

## Focal Abnormalities of P3 ERPs Unveiled in Patients with Cortical Lesions and Primary Progressive Aphasia by Average Reference Recordings

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**Summary:** Event related potentials (ERPs) to an auditory odd-ball paradigm were recorded with the linked earlobe reference (LER) and with a computer calculated average reference (AR), excluding the two linked earlobe derivations. The study was performed in 30 patients with lesions of frontal, parietal, occipital cortex, unilateral and bilateral lesions of the medial temporal lobe (MTL), in four patients affected by Primary Progressive Aphasia (PPA) and in 56 age matched controls. Latencies, amplitudes and scalp distribution of the earlier ERP components (P1, N1, P2, N2) were within normal limits for both LER and AR recordings. P3 scalp distribution in patients was normal when LER was used, with the exception of two patients affected by bilateral MTL lesions. When P3 was recorded using AR, the scalp distribution was statistically different from normal distributions in all patients. A negativity, instead of the positive P3 observed in controls, was recorded in patients from leads corresponding to the affected areas. This finding might have clinical applications, and confirms earlier studies suggesting that P3 is generated simultaneously from different cortical areas.

**Key words:** Event Related Potentials; P3; P300; Cortical lesions; Primary progressive aphasia; Average reference.

### Introduction

The origin of the P300 (or P3) component of Event Related Potentials (ERPs) is still controversial, even though many efforts have been made towards the identification of ERP generators (i.e., recording during brain surgery in patients with brain lesions, recording with multiple electrodes and brain mapping techniques or magnetoencephalography - MEG). The extent of the controversy can be exemplified by the discrepancy between MEG findings (Rogers et al. 1991), showing a focal generator of P3 in the Medial Temporal Lobe (MTL) and the results yielded by Spline Laplacian operators (Nunez and Pilgreen 1991) showing that prefrontal areas are the most "coherent cortical source" of this component. Some reports show normal P3 in patients with unilateral or bilateral MTL lesions (Rugg et al. 1991; Onofrij et al. 1992; Polich and Squire 1993), or with lesions of the parietal

lobe (Desmedt and Debecker 1979), while others describe a focal amplitude attenuation of P3 that could be detected in patients with lesions of temporal, or parietal, or frontal lobes (Knight et al. 1980, 1989; McCarthy et al. 1987; Meador et al. 1987).

The present study explores the possibility that the normal P3 observed in patients with severe cortical lesions could depend on the powerful interference of the earlobe or nose reference, and that the detection of P3 abnormality could be improved by Average Reference (AR). A previous study (Neshige and Luders 1988) showed that earlobes record a robust negative activity simultaneous with scalp P3, while the nose reference could be contaminated by the negativity simultaneous with P3 recorded from nasopharynx (Perrault and Picton 1984).

For this reason, we recorded ERPs to an auditory oddball paradigm with the commonly used Linked Earlobe Reference (LER) and with a computer-calculated AR, including only scalp leads, in controls and in 30 patients with unilateral and bilateral lesions of the MTL and with lesions of right (R) or left (L) frontal, temporal, parietal and occipital cortex. LER and AR ERPs were also recorded in four patients affected by Primary Progressive Aphasia - PPA (Mesulam 1982), with functional alterations of the left hemisphere shown by <sup>99m</sup>Tc-hexamethylpropyleneamine (HMPAO) - Single Photon Emission Computerized Tomography - SPECT (Prohovnik et al. 1988; Eagger et al. 1992).

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We hypothesized that, if the P3 is due to a widespread cortical activity (Wood et al. 1980), the AR should enhance the differences recorded between contiguous electrodes placed above active and silent (lesioned) cortical areas. The rationale behind our assumption was provided by a recent critical reevaluation of the effects of earlobe (or extracephalic) vs AR on the topography of scalp potentials. Desmedt et al. (1990 a, b; 1993) showed that the differences observed between LER and AR recorded Somatosensory Evoked Potentials could not be ascribed only to "a mere addition of a constant value to zero baseline", but complex scalp topography modifications were also involved. Contrary to what Lehman and Skrandies (1980, 1984) and Pasqual Marqui and Lehman (1993 a, b) claim, i.e., that topographic analysis is reference free, Desmedt et al. (1990, 1993) suggested that "ghost field potentials" may be seen under certain circumstances.

In the present study we hypothesized that these effects of the AR, described as "perverse" by Desmedt et al. (1990b), might become useful for the analysis of potentials generated by multiple radial dipoles in patients with brain lesions. In case of absence of one (or a group) of generators, the AR, by avoiding the possible interferences of potentials recorded from an active reference sampling the bottom half of the head or "south hemisphere" (i.e., the south pole of several different dipoles), might reduce the field of the residual generators and induce polarity inverted "ghost fields", thus enhancing the differences recorded between contiguous electrodes.

## Materials and Methods

ERPs were recorded from Ag/AgCl disk scalp electrodes, placed on 19 derivations corresponding to Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 positions of the international 10-20 system. Ground was placed at Fpz. Responses were amplified 50,000 times with filters set at 0.2 and 100 Hz and averaged with a dwell time of 2 ms. digitization at 500 Hz. An artifact rejection system was calibrated on 4 supplementary derivations placed on the eyebrows and the inferior orbital ridges and referenced to the linked earlobes. The head volume was represented on a single plane octagonal projection with center at Cz. Color images of electrical distribution were obtained with the classic 4-nearest neighbors (4-NN) interpolation method and were drawn on paper by a microprocessor based Fujitsu dx 2100 cartridge copier which bit mapped at 100 dots/inc. After computing 3860 pixels at any given latency the map program assigned them to appropriate voltage and color steps. The selected gradient of colors was red for positivities, blue for negativities. The "non target" event (i.e., frequent) was a 1000 Hz binaurally presented

pure tone. The "target" stimulus (i.e., rare) was a 2000 Hz binaurally presented pure tone with an occurrence probability of 20%. All subjects were instructed to count the "target" stimuli first aloud, then mentally. Stimulus characteristics, thresholds evaluation and rejection systems are described in detail in previous papers (Onofrij et al. 1991 a, b; 1992 a, b). Twenty artifact free-responses to rare stimuli and 80 responses to frequent stimuli were recorded and averaged separately for each recording subset. Five subsets were repeated and responses to rare and frequent stimuli were stored on floppy disks. This recording procedure was performed in all subjects with LER (Ears were linked digitally following independent acquisition to avoid current shunts) and with the AR including only the 19 scalp derivations. The different ERP components were initially identified on LER recordings: the P3 was identified on the basis of the "operational definition", suggested by other authors (Fabiani et al. 1987), as a positive component recorded with maximal amplitude on vertex derivations, with a distribution gradient decreasing progressively from Cz-Pz to surrounding derivations, without polarity inverted counterparts over the scalp, with a peak latency appearing later than 230 msec. Furthermore P3 was identified by comparing responses to target with responses to non target stimuli: N2 and P3 were only recorded with target stimuli, whereas P1, N1, P2 components were recorded also with non-target stimuli (Goodin 1986). The correspondence between all ERP components recorded with LER and AR was finally checked by comparing responses from midline derivations. Amplitudes were measured from computer calculated baselines, latencies were measured at the peak of the components recorded from vertex derivations.

## Patients, controls and statistical comparison

ERPs were recorded in 30 patients with cortical or cortico-subcortical lesions evidenced by CT scan and/or MRI Toshiba equipment. The age range of patients was 41-65 years; twelve patients were females. The only criteria that excluded ERP recordings in admitted patients were the presence of intracranial hypertension with decreased level of conscience, or the evidence of subarachnoidal bleeding. Five patients had lesions of the frontal and prefrontal lobe. In three of them, the lesions were due to glioblastomas of 3-5 cm<sup>2</sup> (1 left and 2 right sided), measured by means of MRI, 3-4 cm anterior to the sylvian scissure; in one patient the lesion was due to a left sided typical hemorrhage; in the last one the left frontal lobe was atrophied and an arachnoid cyst was seen extending from the prerolandic convolutions to the frontal pole. All patients had minor behavioral disturbances, consisting of lack of concentration and impersistence at

the tests for the attentional matrix.

Five patients, already described in a previous study (Onofrj et al. 1992a), had lesions of both temporal lobes due to temporo-limbic encephalitis, and all presented a severe amnesic syndrome. Five patients had unilateral lesions of the temporal lobe: glioblastoma in two patients (one with a left sided lesion had a fluent aphasia; the other one with a right sided lesion suffered vertigo and a single seizure), and encephalitis in three patients (two right sided), with a complete atrophy evidenced by MRI. Nine patients were affected by unilateral parietal lobe lesions due to cerebrovascular accidents (5 patients, three right sided, described in a previous study: Onofrj et al. 1992b), and to glioblastoma (4 patients, two right sided), 2-3 cm posterior to the sylvian scissure, extending to supramarginal gyri. All had contralateral numbness, and patients with left sided lesions were aphasic. Six patients had lesions of the occipital lobes (four right sided) due to occlusion of the posterior cerebral artery. All had contralateral homonymous hemianopia. Macular sparing was present in two of them. In all patients not affected by glioblastomas a second recording session was repeated 2-12 weeks after the initial recording.

The four patients affected by Primary Progressive Aphasia (PPA), according to the definition by Mesulam (1982) and subsequent descriptions (Kirshner et al. 1987; Lippa et al. 1991; Broussolle et al. 1992), are described hereafter.

Patient 1 (73 years old male) was seen because of progressive development of dysfluency and anomic aphasia. The first CT scan performed one week after the neuropsychological evaluation, showed asymmetry of perisylvian regions with left sided partial atrophy. The first ERP recordings were performed one week after CT scan. The EEG was within normal limits for age matched controls. In 12 months the patient became definitely non fluent and repetition was impossible. MRI and HMPAO-SPECT scan were performed at this time, followed by ERP recording. Six months later the patient became anarthric and comprehension was severely impaired. A new CT scan showed increase of the left perisylvian atrophy. The EEG at that time showed sporadic theta activity on left temporal derivations.

Patient 2 (58 years old female, left dominant left-handed) presented with modest signs of Transcranial Motor Aphasia. The first CT scan showed a right sided temporo-polar meningioma (3 cm) and ventricular asymmetry, with enlargement of the left ventricle and the left sylvian fissure. The first ERP recording was performed at that time. Four months later the meningioma was resected, but language impairment increased. After 8 months the patient was classified as affected by Global Aphasia at the Aachener aphasia test. MRI, SPECT scan

and a series of ERP recordings were then performed. Three subsequent EEG recordings performed within a 4 months interval, showed widespread theta activities.

Patient 3 (74 years old male) had dysfluency with anomia, intermittent corticoreticular multifocal myoclonus of the right arm and leg, and right alien hand symptoms. CT scan and MRI were reported as normal. ERP recordings were performed one week after MRI. The SPECT scan was performed one month later. The EEG showed a posterior rhythmic activity at 8 Hz, and a 5-6 Hz activity prominent on bilateral temporal derivations.

Patient 4 (66 years old female) had progressive development of language disturbances with hesitation and lack of spontaneity. CT scan showed only enlargement of the frontal horn of the left lateral ventricle and widening of the corresponding sylvian fissure. Neuropsychological tests performed in the following two years showed initial impairment of word generation, developing into non-fluent aphasia, with impairment of repetition and preserved language comprehension. The first ERP recordings were carried out at this time, while MRI, SPECT scan and further ERP recordings were performed 18 months after the initial observations.

All the patients selected for the study underwent a comprehensive neuropsychological evaluation as described in detail in previous papers (Onofrj et al. 1991b; 1992 a,b).

ERP measurements in patients were compared with the ones obtained with the same recording methods in 56 age-matched healthy volunteers selected among 160 controls of different ages studied for the normative data of our laboratory (Onofrj et al. 1991a). Patients and controls were divided into three groups: 46-55 y.o. (16 controls), 56-65 y.o. (18 controls) and 66-75 y.o. (20 controls).

ERPs recorded in controls with LER and AR were separately fed into a Nicolet Pathfinder Mega, running a program for Significance Probability Mapping (SPM) based on Z- statistic and t-Statistic (Duffy 1981, 1982). Reference sets of N1, P2, N2 and P3 components mapped at the peak recorded on Fz (N1, P2, N2) or Pz (P3), with AR or LER were obtained in age-matched controls and compared with individual LER or AR maps of single patients (Z statistic). Student's t test statistics SPM was used to compare ERPs recorded with AR vs LER in controls and LER maps in controls vs patients. Z transform values exceeding  $\pm 3$  (99% of certainty level) were considered as indicative of regional abnormality in patients. ANOVA was performed on data recorded, with LER and AR, from each derivation and between data recorded from midline and external derivations, and between controls and patients grouped according to the site of brain lesion.

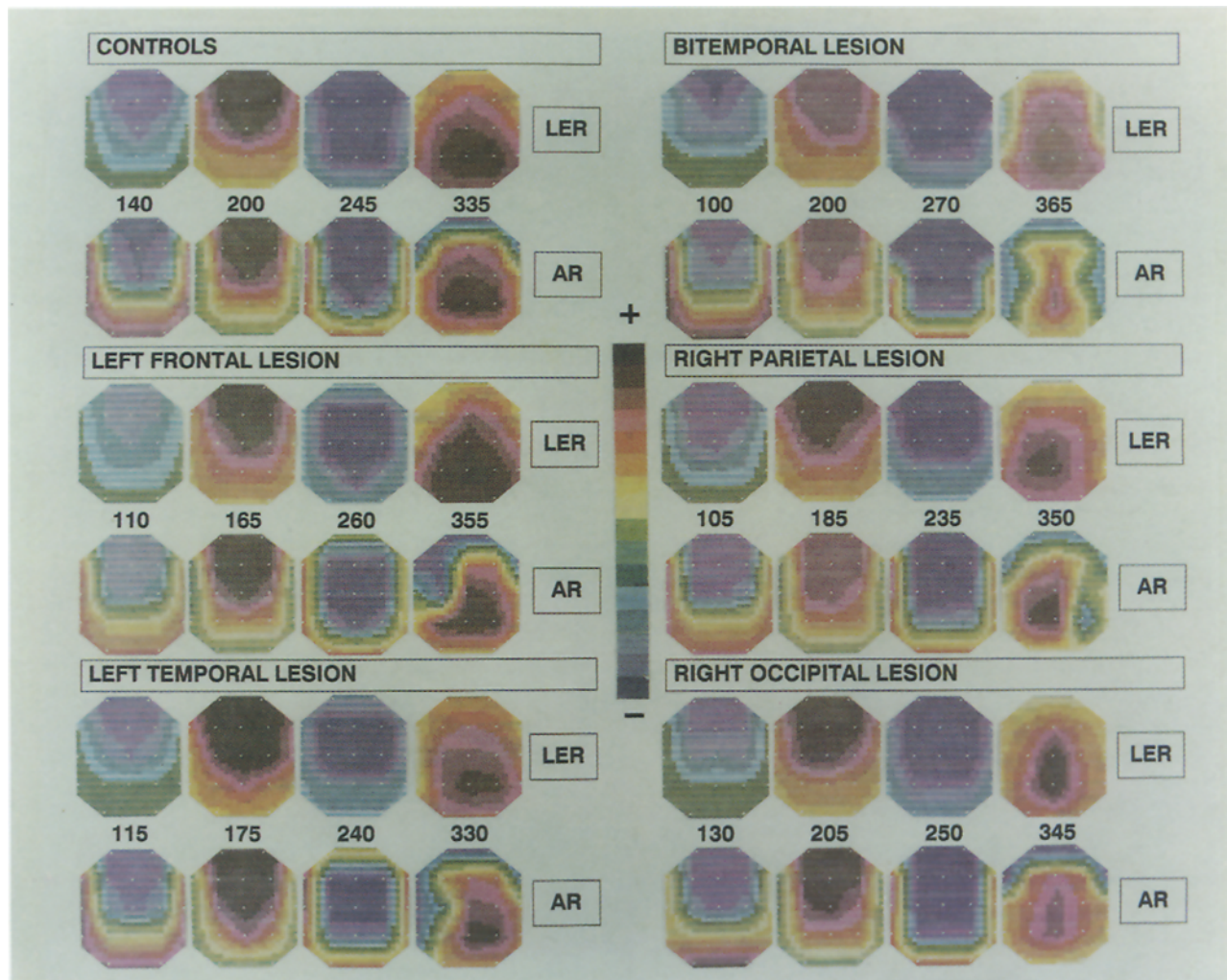


Figure 1. Frozen maps of LER and AR recorded N1, P2, N2 and P3 components of ERPs to target stimuli (corresponding to vertical markers reported on traces of figure 2) in controls and in 5 patients with focal brain lesions. Notice that N2 maps are calculated from the peak of P2, while all other maps are calculated from the baseline. The map calibration is  $24 \mu\text{V}$  for responses obtained with LER reference, while  $12 \mu\text{V}$  for AR (from dark blue-negative to dark red-positive). Notice that the field distribution of the mapped potentials is monopolar when the LER is used. Polarity reversals are instead recorded when AR is used. The area of negative potential recorded with the AR, concomitant with P3, is enhanced and spreads to the derivations overlying lesioned areas in all patients, except the last one with occipital lobe pathology.

## Results

### Controls

With LER, all controls presented ERPs consisting of P1, N1, P2 components to frequent stimuli and of P1, N1, P2, N2, P3 components to rare stimuli. As described in previous reports (Onofrij et al. 1991 a, b; 1992 a, b), all components had a monopolar gradient on the scalp: P1, at 40-90 ms, had the highest amplitude on posterior and mid temporal derivations; N1 was prominent on anterior frontal and central derivations ( $9.6 \pm 5.5 \mu\text{V}$  on Fz); P2 was prominent on frontal derivations ( $10.7 \pm 3.4 \mu\text{V}$  on Fz). The N2 was identified as a separate component following P2 only in 40% of controls, appearing mostly as a negative

notch on the slope of the P2-P3 positivity: if the zero line on the traces (from which N2 maps of figure 1 are computed) was adjusted at the peak of P2, the N2 component appeared as a widespread negativity, prominent on frontal, central and parietal derivations ( $10.1 \pm 2.8 \mu\text{V}$  on Cz).

The P3 was prominent on Cz and Pz, with amplitude decreasing progressively on anterior leads. The descending slope of P3 (or SW, according to McCallum 1987) was prominent on parietal and occipital derivations and a concomitant negativity was recorded from fronto-central leads.

Latencies were:  $133 \pm 12$  ms for N1, in the 46-55 and 56-65 age decades,  $145 \pm 12$  ms in the 66-75 age decade;  $185 \pm 12$  (46-55),  $198 \pm 16$  (56-65),  $206 \pm 13$  (66-75) for P2;  $242 \pm 14$  (46-55),  $245 \pm 14$  (56-65),  $254 \pm 14$  (66-75) for N2;

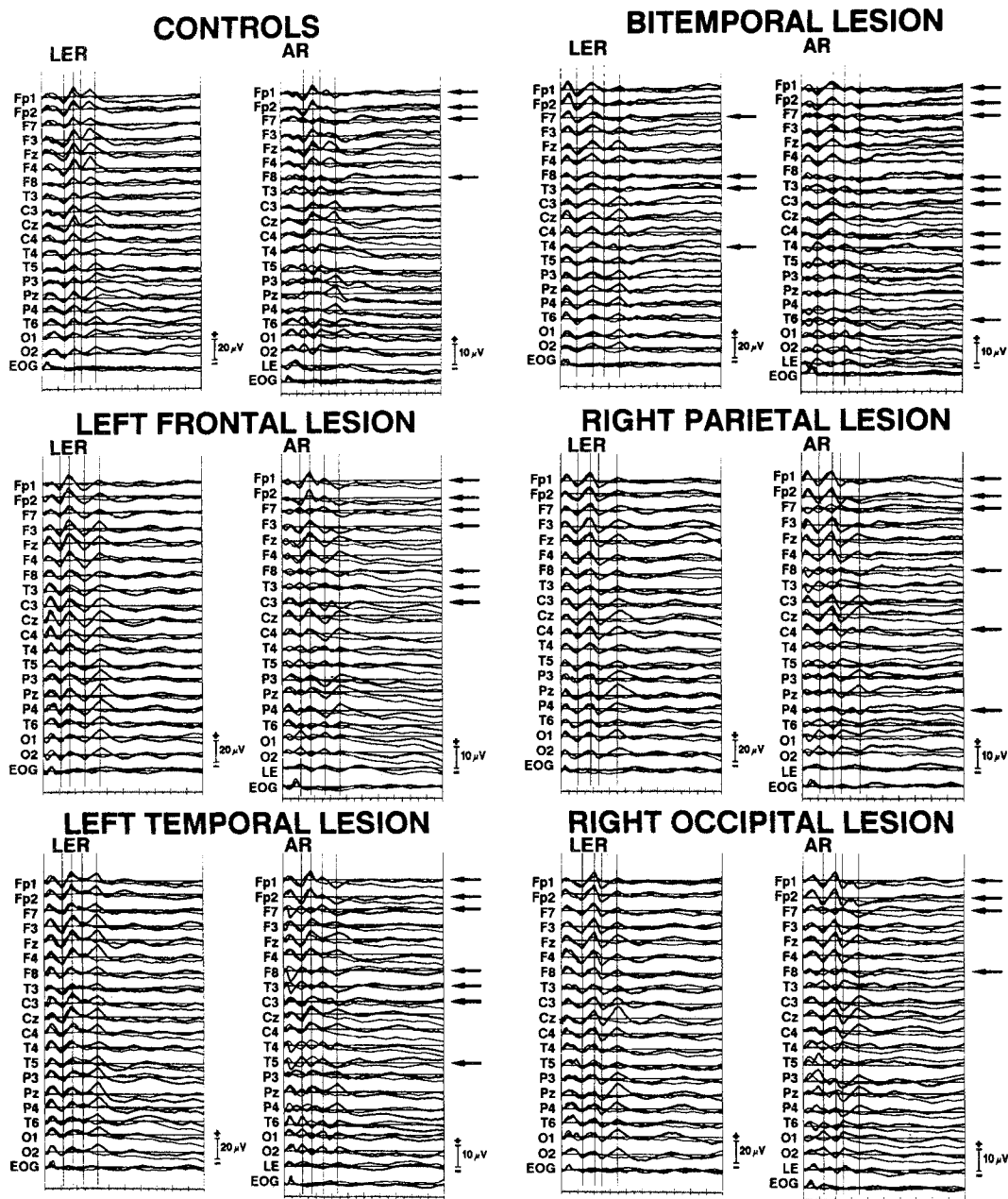


Figure 2. LER and AR responses to target (bold lines) and non target (thin lines) stimuli obtained in 18 controls from 56 to 65 years old (Grand Average), and in 5 patients with cortical lesions. Vertical markers correspond to maps of figure 1. Horizontal arrows aside AR traces indicate the derivations recording negative potentials simultaneously with P3. Notice that only Fp1, Fp2, F7, F8 leads, in controls, record a negativity instead of the P3, while the negativity is recorded in patients also from leads corresponding to the localization of lesions (shown in figure 3). Only in the last patient (occipital lobe lesion) the P3 distribution is the same as in controls. Notice the differential calibration for traces obtained with the two reference systems.

325 ± 19 (46-55), 335 ± 21 (56-65), 342 ± 19 (66-75) for P3.

With AR the same components recorded with LER were recorded from midline frontal, central and parietal leads: peak latencies were overlapping or shifted by ± 2-8 ms (mean 3 ± 1.8), and did not differ statistically in the AR vs. LER comparison of recordings from midline leads. The amplitudes were instead significantly

reduced by AR: amplitude of AR N1 was 4.6 ± 3.2 μV on Fz, of AR P2 was 5.1 ± 2.1 μV on Fz, of AR N2 (zero adjusted) was 4.9 ± 1.6 μV on Cz (LER vs AR: p < 0.05-0.001).

Polarity inverted potentials concomitant with the AR N1, P2 and N2 zero-adjusted were recorded on occipital and lateral derivations (figures 1, 2).

Table I. Mean amplitudes in ( $\mu\text{V}$ ) of P3 recorded with LER and AR in patients and in 56 controls from all scalp electrodes. The symbol (-) indicates that the potential recorded from the corresponding lead with AR is negative. Patients data are grouped according to the site of brain lesions, and are presented as values from derivations ipsilateral or contralateral to the lesion.

**Mean values of P3 amplitude in controls and patients.**

LINKED EARLOBES REFERENCE (LER)											
	Fp1-Fp2	F7-F8	F3-F4	T3-T4	C3-C4	T5-T6	P3-P4	O1-O2	Fz	Cz	Pz
<b>CONTROLS</b>	3.63 (0.85)	3.41 (0.67)	6.31 (1.53)	5.62 (1.05)	9.65 (2.57)	8.38 (1.45)	11.24 (2.91)	9.57 (1.75)	8.13 (2.28)	11.23 (3.36)	12.92 (3.74)
<b>FRONTAL</b>											
<b>ipsi</b>	3.29 (0.36)	3.24 (0.52)	5.27 (0.30)	4.76 (0.26)	8.68 (2.32)	8.14 (0.52)	11.28 (2.38)	11.23 (1.32)	8.56 (0.52)	11.85 (2.66)	12.86 (2.64)
<b>contra</b>	3.35 (0.64)	3.27 (0.38)	6.34 (0.58)	5.53 (0.60)	9.66 (2.22)	8.12 (0.22)	11.32 (2.46)	11.36 (1.12)			
<b>TEMPORAL</b>											
<b>ipsi</b>	4.88 (0.58)	3.23 (0.54)	6.53 (0.82)	4.12 (0.74)	8.07 (2.36)	4.67 (0.72)	9.17 (2.04)	8.16 (1.96)	8.03 (1.54)	9.87 (2.36)	12.14 (2.24)
<b>contra</b>	4.84 (0.42)	3.28 (0.68)	6.58 (0.94)	5.18 (0.82)	9.64 (2.38)	5.59 (1.24)	11.33 (1.98)	8.23 (1.74)			
<b>BITEMPORAL</b>	1.59 (0.58)	-1.73 (0.38)	4.83 (0.52)	-2.98 (0.58)	6.42 (1.52)	5.30 (0.68)	7.39 (1.68)	6.49 (1.00)	6.86 (1.26)	8.04 (2.30)	9.79 (1.80)
<b>PARIETAL</b>											
<b>ipsi</b>	2.73 (1.14)	3.28 (0.58)	6.48 (1.60)	4.96 (1.04)	8.96 (2.26)	5.93 (2.92)	9.12 (2.76)	8.12 (1.10)	7.43 (1.22)	9.73 (2.94)	11.32 (3.36)
<b>contra</b>	2.65 (1.10)	3.24 (0.44)	6.43 (1.68)	5.21 (0.92)	9.72 (2.34)	7.57 (1.20)	11.35 (2.88)	8.15 (0.94)			
<b>OCCIPITAL</b>											
<b>ipsi</b>	2.15 (0.22)	3.25 (0.46)	5.85 (0.72)	4.38 (0.80)	7.15 (2.00)	5.93 (1.18)	8.52 (2.68)	5.08 (1.86)	8.14 (1.86)	11.30 (2.48)	12.91 (2.98)
<b>contra</b>	2.18 (0.36)	3.28 (0.62)	5.78 (0.64)	4.24 (0.82)	7.58 (2.18)	4.32 (1.26)	8.38 (2.00)	6.33 (1.72)			
<b>P.P.A.</b>											
<b>ipsi</b>	4.23 (0.69)	3.32 (0.83)	6.13 (1.33)	5.73 (1.15)	6.23 (2.24)	6.58 (1.39)	8.32 (2.63)	5.29 (1.47)	6.78 (2.10)	9.25 (3.13)	10.78 (3.31)
<b>contra</b>	4.16 (0.73)	3.70 (0.86)	6.24 (1.39)	5.97 (1.23)	6.41 (2.31)	6.93 (1.34)	8.65 (2.54)	5.51 (1.38)			
AVERAGE REFERENCE (AR)											
	Fp1-Fp2	F7-F8	F3-F4	T3-T4	C3-C4	T5-T6	P3-P4	O1-O2	Fz	Cz	Pz
<b>CONTROLS</b>	-6.84 (1.30)	-6.45 (1.22)	3.77 (1.55)	2.24 (1.05)	5.75 (2.08)	2.37 (0.75)	6.94 (2.84)	2.62 (0.90)	4.72 (2.06)	6.80 (2.46)	7.65 (3.12)
<b>FRONTAL</b>											
<b>ipsi</b>	-7.68 (2.00)	-7.42 (2.10)	-7.10 (1.08)	-2.95 (1.00)	-7.12 (1.48)	1.95 (0.44)	5.90 (1.76)	2.94 (1.80)	3.65 (1.26)	6.92 (1.26)	7.83 (1.92)
<b>contra</b>	-7.54 (1.08)	-5.56 (0.90)	3.52 (1.00)	2.90 (0.76)	-5.24 (2.06)	2.90 (0.22)	6.92 (1.64)	2.96 (1.64)			
<b>TEMPORAL</b>											
<b>ipsi</b>	-6.96 (0.98)	-7.62 (1.82)	2.68 (0.50)	-6.62 (1.42)	-3.18 (0.80)	-6.50 (1.32)	2.16 (0.40)	2.86 (1.58)	3.99 (0.76)	5.38 (1.00)	6.61 (2.34)
<b>contra</b>	-6.89 (1.00)	-5.84 (0.64)	3.14 (0.82)	2.10 (0.90)	5.26 (1.70)	2.92 (0.98)	6.14 (0.32)	2.78 (1.92)			
<b>BITEMPORAL</b>	-5.24 (1.12)	-5.44 (1.36)	2.08 (0.60)	-5.80 (2.04)	-2.90 (1.40)	-5.16 (1.88)	1.94 (0.50)	1.85 (1.44)	2.24 (1.02)	3.93 (1.72)	5.54 (2.02)
<b>PARIETAL</b>											
<b>ipsi</b>	-5.36 (0.60)	-5.98 (2.00)	2.86 (0.48)	1.06 (1.70)	-1.93 (0.62)	0.94 (1.72)	-5.12 (0.36)	0.94 (2.00)	2.97 (0.80)	5.84 (1.34)	6.98 (2.14)
<b>contra</b>	-5.28 (0.40)	-5.32 (1.60)	2.90 (0.34)	1.83 (0.90)	5.52 (1.30)	1.16 (0.84)	6.42 (0.80)	1.93 (1.94)			
<b>OCCIPITAL</b>											
<b>ipsi</b>	-6.38 (1.46)	-6.84 (2.12)	3.90 (0.90)	1.15 (0.60)	4.16 (1.80)	1.82 (0.84)	4.10 (2.76)	1.50 (1.82)	4.16 (0.52)	5.65 (1.60)	5.98 (1.88)
<b>contra</b>	-6.52 (1.30)	-6.67 (2.28)	3.87 (0.86)	1.87 (0.40)	4.77 (1.96)	2.06 (1.60)	4.96 (2.48)	1.56 (1.66)			
<b>P.P.A.</b>											
<b>ipsi</b>	-2.68 (0.81)	-3.38 (4.15)	1.43 (2.76)	-5.13 (0.41)	-3.62 (2.46)	-5.35 (1.16)	-4.06 (1.76)	0.74 (0.93)	2.38 (1.12)	3.37 (1.14)	3.96 (1.94)
<b>contra</b>	-2.53 (0.76)	-2.93 (1.32)	3.72 (1.13)	1.15 (1.87)	4.48 (1.82)	2.73 (1.35)	3.43 (1.32)	3.86 (1.38)			

The amplitudes of these polarity inverted counterparts were  $2.3 \pm 1.2 \mu\text{V}$  from F7-8,  $4.5 \pm 2.7 \mu\text{V}$  from T3-4-5-6 and O1-2 corresponding to N1;  $1.9 \pm 0.8 \mu\text{V}$  from F7-8,  $1.6 \pm 0.5 \mu\text{V}$  from T3-4-5-6 and O1-2 corresponding to P2;  $2.7 \pm 1.4 \mu\text{V}$  from F7-8,  $4.9 \pm 2.2 \mu\text{V}$  from T3-4-5-6 and O1-2 corresponding to N2 (zero adjusted).

The AR recorded P3 had, as the other components, similar latency and waveshape as LER recorded P3 on midline (Fz-Cz-Pz) and internal F3, F4, C3, C4, P3, P4, O1, O2 derivations, while a negativity, with a peak shifted by  $8 \pm 6 \text{ ms}$ , was recorded from Fp1, Fp2, F7, F8. The descending limb of P3 (SW) was paralleled by an anterior negativity, as in LER recordings. The amplitudes of LER and AR recorded ERPs were not statistically different in control groups of the three decades. Mean amplitudes of P3 recorded with LER and AR, inclusive of the 56 controls are reported in table I.

The scalp distributions of ERP components were not age dependent: monopolar gradients of N1 P2 N2 P3 were consistently observed in LER recordings of all controls, and polarity inverted counterparts of the N1 P2 N2 P3 recorded from central and internal leads, were consistently recorded with AR, as reported above in all controls. SPM based on Student t test statistic, did not show differences between age groups of the LER recorded or AR recorded N1 P2 N2 P3 components mapped at their peak. LER vs AR comparisons showed highly significant differences between recording from F7, F8, T3, T4, T5, T6 (N1); F7, F8, O1, O2, T3, T4 (P2); Fp1, Fp2, T5, T6 (N2), Fp1, Fp2, F7, F8 (P3) ( $p < 0.001$ ).

#### Patients

Figure 1 shows a comparison of frozen maps of N1, P2,

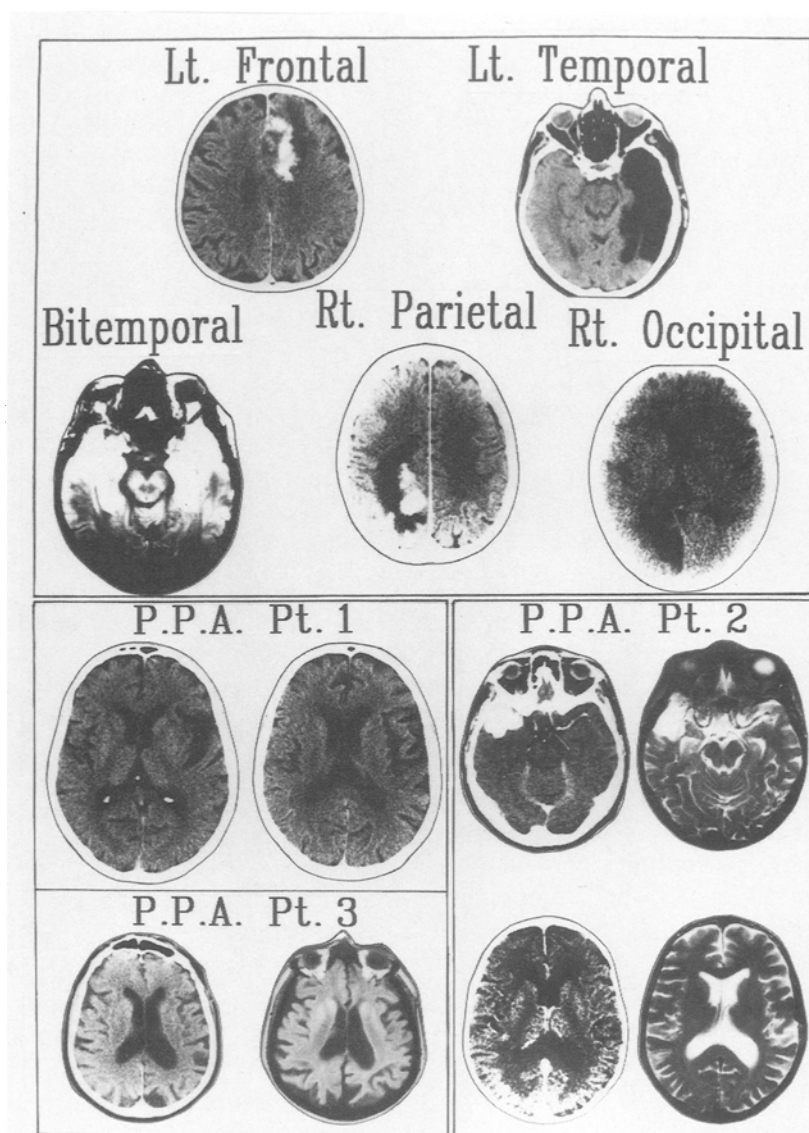


Figure 3. Top half: CT scans and MRI of the five patients (46-51 years old) with cortical brain lesions, whose maps and traces are reported in figures 1 and 2. Notice the hyperdense area due to hemorrhage in the first patient, the lucency of the left temporal lobe secondary to encephalitis in the second patient, the bilateral increased MRI signal areas of the third patient with encephalitic involvement of the two temporal lobes, the right parietal lobe hemorrhage surrounded by a lucency area due to perilesional oedema in the fourth patient, and the ischemic lesion in the right occipital lobe in the last patient. Bottom half: CT scans or MRI in the three PPA patients whose ERP recordings and HMPAO SPECT are shown in figure 4. The CT scans of patient 1 show atrophy of the left perisylvian region. The CT scan and MRI of patient 2 show left perisylvian atrophy and enlargement of the left ventricle. Notice that the patient had, at first admission, a right temporo-polar meningioma, later excised, as shown by the MRI on the right. As described in history, the early dysphasic symptoms were initially attributed to the meningioma, but the enlargement of the left ventricle, the AR P3 distribution, and the HMPAO SPECT shown in figure 4, appropriately addressed the diagnosis of PPA. The CT scan and MRI of patient 3 show ventricular asymmetry, with dilatation on the left, and diffuse cortical atrophy, prevalent in the left hemisphere. Notice that the right of the scalp is on the right in maps, whereas the left side of CT scan or MRI is on the right of pictures.

N2, P3 components, obtained at the peak of each component on midline derivations, in the 56-65 years old matched control group (GA), and in age matched patients affected by lesions of Lt-Frontal, Lt-Temporal,

Bitemporal, Rt-Parietal and Rt-Occipital lobe. The corresponding traces, with responses to non target stimuli, are shown in figure 2. MRI and CT scans of the 5 patients with brain lesions are shown in figure 3.

With LER, the same distributions of P1, N1, P2, N2 and P3 as in controls were observed in patients with lesions of the right or left temporal, parietal, frontal and occipital lobes. The peak latency and amplitude of N1, P2, N2, P3 ERP components recorded from the different derivations were within normal limits. Table I reports the mean amplitudes of LER P3 recorded in patients with different localization of lesions.

SPM based on Z statistics (Duffy 1981, 1982) showed that the distributions of LER recorded components (N1-P2-N2-P3) were within normal limits in all patients but two affected by bilateral temporal lobe lesions. As reported in a previous study (Onofrij et al. 1992b), P3 recorded from F7, F8, T3, T4 in these two patients had smaller amplitudes than the control mean minus 3 SDs (Standard Deviations); Z transform values were in the two patient -3.6, -3.1 for F7-8; -4.4, -4.7, -3.1, -3.9 for T3-4.

SPM based on Student's t-test statistics was also performed between LER maps of the control groups and of the group including all patients, the resultant Z and SPM statistics were not significant. No differences were seen (i.e., F7 F8, T3 T4 leads,  $t = 0.447, 0.321$ ;  $p = 0.657, 0.442$ ).

In AR ERPs of patients the latencies, amplitudes and distributions of P1, N1, P2, N2 were within the limits established in controls. Polarity inverted potentials concomitant with N1, P2 and zero-adjusted N2 were recorded from frontal, temporal and occipital derivations also in patients affected by lesions of frontal, temporal, parietal and occipital lobes (figures 1, 2). Z transform values resulting from SPM (single patient vs. controls) were within  $\pm 2$  for P1, N1, P2, N2 components.

The distribution of P3 was instead abnormal when the AR was used (figures 1, 2; table I, II). Enhancement and spreading of the fronto-temporal negativity, concomitant with the P3 recorded from midline, was observed in all our patients with lesions of frontal, temporal and parietal lobes. The negativity spread ipsilaterally to the side of the lesion, to scalp derivations corresponding to the underlying lesions: i.e., to ipsilateral frontal and central (F3 or F4, C3 or C4) leads in patients with frontal lobe pathology, to T3-T4 and T5-T6 leads in patients with bilateral temporal lobe lesions, to T3 or T4, T5 or T6 leads in patients with unilateral temporal lobe lesions, to posterior central (C3 or C4) and ipsilateral parietal (P3 or P4) leads in all patients with parietal lobe lesions. As shown in figure 1, 2 and in table I, these derivations recorded in all controls positive potentials instead of the negativity recorded in patients. In patients with occipital lobe pathology, P3 ERPs had the same distribution and the polarity gradients as in controls.

Table I reports the mean amplitude values of the P3, or of the corresponding negativity, recorded from each scalp lead with AR, in all patients. A comparison of results reported in table I shows that the AR recorded

negativity, concomitant with P3, had higher amplitude in F7, F8 derivations in patients with lesions of frontal and temporal lobes than in controls (ANOVA:  $p < 0.001$ ), and that in controls frontal, central, parietal and temporal leads recorded only positive P3 potentials (table I). SPM based on Z statistics (table II), showed that AR P3 maps were significantly different in patients as compared to controls, and that high Z transform scores corresponded to leads recording the abnormal negativity (i.e., to frontal leads in patients with frontal lesions, to temporal leads in patients with temporal lesions, to parietal leads in patients with parietal lesions). Mean Z values, with ranges, of AR P3 SPM are reported in the bottom half of table II, grouped according to the localization of brain lesions (i.e., frontal, temporal, bitemporal, parietal, occipital).

### Primary Progressive Aphasia

In the four patients with PPA ERP recordings performed with LER showed a normal sequence of components, with normal latency and normal distribution. When ERP recordings were performed with AR, the distribution of N1, P2, N2 components was within normal limits. P3 distribution was instead markedly abnormal, and a negativity, instead of the positive P3, was recorded from T3, T5, P3 in patients 1 and 2, and from T3, C3, T5, P3 in patients 3 and 4. Furthermore the amplitude of the P3 recorded from Fz, Cz, Pz was smaller than the mean value of controls minus 2 SD in all PPA patients.

Figure 4 shows LER and AR ERP recordings in PPA patients 1, 2 and 3 and a comparison with the HMPAO SPECT findings. Table I reports mean amplitudes values and table II reports the average Z scores obtained in this group of patients by Z statistics SPM, and confirms the different distribution of the P3 evidenced by maps. MRI or CT scans of the three patients are shown in the lower half of figure 3. ERPs recording of patients 2, shown in figure 4, were obtained in the first recording session (described in history), prior to the SPECT supported diagnosis of PPA.

### Discussion

As expected on the basis of previous reports (Desmedt et al. 1990 a; Rodin et al. 1991) the distribution of ERPs in controls is sensibly modified by the use of the AR, which induces phase shifts of components recorded from the different leads. In fact, ERPs recorded from midline and parietal derivations (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz) are surrounded by areas of inverted polarity, while in LER recordings all components have a monopolar gradient on the scalp (figures 1, 2). ERPs recorded from midline had however similar waveshapes and peak latencies in the two recording conditions (LER vs. AR). In all our



Table II. Mean Z transform values (and ranges in parentheses) resulting from the comparison of AR P3 scalp distribution in single patients vs age-matched controls. Notice that Z-values of AR recordings are significant (i.e., >3) in correspondence of leads recording a negativity in place of the P3. Z-values were below 3 for LER recordings, as described in the text.

**SPM Z transform values of AR P3 comparison patients vs controls.**

	Fp1-Fp2	F7-F8	F3-F4	T3-T4	C3-C4	T5-T6	P3-P4	O1-O2	Fz	Cz	Pz
<b>FRONTAL</b>											
<b>ipsi</b>	0.36	-0.07	<b>-7.58</b>	<b>-4.32</b>	<b>-6.47</b>	0.61	0.43	0.72	-0.05	0.45	0.43
	(-0.12/0.48)	(-0.72/0.02)	(-8.26/-7.32)	(-5.02/-4.21)	(-7.21/-5.32)	(-0.13/1.34)	(-0.76/1.01)	(0.15/0.91)	(-0.75/0.08)	(-0.31/0.91)	(-0.32/0.94)
<b>contra</b>	0.28	0.02	0.48	0.48	0.46	0.31	0.01	0.61			
	(-0.14/0.36)	(-0.72/-0.07)	(-0.24/0.79)	(-0.13/0.77)	(-0.13/0.64)	(-0.28/0.57)	(-0.35/1.43)	(0.26/0.82)			
<b>TEMPORAL</b>											
<b>ipsi</b>	1.62	1.51	0.67	<b>-7.36</b>	<b>-4.64</b>	<b>-9.12</b>	-1.38	1.53	0.06	0.36	0.15
	(-0.03/1.95)	(-0.27/1.94)	(-1.29/0.06)	(-8.82/-6.42)	(-5.16/-3.64)	(-10.59/-8.12)	(-2.15/-1.34)	(-1.02/2.13)	(-0.84/0.45)	(-0.99/0.72)	(-0.83/0.67)
<b>contra</b>	1.64	1.24	0.06	0.13	1.07	1.52	0.67	1.32			
	(0.21/1.92)	(0.41/2.21)	(-0.45/0.67)	(-1.36/0.28)	(-0.83/1.93)	(-1.19/1.87)	(-0.61/0.95)	(-0.77/1.84)			
<b>BITEMPORAL</b>	1.58	1.42	-1.83	<b>-7.37</b>	<b>-5.38</b>	<b>-9.89</b>	-1.83	-1.28	-0.96	-0.61	-0.66
	(-0.74/3.36)	(-0.72/3.67)	(-3.27/-0.82)	(-8.78/-5.27)	(-5.51/-3.84)	(-10.85/-8.26)	(-2.67/-1.31)	(-3.31/0.72)	(-4.04/0.01)	(-1.97/-0.14)	(-3.64/-0.04)
<b>PARIETAL</b>											
<b>ipsi</b>	2.57	1.88	-2.32	-1.46	<b>-4.49</b>	-2.29	<b>-5.26</b>	-2.16	-0.04	-0.16	-0.02
	(1.78/2.88)	(1.51/2.77)	(-3.14/-1.13)	(-2.17/-1.01)	(-4.98/-3.99)	(-3.59/-2.24)	(-6.33/-3.62)	(-2.39/-1.23)	(-1.51/0.41)	(-1.42/0.47)	(-1.21/0.46)
<b>contra</b>	2.67	1.84	-2.07	-1.02	0.55	-1.03	0.31	-0.65			
	(1.71/2.83)	(1.46/2.75)	(-2.92/-1.29)	(-1.51/-0.34)	(-1.06/0.91)	(-1.94/-0.58)	(-0.94/0.69)	(-1.58/-0.31)			
<b>OCCIPITAL</b>											
<b>ipsi</b>	0.72	-1.21	-0.68	-1.02	-1.08	-2.54	-0.92	-1.81	-0.16	-0.11	-0.39
	(-0.11/1.46)	(-1.68/0.98)	(-1.32/-0.01)	(-1.64/-0.22)	(-2.14/-0.18)	(-3.29/-0.28)	(-2.13/-0.46)	(-2.62/-0.08)	(-1.51/1.01)	(-1.84/0.62)	(-1.79/0.19)
<b>contra</b>	0.63	0.41	-0.45	-0.84	-0.65	-0.46	-0.48	-1.69			
	(-0.35/1.24)	(-0.38/1.01)	(-1.36/-0.01)	(-1.12/-0.73)	(-2.12/-0.11)	(-1.18/1.37)	(-1.83/0.05)	(-2.27/-0.31)			
<b>P.P.A.</b>											
<b>ipsi</b>	2.46	1.97	-2.18	<b>-7.22</b>	<b>-3.42</b>	<b>-7.47</b>	<b>-5.92</b>	-2.28	-1.09	-1.21	-1.14
	(0.44/2.87)	(-0.12/2.16)	(-3.51/-1.15)	(-8.93/-6.42)	(-4.33/-2.28)	(-8.07/-6.51)	(-6.39/-4.15)	(-3.09/-1.75)	(-1.84/-0.75)	(-1.97/0.12)	(-1.68/-0.86)
<b>contra</b>	2.52	1.85	0.37	-1.01	-0.54	1.45	-0.59	1.08			
	(0.69/2.81)	(-0.24/2.08)	(-0.14/0.59)	(-2.13/-0.12)	(-1.81/1.04)	(0.12/1.98)	(-1.04/1.10)	(0.48/1.96)			

patients the distributions of P1, N1, P2, N2 components recorded with the LER and the AR were not different from those of the same components recorded in controls. An abnormal distribution of the P3 was instead observed when the AR was used, while LER P3 recordings, in the same patients, were always inside normal limits (figures 1, 2, 4; table I, II). When the AR was used, the abnormality of the P3 recorded from electrodes corresponding to the affected areas consisted of a waveshape distortion: a negativity appeared instead of the positive P3 recorded in controls and in patients normal cortical areas. Only in patients with lesions of the occipital lobe the P3 distribution was within normal limits, both in AR and LER recordings (figures 1, 2). In PPA, AR recordings consistently showed an asymmetry of P3 topography, because of the negativity appearing in traces obtained from left frontal, central and parietal leads. The SPECT scan performed in these patients showed definite functional abnormalities of the left hemisphere, supporting the AR-ERPs findings.

SPM based on Z statistics showed that the negativities

recorded with AR from scalp leads overlying altered cortical areas were incompatible (Z-transform values from 3.62 to 10.85) with normal distributions: SPM of LER P3 recordings did not show these relevant differences. The different statistical categorization of patient's maps with AR, in comparison with LER, supports the hypotheses by Desmedt et al. (1990 a, b; 1993) that the use of AR vs. other cranial or extracephalic reference does not simply change the offset level of maps. Desmedt et al. (1990), in a study on "cognitive" SEP components, showed that when signals obtained from the earlobes were subtracted from AR recordings, obtained from scalp leads, results did not add up to reproduce the amplitude and distributions obtained with LER. Similarly in our controls and patients, AR and LER recordings do not differ only because of the addition of an algebraic constant (table I).

In the present study, we hypothesized that the "perverse" effect of an AR, i.e., the exclusion at the "south hemisphere" of the head model, might become useful in the evaluation of cortical lesions, because AR might en-

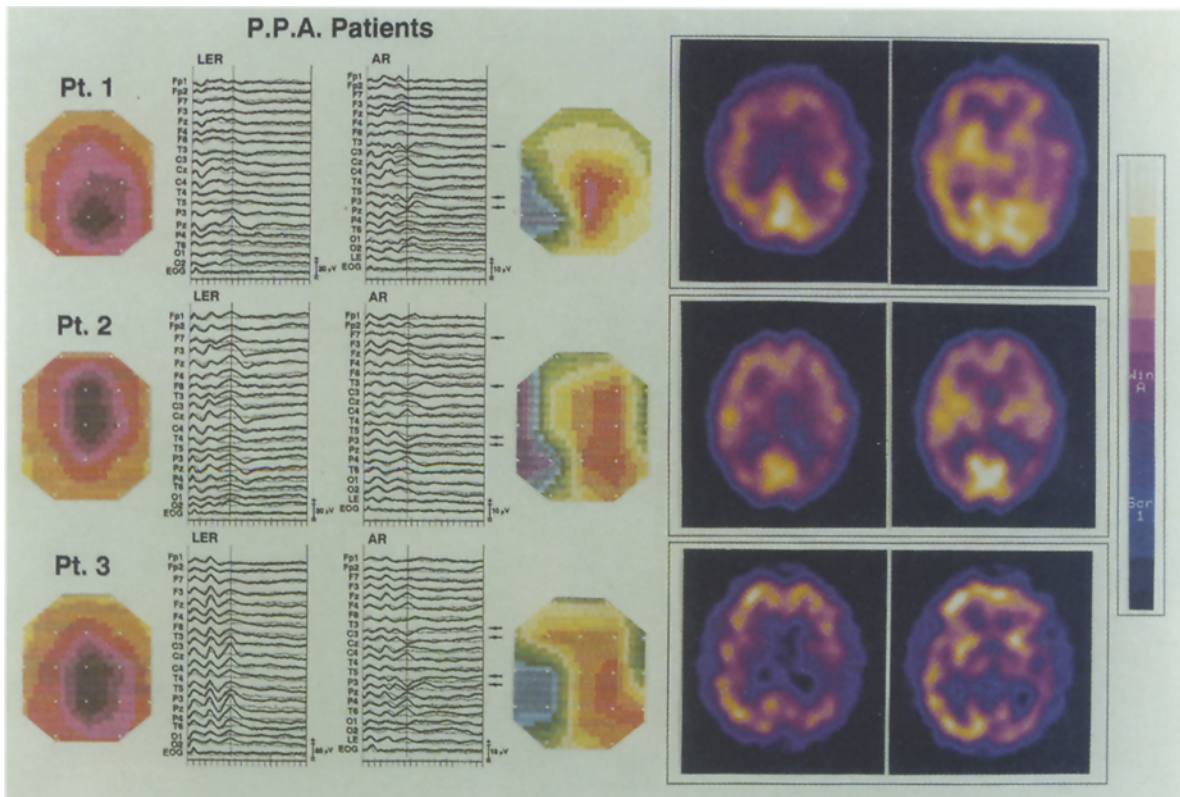


Figure 4. LER and AR P3 maps and ERPs traces in comparison with HMPAO SPECT of the three patients affected by PPA, whose MRI and CT scans are shown in the bottom half of figure 3. Notice that the peak latency of LER and AR P3 is normal. Frozen maps and traces show that the distribution of LER recorded P3 is normal in all patient. AR recordings show that a negativity, instead of the positive component recorded in controls, appears on left central and temporo-parietal derivations (marked by arrows as in figure 2). Compare AR P3 recordings with HM PAO-SPECT shown on the right. The tracer captation is decreased in all patients in the left hemisphere.

hance the difference between contiguous electrodes placed above active and silent cortical areas. A LER or nose reference could instead record the negative pole of P3 potentials (Neshige and Luders 1988; Perrault and Picton 1984) arising from other generators, and the resulting recordings would show widespread P3 components. In order to validate our assumption, the linked earlobes were purposely omitted from our calculations of the AR: we could thus avoid the interference coming from the negative potential with same latency of the P3, recorded by earlobe derivations and previously described by Neshige and Luders (1988), and we could avoid the known dampening of hemispheric asymmetries induced by the earlobes, that can provide a low resistance path (Nunez 1981).

Our study suggests that separate cortical generators from frontal, temporal and parietal areas contribute to the origin of the scalp recorded P3. Whereas it could be argued that AR-P3 distributions observed in patients with cortical lesions may depend on alterations of the

volume conduction from a deep intracranial generator, due to different conduction properties of neoplastic or hemorrhagic masses. Our findings in PPA patients make this argument less tenable, since the degenerative lesions of PPA seem mostly restricted to cortical structures (Mesulam 1982; Kirshner et al. 1987; Lippa et al. 1991; Broussolle et al. 1992).

The effect of an active reference can explain the reason why previous studies performed with linked earlobe reference or nose references produced controversial results showing widespread (Karniski and Blair 1989) or focal generators (Halgren et al. 1986; Smith et al. 1990) of P3, and an abnormal (Knight et al. 1980; Halgren et al. 1986; McCarthy et al. 1987; Meador et al. 1987; Knight et al. 1989) or normal (Desmedt and Debecker 1979; Halgren et al. 1986; Stapleton et al. 1987; Rugg et al. 1991; Polich and Squire 1993) distribution of the P3 in patients with localized cortical lesions. The negativity recorded instead of the P3 in patients can be interpreted as a "ghost field potential" and, in keeping with the description by

Desmedt et al. (1990b), its presence indicates that some P3 generators are radially oriented toward the scalp. The radial orientation explains also the reason why MEG recordings (blind to radial sources) evidenced only tangential sources of P3 in temporal lobes (Rogers et al. 1991).

In conclusion, our findings might suggest further clinical applications of P3 recordings, that are, so far, confined to the evaluation of peak latencies in patients affected by dementia (Pfefferbaum et al. 1984; Goodin and Aminoff 1986; Neshige et al. 1988). Obviously we are not suggesting a role of P3 in localizing anatomical lesions, since we cannot predict any development of P3 recording techniques that will equal the standards provided by MRI or CT scans. But we suggest that ERP recordings, if performed with appropriate techniques, may be able to show focal functional alterations of areas apparently normal (or approximately normal) at MRI or CT scan.

Further studies, performed with an increased number of derivations and possibly with Spline Laplacian operators instead of the simple referential or AR systems, might be able to define precisely the relationship between the extent of cortical lesions and the abnormality of P3 distributions, and may corroborate or invalidate our assumptions.

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