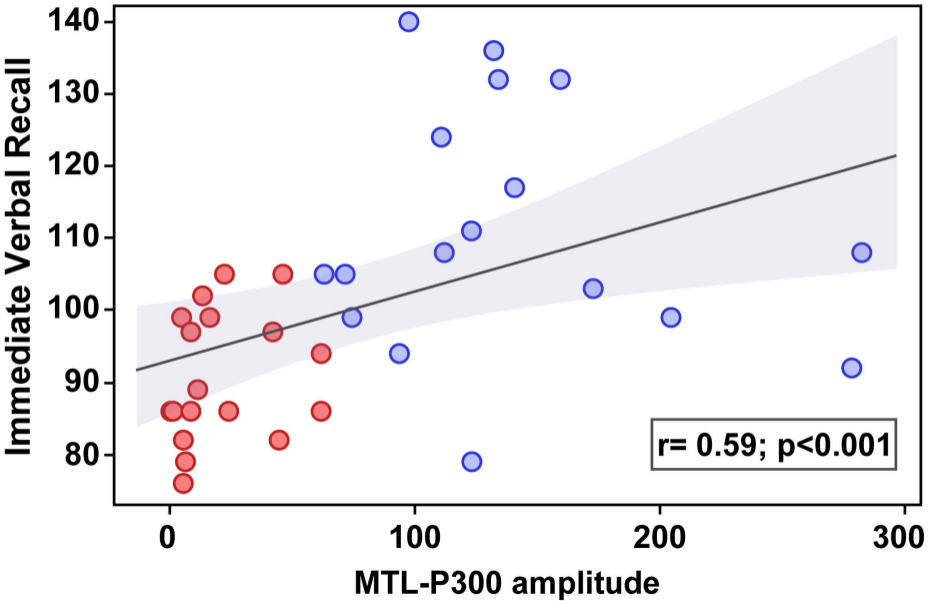
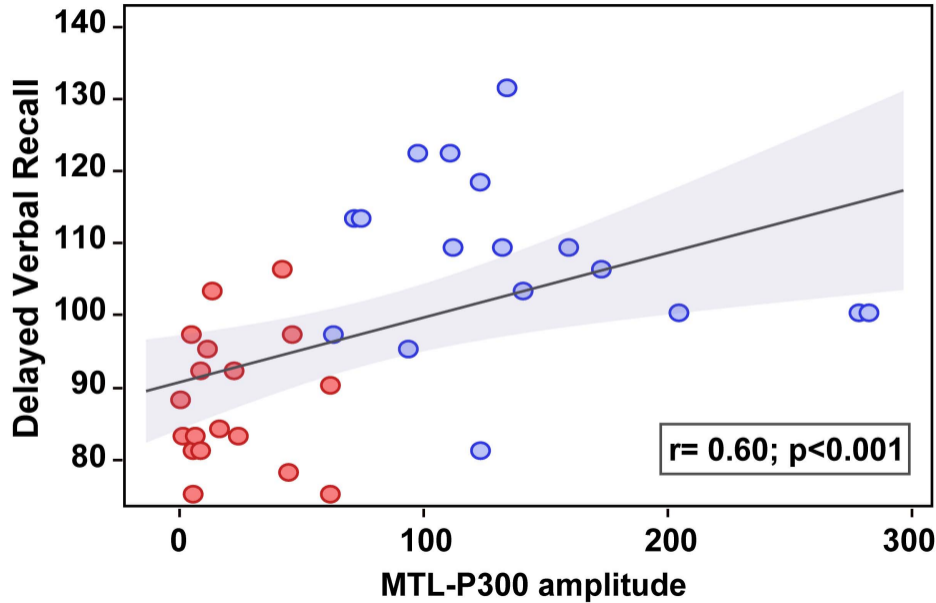
Figure 4: Comparison between absent left MTL-P300 responses and all other responses

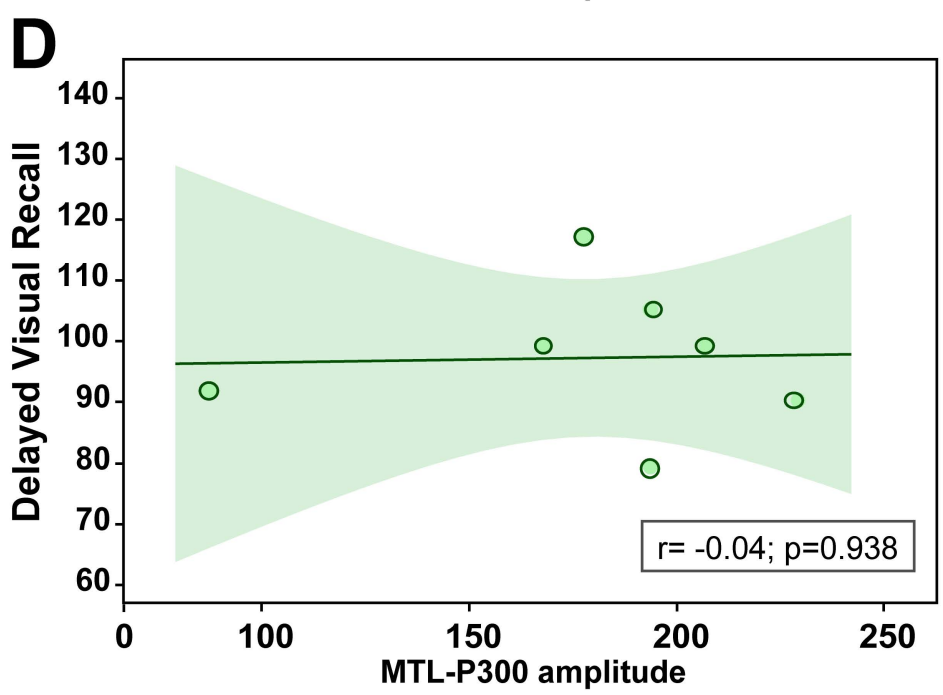
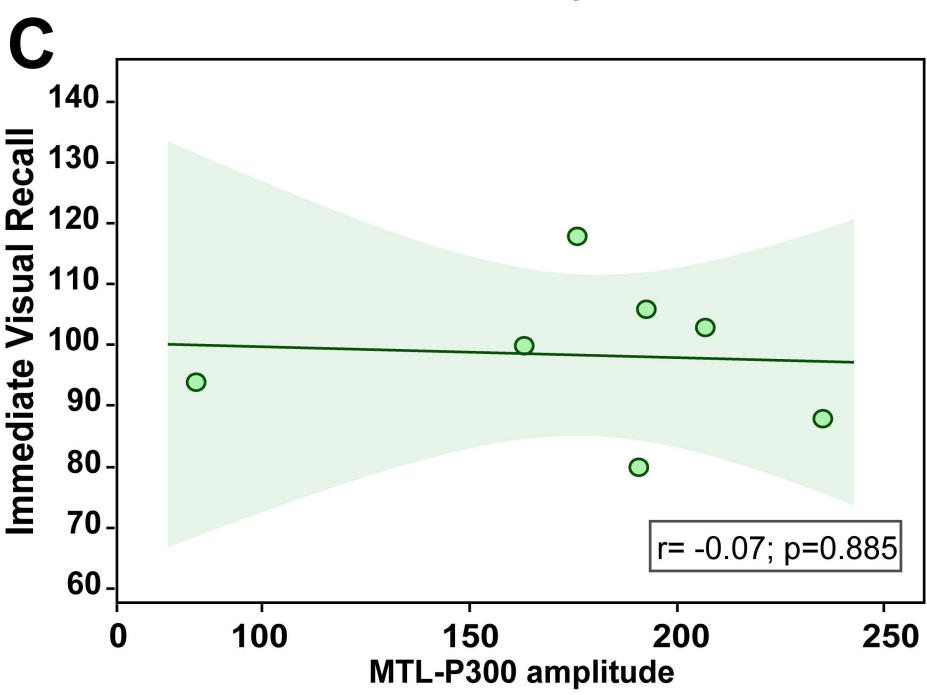
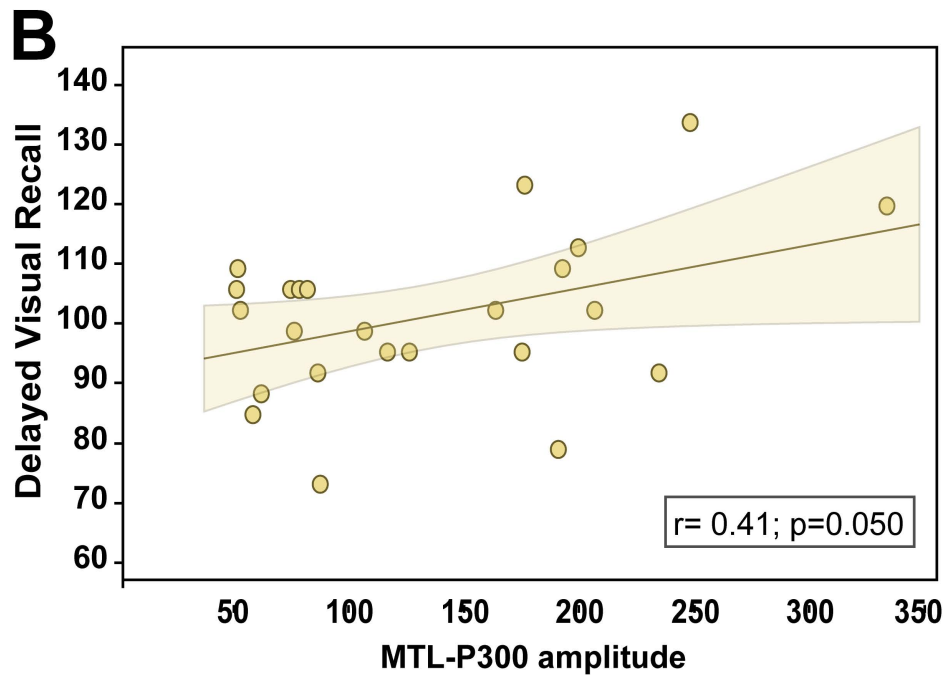
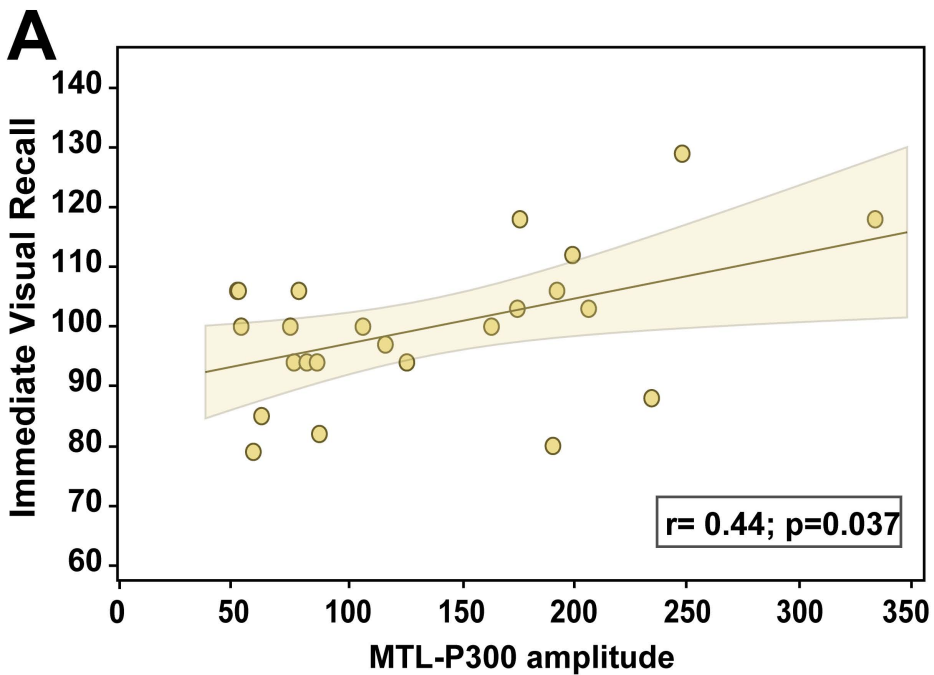
(A) Boxplots of immediate verbal recall score, according to the presence or absence of MTL P300 in the left hippocampus. The patients with an absent left MTL-P300 showing a worse performance in the immediate verbal recall test than other patients ($p < 0.001$).

(B) Boxplots of delayed verbal recall score according to the presence or absence of MTL P300 in the left hippocampus. The patients with an absent left MTL-P300 showing a worse performance in the delayed verbal recall test than other patients ($p < 0.001$).

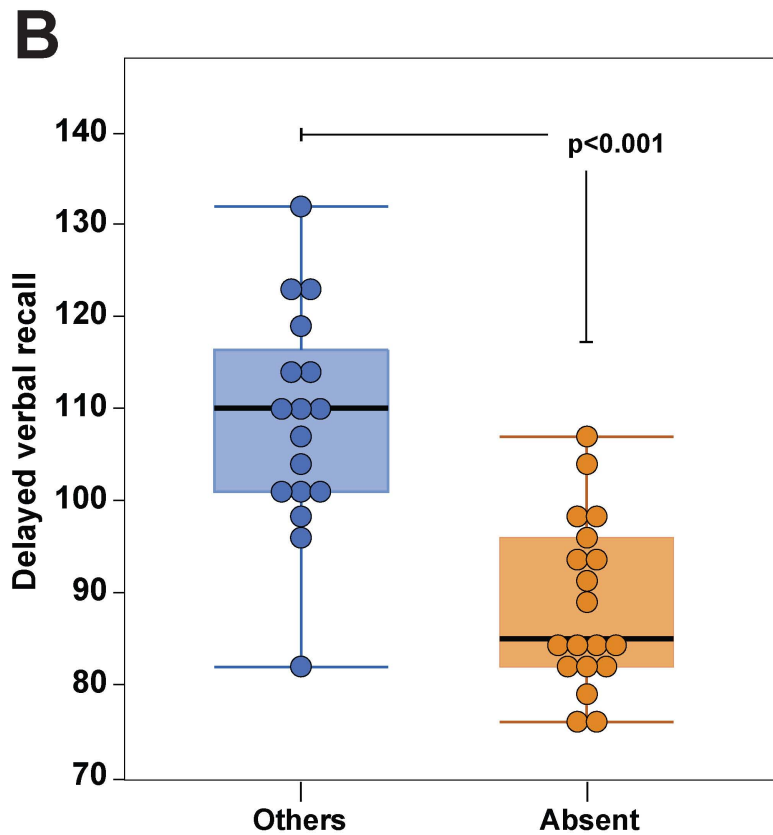
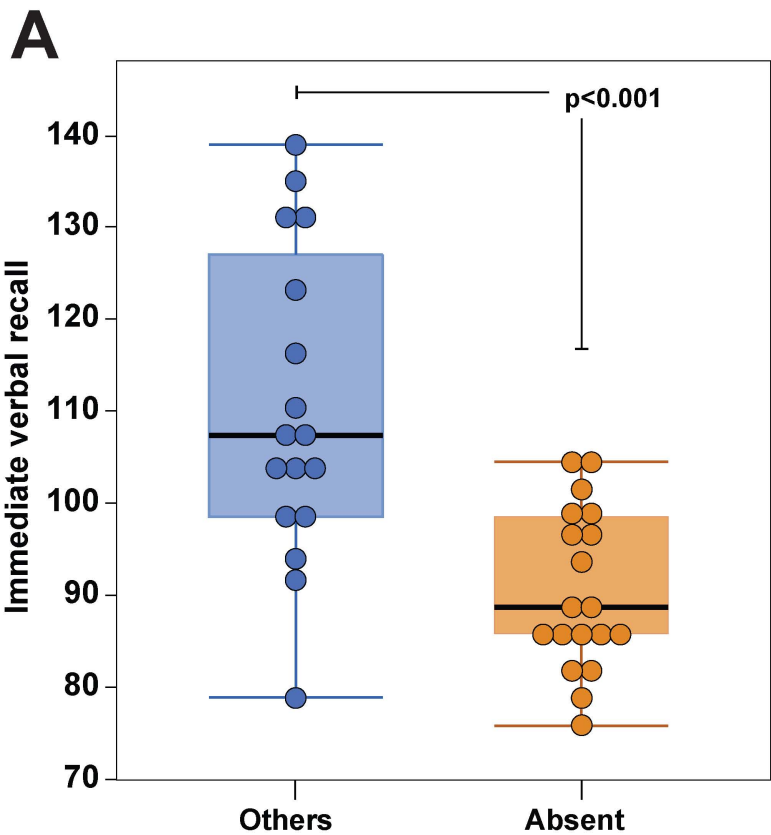
Others: present responses of the right and left MTL-P300, and an absent right MTL-P300.

A**B'****B****C****D**

A**B**



Left MTL-P300 absent



Supplementar Material

Supplementary Table 1

Supplementary Table 2

Supplementary Table 3

Supplementary Table 4

Supplementary Table 5

Supplementary Figure 1 R

Supplementary Figure 2 R

Supplementary Table 1: Frequency distribution of patients by SEEG investigation and EZ classification

Epileptogenic network	Patients (n)	%	Unilaterally	Bilaterally	Hippocampal responses			Total hippocampus
			ERPs	ERPs	EZ	PZ	NIZ	
Unilateral temporal	49	69	28	21	39	24	7	70
Bitemporal	9	12.7	1	8	17	0	0	17
Extratemporal	13	18.3	8	5	0	10	8	18
Total	71	100	37	34	56	49	15	105

Table note.

Abbreviations: SEEG: stereoelectroencephalography, ERPs: Event-Related Potentials, EZ: epileptogenic zone, PZ: propagation zone, NIZ: not participate in the seizures

Supplementary Table 2: 105 MTL-P300 responses obtained from 71 patients

Number of patients	TLE	Seizure Side	Left Hp	Left MTL-P300 p< 0.05	Left MTL-P300 Amplitude (μV)	Left MTL-P300 Latence (ms)	Right Hp	Right MTL-P300 p< 0.05	Right MTL-P300 Amplitude(μV)	Right MTL-P300 Latence (ms)
1	Unilateral	Left	epileptogenic zone	Absent	-36.22	345	no participation in the seizures	Present	-177.66	466
2	Unilateral	Left	epileptogenic zone	Absent	-5.34	431	propagation zone	Present	-87.63	437
3	Unilateral	Left	epileptogenic zone	Present	-90.99	324	propagation zone	Present	-110.22	310
4	Unilateral	Left	epileptogenic zone	Present	93.5	433	Not apply	Not apply	Not apply	Not apply
5	Unilateral	Left	epileptogenic zone	Absent	6.24	432	propagation zone	Present	-76.37	415
6	Unilateral	Left	epileptogenic zone	Absent	-11.31	319	Not apply	Not apply	Not apply	Not apply
7	Unilateral	Right	no participation in the seizures	Present	-62.81	415	epileptogenic zone	Absent	-2.48	579
8	Unilateral	Right	propagation zone	Absent	23.89	375	epileptogenic zone	Present	-206.84	430
9	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Present	-86.6	346
10	Unilateral	Left	epileptogenic zone	Present	-133.91	412	propagation zone	Present	-51.31	316
11	Unilateral	Left	propagation zone	Absent	-8.44	304	no participation in the seizures	Present	-106.89	484
12	Unilateral	Left	epileptogenic zone	Present	-159.16	494	Not apply	Not apply	Not apply	Not apply
13	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Present	-169.46	501
14	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Absent	-10.61	327
15	Unilateral	Left	epileptogenic zone	Absent	-13.21	334	Not apply	Not apply	Not apply	Not apply
16	Unilateral	Left	propagation zone	Not apply	Not apply	Not apply	propagation zone	Present	-62.03	447
17	Unilateral	Left	epileptogenic zone	Present	-132	449	Not apply	Not apply	Not apply	Not apply
18	Unilateral	Left	epileptogenic zone	Absent	-41.88	408	no participation in the seizures	Present	-116.84	543
19	Unilateral	Left	epileptogenic zone	Absent	-11.25	407	propagation zone	Present	58.4	554
20	Unilateral	right	Not apply	Not apply	Not apply	Not apply	propagation zone	Present	-234.74	395
21	Unilateral	Left	epileptogenic zone	Absent	-56.51	454	Not apply	Not apply	Not apply	Not apply

22	Unilateral	Right	propagation zone	Absent	-61.56	517	epileptogenic zone	Absent	-11.13	323
23	Unilateral	right	propagation zone	Present	-110.6	444	Not apply	Not apply	Not apply	Not apply
24	Unilateral	Left	no participation in the seizures	Absent	5.89	349	no participation in the seizures	Present	-53	369
25	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Absent	-27.35	375
26	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Present	-192.77	532
27	Unilateral	Left	propagation zone	Absent	-25.46	426	Not apply	Not apply	Not apply	Not apply
28	Unilateral	Left	epileptogenic zone	Absent	5.38	416	propagation zone	Absent	-0.53	501
29	Unilateral	Left	epileptogenic zone	Absent	1.2	353	Not apply	Not apply	Not apply	Not apply
30	Unilateral	Left	epileptogenic zone	Absent	-45.96	376	Not apply	Not apply	Not apply	Not apply
31	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Absent	-20.51	310
32	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	epileptogenic zone	Absent	-12.26	336
33	Unilateral	Left	epileptogenic zone	Absent	-0.23	318	Not apply	Not apply	Not apply	Not apply
34	Unilateral	Left	epileptogenic zone	Absent	-8.43	382	propagation zone	Present	-78.54	476
35	Unilateral	Left	epileptogenic zone	Absent	0.88	500	Not apply	Not apply	Not apply	Not apply
36	Unilateral	Left	epileptogenic zone	Absent	-22.15	315	no participation in the seizures	Present	-199.67	430
37	Unilateral	Left	epileptogenic zone	Present	-111.8	325	propagation zone	Present	-51.85	344
38	Unilateral	Right	Not apply	Not apply	Not apply	Not apply	propagation zone	Present	-116.16	417
39	Unilateral	Left	epileptogenic zone	Absent	-2.53	371	Not apply	Not apply	Not apply	Not apply
40	Unilateral	Left	epileptogenic zone	Unilateral	-16.16	562	Not apply	Not apply	Not apply	Not apply
41	Unilateral	Right	epileptogenic zone	Present	-6.56	356	epileptogenic zone	Absent	-6.56	356
42	Unilateral	Left	epileptogenic zone	Present	-71.38	424	propagation zone	Present	-82.05	380
43	Unilateral	Left	epileptogenic zone	Absent	-44.45	295	Not apply	Not apply	Not apply	Not apply
44	Unilateral	Right	epileptogenic zone	Present	-418.24	428	epileptogenic zone	Present	-191.06	434
45	Unilateral	Left	propagation zone	Present	-140.5	394	Not apply	Not apply	Not apply	Not apply
46	Unilateral	Left	epileptogenic zone	Present	-74.17	465	no participation in the seizures	Present	-333.63	469
47	Extratemporal	Right	propagation zone	Present	-95.46	501	propagation zone	Absent	-11.67	443

48	Extratemporal	Left	no participation in the seizures	Present	-204.3	336	Not apply	Not apply	Not apply	Not apply
49	Bitemporal	Left	epileptogenic zone	Absent	-0.96	535	Not apply	Not apply	Not apply	Not apply
50	Extratemporal	Right	no participation in the seizures	Present	-90.34	423	no participation in the seizures	Present	-216.75	416
51	Extratemporal	Left	no participation in the seizures	Present	-123.06	554	no participation in the seizures	Present	-74.76	593
52	Extratemporal	Right	Not apply	Not apply	Not apply	Not apply	propagation zone	Present	-163.78	466
53	Bitemporal	NA	epileptogenic zone	Present	-72.85	352	epileptogenic zone	Present	-123.63	370
54	Extratemporal	Right	Not apply	Not apply	Not apply	Not apply	no participation in the seizures	Present	-128.07	410
55	Extratemporal	Left	no participation in the seizures	Present	-282.13	586	propagation zone	Present	-126.35	469
56	Extratemporal	Left	propagation zone	Present	-278.04	445	propagation zone	Present	-175.26	450
57	Extratemporal	Left	propagation zone	Present	-172.56	475	Not apply	Not apply	Not apply	Not apply
58	Bitemporal	NA	epileptogenic zone	Present	-261.33	466	epileptogenic zone	Present	-28.14	412
59	Bitemporal	NA	epileptogenic zone	Present	43.0	575	epileptogenic zone	Present	-206.64	430
60	Bitemporal	NA	epileptogenic zone	Absent	127	535	epileptogenic zone	Present	-53.67	414
61	Extratemporal	Right	Not apply	Not apply	Not apply	Not apply	propagation zone	Present	-176.44	432
62	Extratemporal	Right	Not apply	Not apply	Not apply	Not apply	propagation zone	Absent	-48.8	447
63	Extratemporal	Left	propagation zone	Absent	-4.66	553	Not apply	Not apply	Not apply	Not apply
64	Bitemporal	NA	epileptogenic zone	Absent	-5.1	306	epileptogenic zone	Absent	-35.96	306
65	Bitemporal	NA	epileptogenic zone	Present	-216.5	542	epileptogenic zone	Present	-132.06	410
66	Extratemporal	Left	no participation in the seizures	Present	-122.9	471	Not apply	Not apply	Not apply	Not apply
67	Bitemporal	NA	epileptogenic zone	Present	-257.43	465	epileptogenic zone	Present	-229.05	451
68	Unilateral	Left	propagation zone	Absent	-22.16	487	Not apply	Not apply	Not apply	Not apply
69	Bitemporal	NA	epileptogenic zone	Present	-113.88	402	epileptogenic zone	Present	-127.13	390
70	Unilateral	Left	propagation zone	Present	-97.36	344	propagation zone	Present	-248.21	345
71	Unilateral	Left	epileptogenic zone	Present	-103.96	581	Not apply	Not apply	Not apply	Not apply

Supplementary Table 3: The optimum cut-off point using the Youden's index in conjunction with ROC curve and a second cut-off on the ROC curve for greater sensitivity

Area under the ROC curve	95% CI	p-value	Cut-off *	Sensitivity (%)	Specificity (%)
0.79	0.65 to 0.89	<0.0001	-46 μ V	61.5	93.3
			-86.6 μ V	71.8	73.3

Table note. *Method Youden index; CI: Confidence Interval

Supplementary Table 4: Demographic characteristics in 51 patients with seizures (EZ + PZ) on the right and on the left

Participant's characteristic	Left	Right
n	36	15
Age (years)-mean \pm SD	30.25 \pm 12.69	34.08 \pm 10.33
Epilepsy duration (years)-mean \pm SD	13.17 \pm 10.96	13.55 \pm 10.14
Education (%)		
Primary and middle school	46.67	27.27
Secondary school	16.67	27.27
Postsecondary education	36.67	45.45
Sex male (%)	50.00	33.33
Language (% Left Typical)	83.33	86.67

Table note. Data in average \pm standard deviation

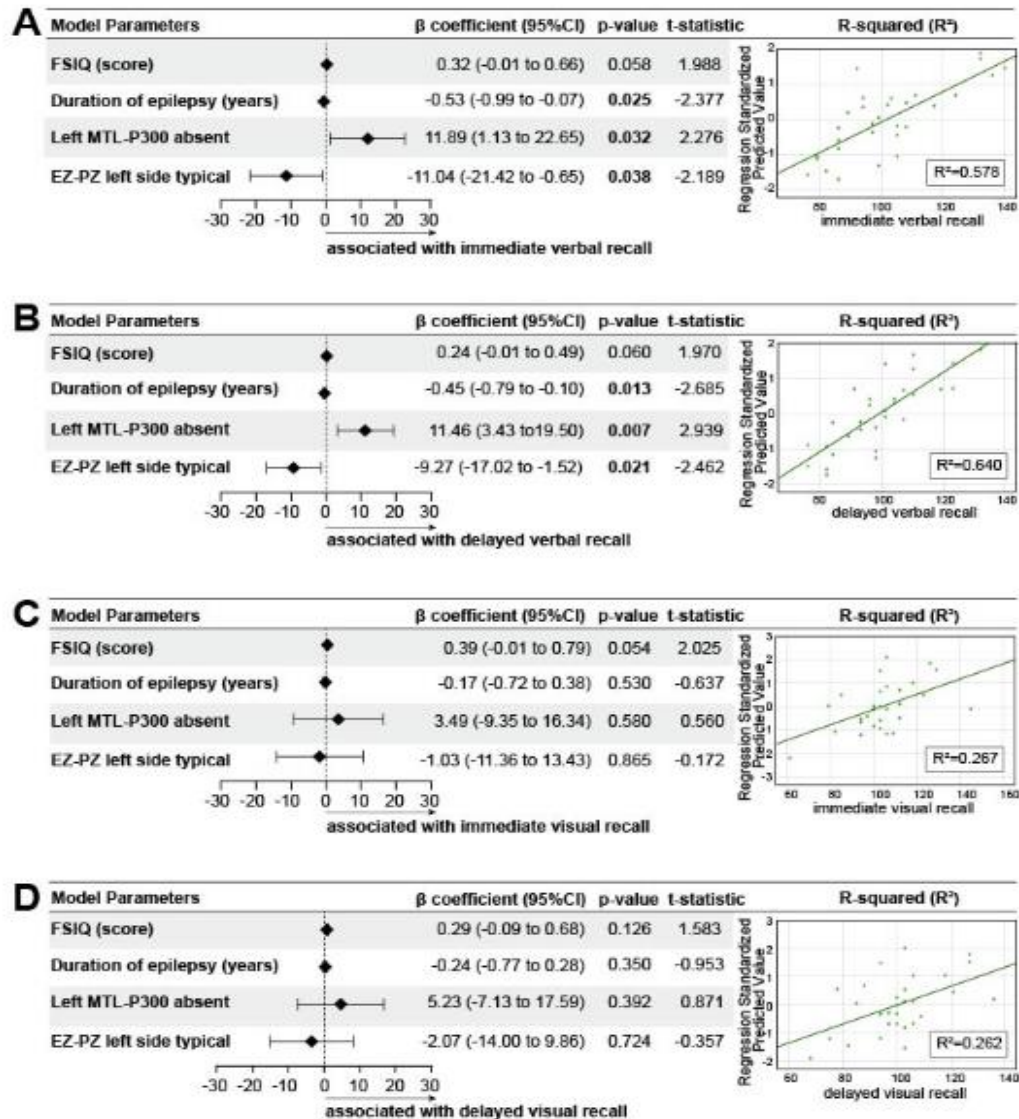
Supplementary Table 5: analysis of the means of the variables (FSIQ, duration of epilepsy in years, verbal and nonverbal tests) in the 51 patients with seizures (EZ + PZ) on the right and on the left.

Parameter	FSIQ	Duration of epilepsy	Immediate verbal recall	Delayed verbal recall	Immediate visual recall	Delayed visual recall
Left seizures	88 \pm 17	13 \pm 11	100 \pm 17	98 \pm 14	102 \pm 14	100 \pm 14
Right seizures	90 \pm 19	14 \pm 11	100 \pm 7	98 \pm 9	104 \pm 18	103 \pm 15

Table note. Data in average \pm standard deviation

Abbreviations: FSIQ: Full-Scale IQ

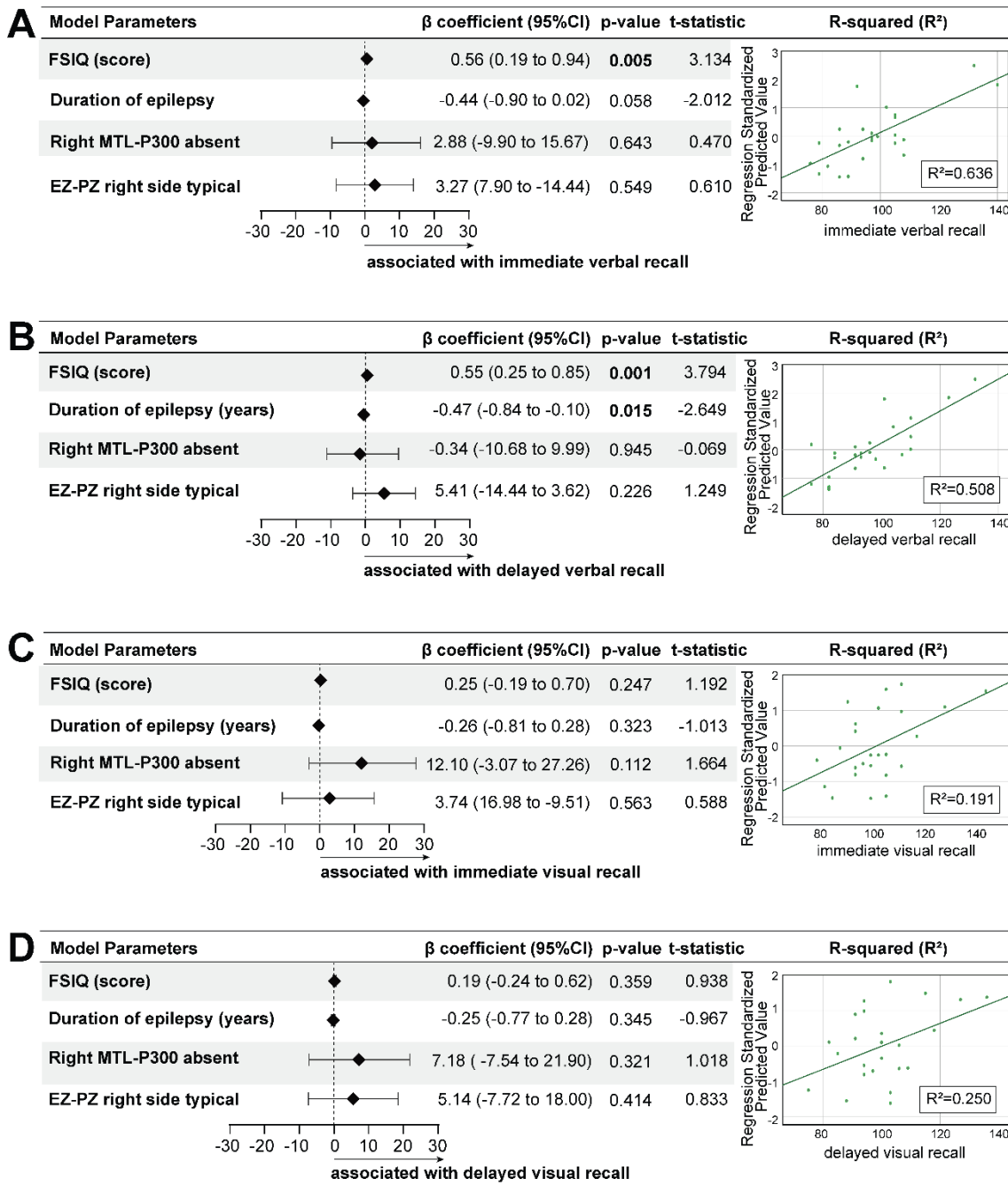
Figures



Supplementary Figure 1: The effect of left hippocampus seizures on verbal and non-verbal memory test performance.

Predictors of verbal memory **(A)** Immediate verbal recall and **(B)** Delayed verbal recall were: the absence of MTL-P300 in the left hippocampus; the involvement of the left hippocampus during the seizure; and being long term epilepsy patients. Predictors of visual memory **(C)** Immediate visual recall and **(D)** Delayed visual recall: no effect was found on the performance of non-verbal tests.

*EZ-PZ left side typical: patient with left epilepsy and typical language organization.



Supplementary Figure 2: Right Hippocampus and 4 models; VERBAL (A) Immediate verbal recall (B) Delayed verbal recall; VISUAL (C) Immediate visual and (D) Delayed visual recall.

Performance on immediate verbal recall was predicted by FISQ, $p=0.005$ (2A), and delayed verbal recall was predicted by the duration of epilepsy ($p=0.015$) and FISQ ($p=0.001$) (2B). There were no predictor variables for immediate and delayed visual recall (2C-2D).

