Original article

Epileptic Disord 2014; 16 (1): 67-73

Auditory event-related potentials (P300) and mesial temporal sclerosis in temporal lobe epilepsy patients

Artemios K. Artemiadis [1], Maria Fili [2], George Papadopoulos [2], Fotini Christidi [2], Stergios Gatzonis [3], Ioannis Zalonis [2], George Nikolaou [1], Nikolaos Triantafyllou [2]

[1] Department of Neurology, 417 Army Share Fund Hospital
[2] University of Athens, 1st Neurological Clinic
[3] University of Athens, Neurosurgical Clinic, Athens, Greece

Received July 06, 2013; Accepted November 09, 2013

ABSTRACT – *Aims*. To investigate the role of centrally recorded P300 in patients suffering from mesial temporal sclerosis-temporal lobe epilepsy (MTS-TLE). *Methods*. Sixteen patients (3 men and 13 women; median age: 32.5 years old) suffering from TLE with MTS and 43 healthy controls (12 men and 31 women; median age: 35 years old) participated in the study. P300 was elicited using an auditory two-stimulus oddball paradigm. In order to address the aim of the study, we adopted two statistical approaches; hierarchical linear regression analyses and ROC curves. *Results*. After adjusting for age, MTS patients had a mean reduction of P300 amplitude by 6.93 μV and a mean increase of P300 latency by 38.78 ms, compared to controls. Age and MTS-TLE status accounted for 32 and 16% of the variance of latency and amplitude, respectively. Diagnostic analyses to detect MTS-TLE status revealed a sensitivity and specificity of 88 and 65% for amplitude and 81 and 70% for latency, respectively. No association between duration of disease and P300 characteristics were found. *Conclusions*. This study, along with other studies, contributes to our understanding and clinical significance of centrally recorded P300s in MTS-TLE patients. Future studies should focus on the association of these P300s with cognition in such patients.

Key words: epilepsy, hippocampal sclerosis, cognitive, event-related, P300

Correspondence:
Artemiadis K. Artemios
Department of Neurology,
417 Army Share Fund Hospital,
Monis Petraki Str.,
10-12 GR-115-21,
Athens, Greece
<kmwartem@yahoo.com>

doi:10.1684/epd.2014.0631

Mesial temporal sclerosis (MTS, also called hippocampal sclerosis) is the most common underlying cause of temporal lobe epilepsy (TLE), detected in 48-56% of cases (Malmgren and Thom, 2012). Several risk factors have been identified, such as history of febrile seizures in early childhood, trauma, inflammatory disorders (*e.g.* autoimmune limbic encephalitis), and genetic and neurodevelopmental factors (Malmgren and Thom, 2012). Interestingly, many researchers deem MTS as a progressive disorder, leading to neocortical atrophy

through a vicious cycle of neuroinflammation, at least in patients with medically intractable seizures (accounting for up to 60-90% of patients) (Yang *et al*., 2010). Pathological examination reveals mild to marked neuronal loss and fibrillary gliosis in the hippocampus, typically bilaterally (20% of cases) (Blümcke *et al*., 2012). There are also extrahippocampal abnormalities (*e.g*. cortical dysplasia, sclerosis or thinning, ischaemic lesion, vascular malformations, etc.) corresponding to the so called "dual pathology" of MTS (Blümcke *et al*., 2012; Malmgren and Thom, 2012).

There are several studies that attest the significant contribution of MTS to cognitive deficits detected in patients with TLE, such as memory and executive function impairments (Oddo *et al*., 2003; Adda *et al*., 2008; Baxendale *et al*., 2010; Tuchscherer *et al*., 2010; Busch *et al*., 2013; Campo *et al*., 2013). There is, interestingly, accumulating evidence in support of an extrahippocampal origin of these cognitive deficits, although some authors raise serious concerns about the speculative confounding effect of frequent seizures and/or antiepileptic drugs (AEDs) (Martin *et al*., 1999; Focke *et al*., 2008; Mueller *et al*., 2012). Also, duration of epilepsy has been linked with more severe MTS and greater hippocampal volume asymmetry, presumably mediating cognitive deficits, although this has not been confirmed by some researchers (Fuerst *et al*., 2001; Kramer *et al*., 2006; Marques *et al*., 2007). Finally, it has been shown that the role of AEDs may be less important relative to the course of the disease itself (Triantafyllou *et al*., 1992; Meador, 2002; Mula *et al*., 2003; Hessen *et al*., 2006; Mula *et al*., 2006; Zhou *et al*., 2008).

In practice, cognitive impairment can be assessed by neuropsychological tools (*i.e*. questionnaires and interviews) and event-related potentials (ERPs) such as P300 (also known as P3) generated by a diffuse-projecting generator located in the temporal-parietal region. P300 is associated with arousal level, processing capacity, attention allocation, and context-dependent stimulus selection (Polich, 2007; Duncan *et al*., 2009). We searched Pubmed using the following keywords: "P300" or "P3" or "event related potentials" and "temporal lobe epilepsy" or "mesial temporal sclerosis" or "hippocampal sclerosis".

Previous studies have shown that P300 latencies are prolonged in TLE patients, especially in those with bilateral temporal EEG foci, irrespective of the antiepileptic treatment (Fukai *et al*., 1990). In a study by Bocquillon *et al*., patients with TLE exhibited a reduction in temporal, and to a lesser extent frontal, sources of P300, while it is suggested for MTS-TLE patients that a modification of the location of the generators may have taken place (Bocquillon *et al*., 2009). Regarding the laterality of foci, spectral power of the ERP appears to be decreased to a greater extent with left-sided MTS than with right-sided MTS, although there are studies which do not support this (Meador *et al*., 1992; Trinka *et al*., 2001). Absence of limbic P300s indicate (with a sensitivity of 100%) the presence of MTS, and the presence of limbic P300 abnormalities is useful in the evaluation of patients for epilepsy surgery (Puce *et al*., 1989; Nelson *et al*., 1991; Psatta and Matei, 1995). In a more recent study, limbic P300 amplitudes were reduced at the site of MTS, bilaterally for left-sided MTS, and latencies were prolonged bilaterally irrespective of the recording site of P300 (Grunwald *et al*., 1999). In another study, P300 latencies (using P3 and P4 electrodes) in TLE patients were significantly longer than those in patients with idiopathic generalised epilepsy and controls (Chen *et al*., 2001). In the same study, seizure frequency, and not age or duration of illness, was associated with abnormal frequencies in TLE patients. In a study by Rocha *et al*., MTS-TLE patients had longer P300 latencies and decreased P300 amplitudes (using C3 and C4 electrodes) compared to controls, with no evidence of any effect of laterality of MTS location (Rocha *et al*., 2010). In another study, however, no differences were noted between patients with TLE (8 with MTS; 12 in total) and healthy volunteers (8 in total) concerning P300 amplitude and latency recorded at Pz electrode (Nishitani *et al*., 1999).

The aim of this study was to expand the literature on the role of centrally recorded P300 in MTS-TLE patients.

Materials and methods

Sixteen patients suffering from TLE with MTS (*table 1*) were studied. MTS was ascertained by MRI. Dual pathology was defined as MRI abnormalities except for hippocampal atrophy, abnormal T2 signal intensity, and disturbed internal architecture of the hippocampus (Malmgren and Thom, 2012). Some examples of dual pathology in our patients were white matter loss, cortical dysplasia, and fornix or amygdala atrophy. All patients were right-handed with no history of substance abuse, psychiatric illness or other disease of the central nervous system (CNS), except for epilepsy. All patients were receiving antiepileptic drugs and were free of seizures for at least six months. Forty-three normal subjects (*table 1*) were selected as controls. None of them received any medication or suffered from any medical illness or disease. All subjects were fully informed about the aims of the study and gave their written consent.

Recording procedure

The P300 ERP was elicited using an auditory two-stimulus oddball paradigm. EEG recordings were

Table 1. Patients *vs*. controls: main characteristics.

	Median age (years)	Age range (years)	Males	Females	Median duration of disease (years)	Range of duration of disease (years)	Dual pathology (yes/no)
Patients (*n*=16)	32.5	17-57	3	13	24.5	0-35	10/6
Controls (*n*=43)	35	19-61	12	31	-	-	-

obtained using one scalp site (Pz) according to the international 10-20 electrode system. Activity was recorded with Ag-AgCl electrodes filled with paste, attached to the scalp with collodion, using the left mastoid (A1) for online reference and the linked mastoids (A1/A2) for off-line reference. The ground electrode was placed on the mid-forehead. Impedances were kept below 5 KOhm, the amplification gain was 20,000 times, the sampling rate was 128 Hz per channel, and the data were filtered using a band-pass of 0.1-50 Hz. Each subject was presented with a series of binaural 1,000-Hz frequent (standard) and 2,000-Hz less common (target) tones at 40 dB with a 10-ms rise/fall and 100-ms plateau time. Tones were presented at a rate of one tone every two seconds, in a random sequence with target tones occurring with a probability of 0.2. Subjects sat with their eyes closed and were instructed to mentally count the number of target tones, but not standard tones, and then asked to report the number of target tones counted at the end of each run. Off-line processing of the data was achieved using a commercial (Nihon Kohden Neuropack 8, MEB-4200 K) apparatus which also controlled the stimulus presentation and artefact rejection. Averaging was performed for only the artefact-free epochs (1,024 ms after the target stimulus), which were visually recognised and rejected using a band-pass filter of 0.01-20 Hz. ERPs were displayed using low-pass filtering of 12 Hz. P300 amplitude and latency were measured only for the Pz electrode. The procedure was terminated after the presentation of 40 target stimuli. Recognition of P300 was achieved using the following two criteria: (1) identification of the first positive wave on a time range of 280-420 ms; and (2) identification of the first positive wave after recognising the triplet N100-P200-N200.

Statistical analyses

Descriptive measures (medians and ranges) were used to present main characteristics of our sample (*table 1*). We used a hierarchical linear regression analysis in order to investigate the association between group and P300 amplitude and latency (as dependent variables), adjusting for age. All assumptions of linear regression were checked and diagnostics for goodness of fit (influential statistics) and generisability of our model were performed. Correlations between duration of disease and P300 characteristics were performed using Kendall's tau due to our small sample. The ability to predict disease status using P300 was investigated using receiver operating characteristic (ROC) curves under the null assumption of an area under the curve (AUC) equal to 0.5. Cut-offs with the highest sensitivity and specificity were identified by calculation of the higher delta distance according to the formula: (1-specificity-sensitivity)/$2^{1/2}$. The level of significance for all analyses was 0.05 and 95% confidence intervals were calculated (95% CI) when appropriate. For data analyses, we used the SPSS for Windows (version 17.0) statistical software (SPSS Inc., Chicago, IL).

Results

Table 1 presents the main baseline characteristics of our sample. Concerning P300, patients had a median amplitude and latency of 14 μV (from 7.3 to 31.3 μV) and 377 ms (from 320 to 448 ms), respectively. Corresponding values for controls were 21.5 μV (from 9.6 to 37 μV) and 346 ms (from 288 to 408 ms), respectively.
Tables 2 and 3 present the results of hierarchical linear regression analyses for P300 amplitude and latency. Age had a minimal, non-significant effect on both P300 attributes, with the exception of age, showing a small positive association with P300 latency when the group variable was included in the model (*table 3*). After adding group category (with controls as reference) in initial models (model 1), amplitude and latency variance were increasingly accounted for in the final models (P300 amplitude: ΔR^2=0.18; p=0.001, P300 latency: ΔR^2=0.26; $p<0.001$). Predictability of final models was better for latency than amplitude (32% *vs* 16%, respectively). According to our results, patients had a mean reduction of P300 amplitude of 6.93 μV and a mean greater P300 latency by 38.78 ms after adjusting for age (*tables 2* and 3).

Table 2. Hierarchical linear regression models with P300 amplitude as dependent variable.

	B	SE B	Standardised coefficients (beta)	*p* value
Model 1				
Constant	17.97	3.36		0.00***
Age	0.06	0.09	0.09	0.52
Model 2				
Constant	21.38	3.22		0.00***
Age	0.02	0.08	0.02	0.85
Group (ref.: controls)	-6.93	1.96	-0.43	0.00***

Model 1: Adjusted R^2=0.01, F (1, 57)=0.427, p=0.516.
Model 2: Adjusted R^2 =0.16, F (3, 55)=6.532 , p=0.003.
ΔR^2=0.18 for model 2 (p=0.001).
Reference: controls for group.
*p<0.05, **p<0.01, ***p<0.001.

Table 3. Hierarchical linear regression models with P300 latency as dependent variable.

	B	SE B	Standardised coefficients (beta)	*p* value
Model 1				
Constant	327.59	15.21		0.00***
Age	0.76	0.4	0.24	0.06
Model 2				
Constant	308.5	13.64		0.00***
Age	1.0	0.35	0.32	0.01**
Group (ref: controls)	38.78	8.3	0.52	0.00***

Model 1: Adjusted R^2=0.06, F (1,57)=3.55, *p=0.064*.
Model 2: Adjusted R^2=0.32, F (2,56)=13.36, *p<0.001*.
ΔR^2=0.26 for model 2 *(p<0.001)*.
References: man for gender, controls for group.
*p<0.05, **p<0.01, ***p<0.001.

Duration of disease was not significantly correlated with P300 characteristics (P300 amplitude: Kendall's tau=-0.246, *p=0.27*; P300 latency: Kendall's tau=0.11, p=0.63), although there was a tendency towards lower amplitude and longer latency with longer duration of the disease.

Figure 1 presents the ROC curves which signify the ability to predict MTS using P300 amplitude and latency. It is evident that both P300 characteristics are good predictors of MTS. For P300 amplitude, the AUC (standard error [SE]) was 0.798 (0.07); p<0.001. The maximum delta distance was 0.37 corresponding to a value of less than 18.75 μV, indicative of MTS with a sensitivity of 88% and a specificity of 65%. For P300 latency, the AUC (SE) was 0.784 (0.07); p<0.001. The maximum delta distance was 0.36 corresponding to a value of more than 356 ms, indicative of MTS-TLE with a sensitivity of 81% and a specificity of 70%.

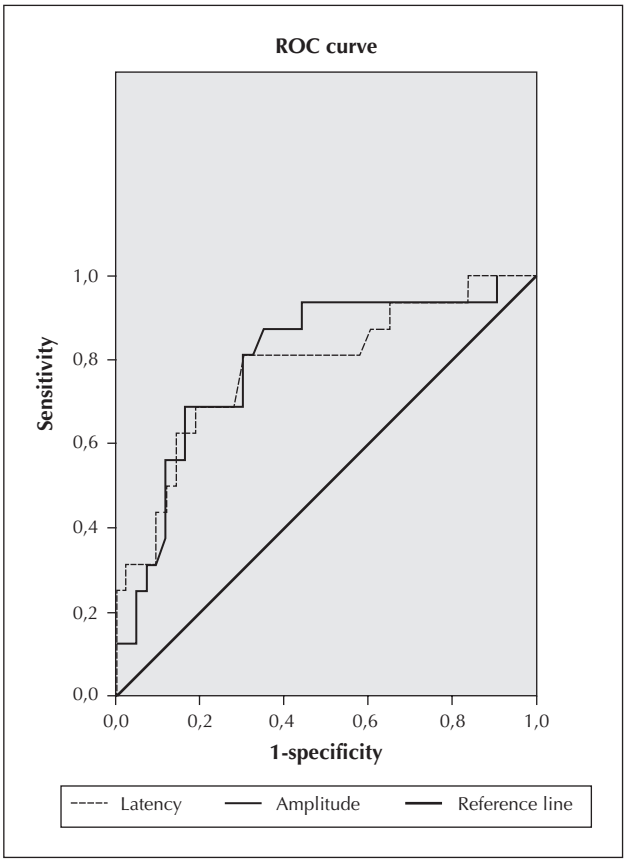

Figure 1. ROC urves showing the sensitivity and specificity of P300 amplitude and latency which is useful for the diagnosis of mesial temporal sclerosis-temporal lobe epilepsy (MTS-TLE) status.

Discussion

This study has shown that in MTS-TLE patients, the centrally recorded P300 event-related potential is disturbed in terms of longer latency and lower amplitude, after adjusting for age. No effect of the duration of the disease on P300 was noted. Diagnostic analysis revealed that centrally recorded P300 may be a good electrophysiological marker of MTS-TLE status, possibly corresponding to impaired cognition which was not ascertained in this study.

Our results are in accordance with previous studies with centrally recorded P300s (Fukai *et al*., 1990; Chen *et al*., 2001; Rocha *et al*., 2010). Other studies have focused on limbic P300, showing reduced amplitudes and prolonged latencies, which is similar to our findings for centrally recorded P300 (Puce *et al*., 1989; Nelson *et al*., 1991; Psatta and Matei, 1995; Grunwald *et al*., 1999; Rocha *et al*., 2010). A possible explanation for a diffuse P300 disturbance is the presence of a diffuse-projecting P300 generator, most likely also involving temporal regions of the brain (Polich, 2007; Duncan *et al*., 2009). The significance of laterality of MTS has also been noted, with left MTS causing bilateral prolongation of P300 (Grunwald *et al*., 1999; Rocha *et al*., 2010) which is in accordance with the presence of a left hemisphere (in parieto-temporal junction) generator (Polich, 2007; Duncan *et al*., 2009), although laterality effects have not been confirmed in other studies (Meador *et al*., 1992; Trinka *et al*., 2001). In our study, no effect of laterality of MTS on P300 amplitude and latency was observed, however, we should note that, due to our small sample and unbalanced non-parametric analysis (5 patients with left-sided MTS and 11 with right-sided MTS), results were not robust (data not shown).

The neurofunctional and neurobehavioural significance of P300 has been a matter of controversy for many years (Polich, 2007; Duncan *et al*., 2009). Both amplitude and latency are influenced by numerous factors such as frequency and complexity of the target stimulus, time of day, season, drugs, IQ, and genetic factors (Polich, 2007; Duncan *et al*., 2009). The full description of P300 theory is beyond the scope of this study. Collectively, smaller P300 amplitudes are indicative of impaired attention, reduced concentration, and processing brain capacity (Polich, 2007; Duncan *et al*., 2009). Congruently, prolongation of P300 appearance is linked to reduced processing speed (Polich, 2007; Duncan *et al*., 2009). Dual pathology in MTS has been shown to mediate cognitive impairment in these patients and possibly affect P300 (Martin *et al*., 1999; Focke *et al*., 2008; Mueller *et al*., 2012). However, in our study, no effect of the presence of dual pathology on P300 amplitude and latency was noted (data not shown due to our small sample).

This study has a number of limitations that should be addressed. First of all, we used a small, non-random, convenience sample, thus our overall results and reported cut-offs for P300 amplitude and latency should be regarded with caution. Our sample consisted of patients that were seizure-free for at least six months, in order to avoid any physical, mental, or psychological effects of a recent seizure or drug modification. For this reason, our patients were more likely to belong to the minority of non-drug resistant patients, thus interpretation of the results overall should apply only to this subgroup of patients. Secondly, our sample of MTS patients was too small to examine the effect of laterality of MTS and presence of dual pathology on P300. As noted above, no effect was found after performing non-parametric tests (data not shown). Moreover, results should be interpreted with caution, since the control group consisted of healthy people rather than TLE patients without MTS, thus differences could be due to a variety of factors beyond MTS (*e.g.* interictal discharges, aetiology of the epilepsy, and antiepileptic drugs), although P300

disturbances have been detected irrespective of AEDs, age, and duration of illness (Fukai *et al*., 1990; Chen *et al*., 2001).

In summary, this study contributes to our understanding of the centrally recorded P300 disturbances in MTS-TLE patients. Future studies should focus on the association between P300 and neuropsychological measurements in MTS patients. According to the available evidence so far, the clinical use of P300 ERPs corroborates neuropsychological testing for cognitive impairment. □

Disclosures.
None of the authors have any conflict of interest to disclose.

References

Adda CC, Castro LH, Além-Mar e Silva LC, de Manreza ML, Kashiara R. Prospective memory and mesial temporal epilepsy associated with hippocampal sclerosis. *Neuropsychologia* 2008; 46: 1954-64.

Baxendale S, Heaney D, Thompson PJ, Duncan JS. Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. *Neurology* 2010; 75: 705-11.

Blümcke I, Coras R, Miyata H, Ozkara C. Defining clinico-neuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. *Brain Pathol* 2012; 22: 402-11.

Bocquillon P, Dujardin K, Betrouni N, *et al*. Attention impairment in temporal lobe epilepsy: a neurophysiological approach via analysis of the P300 wave. *Hum Brain Mapp* 2009; 30: 2267-77.

Busch RM, Chapin JS, Haut JS, Dulay MF, Naugle RI, Najm I. Word-finding difficulties confound performance on verbal cognitive measures in adults with intractable left temporal lobe epilepsy. *Epilepsia* 2013; 54: e37-40.

Campo P, Garrido MI, Moran RJ, *et al*. Network reconfiguration and working memory impairment in mesial temporal lobe epilepsy. *Neuroimage* 2013; 72C: 48-54.

Chen RC, Tsai SY, Chang YC, Liou HH. Seizure frequency affects event-related potentials (P300) in epilepsy. *J Clin Neurosci* 2001; 8: 442-6.

Duncan CC, Barry RJ, Connolly JF, *et al*. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin Neurophysiol* 2009; 120: 1883-908.

Focke NK, Thompson PJ, Duncan JS. Correlation of cognitive functions with voxel-based morphometry in patients with hippocampal sclerosis. *Epilepsy Behav* 2008; 12: 472-6.

Fuerst D, Shah J, Kupsky WJ, *et al*. Volumetric MRI, pathological, and neuropsychological progression in hippocampal sclerosis. *Neurology* 2001; 57: 184-8.

Fukai M, Motomura N, Kobayashi S, Asaba H, Sakai T. Event-related potential (P300) in epilepsy. *Acta Neurol Scand* 1990; 82: 197-202.

Grunwald T, Beck H, Lehnertz K, *et al*. Limbic P300s in temporal lobe epilepsy with and without Ammon's horn sclerosis. *Eur J Neurosci* 1999; 11: 1899-906.

Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. *Epilepsia* 2006; 47: 2038-45.

Kramer U, Kipervasser S, Neufeld MY, Fried I, Nagar S, Andelman F. Is there any correlation between severity of epilepsy and cognitive abilities in patients with temporal lobe epilepsy? *Eur J Neurol* 2006; 13: 130-4.

Malmgren K, Thom M. Hippocampal sclerosis-origins and imaging. *Epilepsia* 2012; 53(S4): 19-33.

Marques CM, Caboclo LO, da Silva TI, *et al*. Cognitive decline in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsy Behav* 2007; 10: 477-85.

Martin R, Dowler R, Gilliam F, Faught E, Morawetz R, Kuzniecky R. Cognitive consequences of coexisting temporal lobe developmental malformations and hippocampal sclerosis. *Neurology* 1999; 53: 709-15.

Meador KJ. Neurodevelopmental effects of antiepileptic drugs. *Curr Neurol Neurosci Rep* 2002; 2: 373-8.

Meador KJ, Loring DW, Gallagher BB, *et al*. Differential effects of left versus right seizure focus on human hippocampal evoked responses. *Int J Neurosci* 1992; 66: 87-91.

Mueller SG, Laxer KD, Scanlon C, *et al*. Different structural correlates for verbal memory impairment in temporal lobe epilepsy with and without mesial temporal lobe sclerosis. *Hum Brain Mapp* 2012; 33: 489-99.

Mula M, Trimble MR, Sander JW. The role of hippocampal sclerosis in topiramate-related depression and cognitive deficits in people with epilepsy. *Epilepsia* 2003; 44: 1573-7.

Mula M, Sander JW, Trimble MR. The role of hippocampal sclerosis in antiepileptic drug-related depression in patients with epilepsy: a study on levetiracetam. *Seizure* 2006; 15: 405-8.

Nelson CA, Collins PF, Torres F. P300 brain activity in seizure patients preceding temporal lobectomy. *Arch Neurol* 1991; 48: 141-7.

Nishitani N, Ikeda A, Nagamine T, *et al*. The role of the hippocampus in auditory processing studied by event-related electric potentials and magnetic fields in epilepsy patients before and after temporal lobectomy. *Brain* 1999; 122: 687-707.

Oddo S, Solís P, Consalvo D, *et al*. Mesial temporal lobe epilepsy and hippocampal sclerosis: cognitive function assessment in Hispanic patients. *Epilepsy Behav* 2003; 4: 717-22.

Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol* 2007; 118: 2128-48.

Psatta DM, Matei M. Investigation of P300 in various forms of epilepsy. *Rom J Neurol Psychiatry* 1995; 33: 183-202.

Puce A, Kalnins RM, Berkovic SF, Donnan GA, Bladin PF. Limbic P3 potentials, seizure localization, and surgical pathology in temporal lobe epilepsy. *Ann Neurol* 1989; 26(3): 377-85.

Rocha CN, Miziara CS, Manreza ML, Schochat E. Electrophysiological and auditory behavioral evaluation of individuals with left temporal lobe epilepsy. *Arq Neuropsiquiatr* 2010; 68: 18-24.

Triantafyllou NI, Zalonis I, Kokotis P, *et al*. Cognition in epilepsy: a multichannel event related potential (P300) study. *Acta Neurol Scand* 1992; 86: 462-5.

Trinka E, Unterrainer J, Luef G, Ladurner G. Multimodal P3 under different attentional states in mesial temporal lobe epilepsy. *Eur J Neurol* 2001; 8: 261-6.

Tuchscherer V, Seidenberg M, Pulsipher D, Lancaster M, Guidotti L, Hermann B. Extrahippocampal integrity in temporal lobe epilepsy and cognition: thalamus and executive functioning. *Epilepsy Behav* 2010; 17: 478-82.

Yang T, Zhou D, Stefan H. Why mesial temporal lobe epilepsy with hippocampal sclerosis is progressive: uncontrolled inflammation drives disease progression? *J Neurol Sci* 2010; 296: 1-6.

Zhou B, Zhang Q, Tian L, Xiao J, Stefan H, Zhou D. Effects of levetiracetam as an add-on therapy on cognitive function and quality of life in patients with refractory partial seizures. *Epilepsy Behav* 2008; 12: 305-10.