Attention Impairment in Temporal Lobe Epilepsy: A Neurophysiological Approach via Analysis of the P300 Wave

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Abstract: *Purpose:* Attention is often impaired in temporal lobe epilepsy (TLE). The P300 wave (an endogenous, event-related potential) is a correlate of attention which is usually recorded during an “oddball paradigm,” where the subject is instructed to detect an infrequent target stimulus presented amongst frequent, standard stimuli. Modifications of the P300 wave’s latency and amplitude in TLE have been suggested, but it is still not known whether the source regions also differ. Our hypothesis was that temporal lobe dysfunction would modify the P3 source regions in TLE patients. *Methods:* A comparative, high density, 128-channel electroencephalographic analysis of the characteristics of P300 (P3b latency and amplitude) was performed in 10 TLE patients and 10 healthy controls during auditory and visual oddball paradigms. The P3b sources were localized on individual 3D MR images using the LORETA method and intergroup statistical comparisons were performed using SPM2[®] software. *Results:* Our main results (in both individual analyses and intergroup comparisons) revealed a reduction in temporal (and more particularly mesiotemporal) sources and, to a lesser extent, frontal sources in TLE patients, compared with controls. *Discussion:* This reduction may reflect direct, local cortical dysfunction caused by the epileptic focus or more complex interference between epileptic networks and normal attentional pathways. *Hum Brain Mapp* 30:2267–2277, 2009. © 2008 Wiley-Liss, Inc.

Key words: oddball paradigm; cortical sources; event related potentials; LORETA

INTRODUCTION

It is known that memory, language, executive function, visual processes, and musical perception are impaired in

temporal lobe epilepsy (TLE) [Doyon and Milner, 1991; Kester et al., 1991; Lassonde et al., 2000]. Most of the epileptic patients complain of attentional disorders. A decrease in attentional performance [as evidenced by the Trail-Making Test, the Stroop Test and the Continuous Performance Test (CPT)] has been noted in TLE patients presenting complex, partial seizures [Stella and Maciel, 2003]. Furthermore, reaction times (RTs) in a choice RT test and the CPT are longer in TLE [Fleck et al., 2002]. Attention is defined as a complex neuropsychological process that enhances constant mental activity, helps to select a salient stimulus from amongst others, and resists interference [Stella and Maciel, 2003].

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Received for publication 25 March 2008; Revised 12 July 2008;
Accepted 25 August 2008

DOI: 10.1002/hbm.20666

Published online 25 November 2008 in Wiley InterScience (www.interscience.wiley.com).

The P300 wave is an endogenous, long latency, cognitive event-related potential (ERP) that has demonstrated value for investigating attention disorders [Polich and Kok, 1995]. It was first described in 1965 that the [Sutton et al., 1965] P300 occurs when a subject has to detect an expected but unforeseeable stimulus, such as that during an “oddball paradigm” [Hansenne, 2000]. This paradigm consists of detecting an infrequent target stimulus from amongst frequent standard stimuli, with a sufficient degree of difficulty in discriminating between the two types. Typically, two P300 components are described [Squires et al., 1975]. The earlier (220–280 ms) frontocentral P3a component occurs when the subject is presented with an unexpected stimulus in the absence of any prior instruction. It acts as an automatic evaluation of the stimuli or as an attentional alert [Friedman et al., 1978; Hansenne, 2000]. The later (310–380 ms) centroparietal P3b component requires prior provision of a precise processing instruction concerning the deviant stimulus to be observed. It is supposedly related to an update in working memory processes following the presentation of new information [Donchin, 1981; Donchin and Coles, 1988] or an information processing closure [Verleger, 1988], corresponding to deactivation of the brain areas controlling perception. The P3b component therefore engages a voluntary attentional process.

Many researchers have sought to localize the brain areas involved in attention and working memory, using approaches as various as lesional studies, functional magnetic resonance imagery, and P300 source density analysis. These different methods have provided evidence of the involvement of several areas in the generation of P3b: (1) the inferior parietal lobe and temporoparietal junction [Anderer et al., 2003; Menon et al., 1997; Mulert et al., 2004; Yamazaki et al., 2001]; (2) the superior and posterior parietal areas [Halgren et al., 1995; Linden, 2006; Moores et al., 2003]; (3) the cingulum [Linden, 2006; Mulert et al., 2004; Wang et al., 2005]; (4) the temporal lobe [Anderer et al., 2003; Hegerl and Frodl-Bauch, 1997; Mulert et al., 2004; Opitz et al., 1999; Tarkka and Stokic, 1998; Winterer et al., 2001]; and (5) the frontal and prefrontal areas [Anderer et al., 2003; Linden, 2006; Mulert et al., 2004; Smith et al., 1990; Yamazaki et al., 2001]. On the basis of intracranial recordings made during the presurgical investigation of epileptic patients, mesiotemporal structures (and particularly the hippocampus and amygdala) were initially proposed as P300 generators [Halgren et al., 1980; McCarthy and Wood, 1987b; McCarthy et al., 1989]. However, other researchers found few or no effects of temporal lesion or resection on scalp P300 characteristics [Halgren et al., 1986; Johnson, 1988, 1989; Johnson and Fedio, 1987; Rugg et al., 1991; Stapleton and Halgren, 1987]. This argues against the predominant involvement of mesiotemporal structures in P300 generation but does not exclude the combined involvement of mesiotemporal and neocortical sources [Linden, 2006]. Studies of P300's characteristics in epilepsy have mainly concerned changes in latencies

and amplitudes, with increased latencies and a trend toward lower P300 amplitudes in epileptic subjects [Abubakr and Wambacq, 2003; Drake et al., 1986; Fukai et al., 1990; McCarthy et al., 1987a; Meador, 2002; Naganuma et al., 1991; Puce and Bladin, 1991; Rodin et al., 1989; Triantafylou et al., 1992; Tuunainen et al., 1995; Verma et al., 1993].

The aim of this study was to investigate selective attention abilities in TLE patients by studying the brain source areas involved in the generation of the P3b, compared with healthy controls. A standard oddball paradigm was performed under both visual and auditory conditions. Our hypothesis was that temporal lobe dysfunction would modify the P3 source regions in TLE patients.

MATERIALS AND METHODS

Subjects

Ten right-handed patients with drug-resistant TLE were investigated (six females and four males, five right sided and five left sided; mean $\pm$ SD age, 29 ± 9.2 years old; age range, 18–49). Epilepsy was symptomatic in nine cases (five cases with hippocampal sclerosis, two with cortical dysplasia, one with both hippocampal sclerosis and cortical dysplasia, and one with pilocytic astrocytoma) and cryptogenic in one case. The TLE patients' clinical features are summarized in Table I. The time interval since the last seizure was always greater than 17 h, except for one patient (patient 7: time interval = 1 h). However, given that the subsequent analyses performed with and without data from this patient led to the same results, these data were not discarded. Attention impairment was assessed with the d2 cancellation test (Hogrefe France) and a subtest of the French version of the Wechsler Adult Intelligence Scale [Wechsler, 1981]. Patients were recruited from the Clinical Neurophysiology Department at Lille University Medical Center and compared with 10 right-handed, healthy controls (four females and six males; mean age, 28.6 ± 6.5 ; age range, 24–42) who had no history of neurological or psychiatric conditions or psychoactive drug use.

All study participants provided their informed written consent. None presented with noncorrected visual or auditory impairments. There were no significant differences between TLE patients and controls in terms of either gender ratio or age.

Recording Procedure

Subjects were seated comfortably and stared at a fixed, central point on a monitor screen placed 120 cm away. They were subjected to a classic two-stimulus oddball paradigm in visual and auditory modalities. For the auditory session, the stimuli were monophonic, 90-dB, 40-ms sound bursts, with a 10 ms rise- and falltime and a frequency of 1,000 Hz (standard stimulus) and 1,500 Hz (target stimulus). The interstimulus interval was $1,500 \pm 100$ ms. In the visual modality, the stimuli were 110 mm $\times$ 95 mm blue

TABLE I. Clinical features of TLE patients

Patients/sex	Age	Epileptic focus	Etiology	Epilepsy onset age (years)	Treatment (mg per day)	Delay since last seizure
1 F	23	Left	Hippocampal Sclerosis	8	-Levetiracetam (1500) -Lamotrigine (400)	10 weeks
2 F	29	Left	Hippocampal Sclerosis	Childhood	-Levetiracetam (500) -Lamotrigine (600) -Topiramate (200)	4 days
3 M	28	Left	Cryptogenic	Childhood	-Levetiracetam (1500) -Lamotrigine (500)	2 weeks
4 M	33	Left	Hippocampal Sclerosis	Childhood	-Oxcarbazepine (1600) -Levetiracetam (1500)	15 days
5 M	49	Left	Hippocampal Sclerosis	14	-Lamotrigine (200) -Carbamazepine (1600)	6 weeks
6 F	18	Right	Cortical Dysplasia Hippocampal Sclerosis	7	-carbamazepine (600) -Lamotrigine (400) -Clobazam (20)	11 days
7 F	19	Right	Hippocampal Sclerosis	10	-Vigabatrin (1000) -Lamotrigine (25) -Carbamazepine (1200)	1 h
8 M	22	Right	Cortical Dysplasia	16	-Carbamazepine (1400) -Levetiracetam (2000) -Clobazam (15)	17 h
9 F	27	Right	Cortical dysplasia with amygdalo-hippocampal implication	14	-Oxcarbazepine (750) -Levetiracetam (3000)	47 h
10 F	40	Right	DNET	39	-Levetiracetam (2000) -Carbamazepine (1200)	46 h

rectangles (standard, dark blue; target, light blue), with a presentation time of 200 ms and an interstimulus interval of $2,000 \pm 200$ ms. In both conditions, target stimuli accounted for 15% of the total (60 out of 400). The stimuli were presented in the same, randomized order to all subjects. The subjects were instructed to press a response key every time they detected the target stimulus.

Electroencephalographic (EEG) activity was recorded from 128 scalp sites using an ANT DC amplifier (ANT Software BV, Enschede, the Netherlands) and a Quick-cap[®] 128 Ag—Cl electrode cap placed according to the 10/05 international system, with a linked mastoid reference. Impedances were kept below 5 k Ω . An electrooculogram (EOG) was recorded to detect eye movement artifacts. The EEG and EOG data were digitized with a sampling rate of 512 Hz and recorded with EEProbe[®] software (ANT Software BV, Enschede, the Netherlands). The electrode location was digitized relative to three reference points (nasion and left and right tragi) with a magnetic Fastrak[®] (POLHEMUS) captor and EETrak software (ANT Software BV, Enschede, the Netherlands).

Data Analysis

EEG signals were bandpass filtered at 0.1–30 Hz. EEG epochs that contained eye movement artifacts were automatically detected and corrected. A manual rejection pro-

cess excluded epochs with paroxysmal activities and omitted trials. To identify the cognitive ERPs, the resulting signals were averaged in epochs of 1,000 ms (–100 to +900 ms from the stimulus) for the two different curves (i.e. standard and rare stimuli). P3b was then selected as the largest positive wave occurring between 250 and 600 ms on the rare stimulus curve.

In each condition and for each subject, we measured the P3b latency and amplitude on electrodes from eight areas: frontal (AFF1, AFF5h, F1, F3, F5, FFC1h, FFC3h, FFC5h, FC1, FC3, FC5 on the left and AFF2, AFF6h, F2, F4, F6, FFC2h, FFC4h, FFC6h, FC2, FC4, FC6 on the right), central (FCC1h, FCC3h, FCC5h, C1, C3, C5, CCP1h, CCP3h, CCP5h on the left and FCC2h, FCC4h, FCC6h, C2, C4, C6, CCP2h, CCP4h, CCP6h on the right), parietal (CP1, CP3, CP5, CPP1h, CPP3h, CPP5h, P1, P3, P5, PPO1, PPO5h on the left and CP2, CP4, CP6, CPP2h, CPP4h, CPP6h, P2, P4, P6, PPO2, PPO6h on the right), and temporal (FT7, FTT9h, T7, TTP7h, TP7, TPP9h on the left and FTT10h, T8, TTP8h, TP8, TPP10h on the right).

Amplitude was defined as the voltage difference between the prestimulus baseline and the largest positive wave peak in the time window described above. Latency was defined as the time difference between the stimulus and this peak [Polich and Kok, 1995]. In each condition and for each subject, we also measured RTs and number of omissions and false alarms.

P300 Source Localization Using LORETA

Three-dimensional 180-slice T1-weighted MR images were obtained for each subject, using a 1.5 Tesla Philips[®] Achieva machine.

Source localization of P3b was performed with the mathematical LORETA (low-resolution electromagnetic tomography) method [Pascual-Marqui et al., 1994], using ASA[®] software (ANT Software BV, Enschede, the Netherlands). This method enables identification of the 3D inverse solution of the current density distribution. These solutions were obtained after computing the distributed activity throughout the gray matter determined by segmentation of the 3D MR image; this consisted of semiautomatic identification of the various brain compartments (brain/cerebellum/ventricles/white matter/gray matter, with the latter being defined as the matter remaining after subtraction of the white matter, cerebellum, and ventricles from the brain area). This segmentation also allowed identification of the scalp and skull compartments and thus generation of a realistic 3D head model on which the electrodes set could be repositioned virtually after localization of the three reference points mentioned above (see Fig. 1).

The source space defined by the gray matter was discretized as a dense, 3D grid with electric sources placed on each grid point (n = about 800–1,000). The strength and direction of the sources determined the electric field that could be measured on the scalp. The most meaningful solutions leading to the measured surface fields were determined while taking account of the temporal synchronization between neighboring neurons, with each source being considered if sufficient synchronism was noted. Hence, the LORETA analysis could be performed inside the gray matter compartment of the segmented MRI. The results were expressed as topographic maps.

Spatial Normalization

The LORETA analysis was performed on individual MR images for each subject in both auditory and visual conditions.

As these dipoles were expressed in individual space coordinates, we had to normalize their position in Talairach space. To perform this coordinate transformation, we placed several markers on the individual MRIs: the anterior commissure (AC), the posterior commissure (PC) and an interhemispheric point located in the interhemispheric fissure (to define the AC–PC system), plus additional points defining the brain's boundary in all directions (extreme anterior, posterior, superior, inferior, left, and right points). The new coordinates of Talairach space were assigned to these points and the PC; as a result, the brain could be "shrunk" or "stretched."

The LORETA solution was then exported into an Analyze 3D image file in normalized Talairach coordinates, in order to compute a statistical group comparison. This export consisted of two interpolation procedures. First, an

image was generated from the dipoles that matched the properties of the subject's MR images. Thus, the image dimensions and pixel and slice steps were identical to those in the subject's MR image. In general, the spatial resolution of the dipole distribution was lower than the image resolution. To achieve a higher resolution in the subject image, trilinear interpolation was used. The mean magnitude (multiplied by 1.10^9) of the dipoles over the time interval used for LORETA computation was used as an input for the trilinear interpolation. In the second step, the image with the LORETA solution in Talairach space was created, with dimensions of $240 \text{ mm} \times 240 \text{ mm} \times 240 \text{ mm}$ and a voxel distance of $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$. For each of the 12 subcubes (defined by the Talairach markers), a transformation object was defined; it included the translation, rotation, and scaling needed to transfer from the original MR image to the Talairach space MR image, and vice versa. For a voxel in the Talairach space MR image, the corresponding voxel in the LORETA image and its respective neighbors were retrieved. The new value assigned to the voxel was a trilinear interpolation of the values from the LORETA image. The second transformation and interpolation procedure provided images which, independently of the original image, had the same dimensions and pixel spaces. Furthermore, they were anatomically aligned by Talairach transformation of the LORETA solutions. As these data were coaligned and had identical pixel properties, pixel-wise statistical procedures could thus be applied.

Intensity Normalization

An intensity normalization of current densities was also required for group comparison, as regional activity can be perturbed by the overall activity of the cortical lobes (which can vary greatly from subject to subject). To reduce the confounding effects of this subject-specific activity, we performed an intensity normalization based on proportional scaling, as used in PET studies [Friston et al., 1990]. This procedure follows the basic assumption that local electrical activities are proportional to the overall neural activity in each subject [Park et al., 2002].

Gaussian Smoothing

A Gaussian smoothing with a 12-mm full width at half maximum (FWHM) kernel was performed in order to increase the signal-to-noise ratio and ensure that intersubject differences were assessed on a reasonable spatial scale with regard to the functional anatomy.

Statistical Analysis

Behavioral data (number of omission errors, commission errors and RT) were compared using nonparametric tests

Figure 1.

Methodology of the P300 source density analysis using LORETA. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(Mann-Whitney rank sum tests for evaluating the effect of “group” and Wilcoxon signed rank tests for the effect of “condition”).

Three-factor repeated-measures analyses of variance (ANOVAs), with area (left and right frontal, central, parietal, temporal areas) and condition (auditory and visual) as within-group factors and subject type (patients and controls) as a between-group factor were performed on the P300 latency and amplitude data. Greenhouse-Geisser correction was used when the assumption of sphericity was violated.

The Significance Threshold was Set at $P < 0.05$ for all These Analyses

To compare the P300 generators in TLE patients with those in healthy controls, we used SPM2[®] software (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK) to define the regions of the brain source space (voxels) in which the P300 current density was lower in patients than in control subjects. Statistical parametric mapping with a two-sample t test was applied to the normalized current

TABLE II. TLE patients and controls performances: mean (SD)

Condition	Auditory		Visual	
	Patients	Controls	Patients	Controls
Reaction time (ms)	450.20 (150.5)	456.3 (98.21)	587.19 (198.05)	557.2 (75.75)
% Hits	99.5 (0.81)	99.83 (0.53)	98.36 (2.44)	100 (0)
% False alarms	0.18 (0.32)	0.15 (0.29)	0.56 (0.70)	0.15 (0.37)

density images, according to the method described by Park et al. [2002]. In view of the multiple comparisons performed, SPM[®] uses Gaussian random field theory [Friston et al., 1996; Worsley et al., 1996] to protect against family-wise false positivities over the search volume. The random field correction (or adjustment to the P values derived from continuous, spatially extended data) plays the same role as the Bonferroni correction for discrete data. The paired t test was chosen with a control-patient contrast in order to highlight intergroup differences, with the goal of revealing missing generators in TLE patients. The height threshold was set to zero, with a P value below 0.001 and cluster size of 10 voxels. These P -value threshold and cluster size values were chosen to avoid false positives.

Individual Source Analysis

Although the analytical method described earlier enables a valuable statistic comparison of generator locations in the two groups, the spatial normalization and the smoothing required for application of SPM2 can induce a loss of precision in the source definition. This is why we sought to confirm our results with an individual analysis of the occurrences of each generator in each gyrus, in both groups and both conditions. This localization was performed using the maximum current density of each generator defined with the LORETA method, using ASA software. We then counted these gyri in the frontal, parietal, occipital, and internal temporal lobes (corresponding to the amygdala, hippocampus, entorhinal cortex, uncus, and parahippocampal gyrus) and external temporal lobes (cor-

responding to the fusiformis gyrus, superior, medius, and inferior temporalis gyri and insula).

This intergroup comparison of the generator distribution in the various cortical areas was performed with a Chi2 test. The significance threshold was set at $P < 0.05$.

RESULTS

Task Performance

The mean (SD) results are shown in Table II. No significant differences in omission or commission errors were noted when comparing the auditory and visual conditions in each group or when comparing patients and controls (in each condition and in both conditions taken together). In both groups, RTs were significantly shorter in the auditory condition than in the visual condition ($P < 0.01$). In the visual condition, the RTs were shorter in controls than in patients ($P < 0.05$). In the auditory condition, the RTs were longer in controls than in patients ($P < 0.01$).

P3b Latency

The ANOVA showed a significant main effect of "condition" on P300 latency, with shorter latencies in the auditory condition ($F_{(1,126)} = 180, P < 0.001$). No other main effects or interactions were observed.

P3b Amplitude

Table III and Figure 2 show the mean P3b amplitudes measured for both conditions in the two groups and in the

TABLE III. P3b amplitudes (μV : mediane [1st quartile; 3rd quartile])

Area	Auditory/controls	Visual/controls	Auditory/Patients	Visual/patients
Left frontal	6.119 (2.984; 9.329)	5.677 (3.793; 8.594)	4.749 (1.891; 7.583)	4.107 (1.714; 5.318)
Left central	7.589 (4.021; 9.247)	7.444 (5.822; 9.698)	5.321 (3.03; 8.583)	5.819 (2.996; 9.2)
Left parietal	6.701 (5.418; 7.903)	9.231 (5.604; 11.445)	6.412 (3.988; 10.017)	6.881 (4.221; 10.736)
Left temporal	4.022 (2.314; 7.5)	5.656 (4.3; 7.081)	3.607 (1.073; 4.921)	2.785 (1.209; 5.737)
Right frontal	5.28 (2.129; 9.164)	6.185 (3.598; 8.682)	3.888 (1.978; 7.319)	3.764 (1.902; 7.464)
Right central	6.837 (5.23; 9.201)	8.101 (5.858; 12.266)	6.228 (3.012; 10.061)	5.69 (3.11; 8.624)
Right parietal	6.768 (5.601; 7.829)	10.127 (5.681; 12.434)	6.547 (2.818; 11.326)	7.266 (4.639; 10.661)
Right temporal	3.916 (2.111; 6.154)	4.543 (3.307; 7.515)	2.285 (0.949; 5.497)	2.246 (1.55; 5.31)
All	6.162 (3.879; 8.81)	6.991 (4.873; 10.163)	4.824 (2.52; 8.63)	5.08 (2.525; 8.408)

Figure 2.

Grand average curves (a) and scalp amplitude mapping (b) of the mean P300 in patients and controls under auditory and visual conditions in the Fz, Cz, and Pz electrodes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

eight brain areas. The ANOVA revealed a significant main effect of "area" ($F_{(7,126)} = 12.52$, $P < 0.001$), corresponding to the well-known anterior-posterior amplitude gradient; amplitudes for the temporal areas were lower than those in other regions. No other effects or interactions were observed. Nevertheless, a trend toward lower P300 amplitude in the visual condition was noted.

Localization of P3b cortical generators with the LORETA method: comparison of the TLE and control groups using SPM.

Figure 3 shows the SPM of two-sample T-statistics for P3b LORETA generators comparing controls and TLE patients in both conditions. In the auditory condition, these maps displayed a significantly lower P3b current density for TLE patients in the right superior temporal gyrus, the left inferior temporal and fusiform gyri, the right inferior frontal gyrus, and the right postcentral gyrus. In the visual condition, this source reduction was noted in the right in-

ferior, middle and superior temporal gyri, the bilateral fusiform gyrus, the right dorsolateral frontal cortex, and the right postcentral gyrus.

Localization of P3b Cortical Generators With the LORETA Method: Individual Analysis Comparing TLE Patients and Controls

As shown in Table IV, the number of generators in the mesiotemporal area was significantly lower ($P < 0.05$) in the patient group (compared with the controls) in the auditory condition, but there was only a trend toward a significant difference in the visual condition.

DISCUSSION

Our main result is a significant decrease in the temporal sources and, to a lesser extent, the frontal sources of P3b

Figure 3.

Statistical parametric maps of two-sample T-statistics of P3b LORETA generators when comparing controls and TLE patients (**a**, auditory condition; **b**, visual condition; $P < 0.001$; cluster size > 10 voxels).

in TLE patients, in both auditory and visual oddball paradigms.

Two uncontrolled methodological factors may have influenced our results: the effects of antiepileptic drugs and the aetiology of the epilepsy.

TABLE IV. Individual occurrences of generators in each region for each condition and group of subjects

Lobes	Auditory/ controls	Visual/ controls	Auditory/ patients	Visual/ patients
External temporal	14	13	13	14
Internal temporal	10	7	2 ^a	3
Parietal	11	11	11	8
Frontal	16	22	20	18
Occipital	8	8	9	9
Total	59	61	53	52

^a Comparison between groups shows a significant diminution of sources in mesiotemporal lobe in auditory condition for patients group ($P < 0.05$).

Antiepileptic drugs (AEDs) can be responsible for cognitive impairment, due to their negative influence on attention, vigilance, and information processing speed [Meador, 2002]. Triantafyllou [1992] showed that AEDs increased the P300 latency and that the effect was greater with multiple drug therapy. As our patients were taking two or even three drugs, this potential impact must therefore be taken into account. However, the less-intense effect of AE drugs in epileptic patients than in healthy controls was reported by Zhou, who showed an improvement in the Trail Making Test and the Wisconsin Card Sorting Test with levetiracetam as an add-on treatment in patients with refractory partial seizures [Zhou et al., 2008]. Likewise, no improvements in performance in attention and RT tests were found after withdrawal of carbamazepine and valproate in epileptic patients [Hessen et al., 2006]. Hence, in patients, the role of AEDs may be less important than that of the disease itself. This hypothesis is supported by Kälviäinen et al.'s observation of difficulties in tasks requiring memory, sustained attention, and flexible mental processing in

~30% of patients with newly diagnosed, untreated, cryptogenic epilepsy [Kalviainen et al., 1992].

The role of the epilepsy's aetiology must also be considered. Drake et al. [1986] showed a longer latency of P3 in partial nonlesional epilepsy. Hippocampal sclerosis (HS) appears to have a specific impact too, since Grunwald showed a bilateral P300 latency increase in this population [Grunwald et al., 1999]. Given that 6 of our 10 patients suffer from HS, the impact of this specific aetiology should not be underestimated. Nevertheless, the HS patients in our study had either focal lesions or none at all. Furthermore, the P300 generators were also modified in some lesion-free regions—an observation which argues against a causal relationship with HS damage only. However, this study did not set out to evaluate the impact of these factors on P300 modifications, and indeed, our data do not enable comparisons between different aetiologies of TLE or different types of treatment.

Our main results concern changes in the location of P300 generators in TLE. We observed a decrease in temporal and frontal generators in TLE patients, whatever the test condition. Our individual analysis revealed that the decrease in temporal lobe generators appears to be more precisely located in mesiotemporal areas: this decrease was significant in the auditory condition (2 vs. 10), and there was a clear trend toward a decrease in the visual condition (three vs. seven). The pathophysiology of attention disorders in TLE patients remains unclear. The temporal lobe could play a role in attention, since Stella and Maciel [2003] observed more attentional disorders in TLE than in other partial epilepsies. Frontal areas (particularly cingulate and prefrontal cortices) have also been implicated in the attentional and working memory processes underlying P3b generation [Nagahama et al., 2001; Ng et al., 2007].

In their neuroanatomical model of attention, Corbetta and Shulman [2002] suggested that two cortical networks are involved in orienting attention to stimuli: a dorsal frontoparietal network involved in goal-driven attention (related to top-down selection of stimuli and responses) and a ventral frontoparietal network (including the temporoparietal and inferior frontal cortex) specialized in the detection of unexpected but relevant stimuli to which attention has to be reoriented. Although standard oddball paradigms are not designed to study the reorientation of spatial attention to environmental relevant stimuli, the rare target can be considered to produce a kind of attention reorientation, which thus engages the ventral frontoparietal network [Corbetta, 2008]. In light of this model, the decrease in P300 generators in both the frontal and temporal areas in our TLE population suggests dysfunction of the ventral fronto-temporo-parietal attention system in TLE. Further studies (using attention tasks specifically designed to engage both attention networks) are needed to investigate this hypothesis but one can legitimately suppose that attention impairment in TLE is related to dysfunction of the ventral network's temporal node.

The changes in P3b generators revealed in our study of TLE may thus suggest that the neuronal networks near to the epileptic zone are disorganized and result in attentional disorders. This disorganization could be directly or indirectly related to the epileptic zone.

One can assume that ictal and interictal epileptic activity can generate local dysfunction and an alteration in cognitive neuronal networks which depend on temporal structures. This could explain the deficit of temporal P300 sources but not the observed difference between TLE patients and controls in terms of generators in the frontal regions.

Another hypothesis involves more complex interference between epileptic networks and normal cognitive networks, which would explain why frontal generators are missing in TLE patients. This is supported by the fact that although attention disorders are rarely isolated in TLE, they are frequently associated with memory and language impairments [Stella and Maciel, 2003]. In such a case, one could imagine that there are abnormal connections between temporal structures and other neuronal networks, rather than a direct impact of the temporal epileptic focus on the P300 wave and disappearance of its temporal generators. These abnormal connections would lead to redeployment of attentional processes into other parts of the attentional networks, in order to compensate for the altered temporal functions [Silvia et al., 2003]. Such connection abnormalities have also been suggested in executive impairment in TLE, in which temporal lobe involvement was thought to result from a lack of connections between the temporal lobe and frontostriatal networks [Drake et al., 2000; Silvia et al., 2003].

An outstanding question relates to the nature of the abnormal connections. Do they result from (i) "interruption" of normal connections between temporal and extratemporal structures (due to direct temporal cortical dysfunction), as proposed by Hermann in an attempt to explain executive dysfunction in TLE or (ii) interference between these normal connections and a more extended, pathological, epileptogenic network connecting the temporal and frontal lobes (allowing the temporal epileptogenic zone to affect the frontal and prefrontal regions), as suggested by Rzezak [Hermann and Seidenberg, 1995; Rzezak et al., 2007]?

In conclusion, this study sheds some light on the pathophysiology of attentional disorders in TLE. Our results suggest that temporal areas are involved in focusing attention on relevant information.

ACKNOWLEDGMENTS

The authors wish to thank David Fraser for helpful comments on the manuscript's English.

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