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P300 amplitude as a possible correlate of frontal degeneration in schizophrenia

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Abstract

The existence of neurodegeneration is a debated issue in schizophrenia research. The P300 component of event-related electrical potentials (ERP) has been related to the different degree of damage to gray and white matter. This study explores the possible relationship between P300 amplitude and/or latency and the existence of degenerative processes in schizophrenia, by assessing its correlation with volume of sulcal CSF and duration of illness, as transversal indicators of neurodegeneration.

Nineteen patients (14 males, 5 females) and 13 controls (6 males, 7 females) were studied with MRI and electrophysiological records (P300). The possible influence of sex and age at the time of the exploration was statistically controlled in both groups.

The results show a significant negative correlation between P300 amplitude and prefrontal CSF volume in the patient group. A lower though still significant correlation was also found between P300 amplitude and duration of illness, whereas no correlation was found in the control group. These results support the hypothesis that P300 amplitude may be interpreted as a marker of neurodegeneration in schizophrenia.

Keywords: Event-related electrical potentials; Neurodegeneration; P300 amplitude; Schizophrenia

1. Introduction

The auditory P300 event-related potential (ERP) has been claimed to be abnormal in schizophrenia (Blackwood, 2000). Some studies report a decrease in P300 amplitude (Ford et al., 1999; Kawasaki et al., 1997), while others report a P300 latency increase (O'Donnell et al., 1995; Coburn et al., 1998; Laurent et al., 1999). These results have not been unanimously replicated: amplitude reduction may be affected by the referential method (Strik et al., 1994), and latency increase has failed to be reported on several occasions (Ford et al., 1994). On the other hand, changes in P300 parameters can also depend on a number of factors which could partially

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explain the diverging results (Turetsky et al., 1998; Frodl-Bauch et al., 1999b; Gerez and Tello, 1995). One of these factors could be the possible existence of neurodegeneration in a subgroup of patients, as in Alzheimer's disease where neurodegeneration is known to be associated with alterations in this ERP (Knott et al., 1999).

Some longitudinal studies in schizophrenia suggest the existence of a cerebral degenerative process in, at least, some patients (Nair et al., 1997; DeLisi et al., 1997; Gur et al., 1998). Neurodegeneration might be more pronounced in the frontal lobes, according to recent findings (Gur et al., 1998; Rapoport et al., 1999). It is well known that, in addition to temporal lobe structures, frontal lobes contribute at least partially to P300 generation, even considering that its highest amplitude shows a parietal maximum (for a review and recent data, see Tarkka and Stokic, 1998). Thus, any process affecting frontal regions could also potentially modify P300 parameters.

As described by Woods (1998), sulcal CSF is a good indicator of cerebral tissue loss after skull fissures close. If neurodegeneration occurs in schizophrenia, a correlation might be expected between P300 parameters and neurodegeneration markers, as relative sulcal CSF, gray matter volumes or demographic variables (duration of illness, age of onset).

The present study tries to establish the relationship between transversal correlates of neurodegeneration in schizophrenia (hemispheric and prefrontal sulcal CSF volume) and P300 parameters. Our hypothesis is that patients with a higher likelihood of frontal degeneration (i.e. higher relative CSF values) would show lower P300 amplitude and/or larger latency. We have also explored the possibility of a negative correlation between P300 parameters and duration of illness, that would also bear out the existence of neurodegenerative processes in schizophrenia.

2. Materials and methods

2.1. Subjects

Nineteen patients (five women) were studied. Mean age was 29.8 years (range 18–42). They were diagnosed with paranoid schizophrenia, according to DSM-IV (American Psychiatric Association, 1994). Twelve patients had been treated previously (mean duration of illness 10.98 years, S.D. 9.87), whereas the other seven were recent-onset patients who had never been treated before (mean duration of illness 1.34 years, S.D. 0.69). They were all outpatients from a psychiatric clinic in Madrid. Mean duration of illness was 8.6 years (range 0.5–19).

All patients were receiving haloperidol (10 mg/day) at the moment of P300 exploration. To keep the differences in pharmacological conditions to a minimum, all patients previously on another treatment were switched to haloperidol at least 4 weeks before EEG examination.

Exclusion criteria were: presence of neurological illness, past history of drug or alcohol abuse, cranial trauma with loss of consciousness, other Axis I psychiatric processes or treatment with other drugs with known potential effect on central nervous system.

Thirteen normal subjects (seven women) receiving no medication and with no history of psychiatric illness were included in the study as a control group. Mean age was 31.4 years (range 18–51). Exclusion criteria for this control group were the same as above. All patients and controls were right-hand dominant.

2.2. Electrophysiological recordings

Standard odd-ball paradigm was used to elicit the P300 component. Subjects were exposed to binaural tone-bursts (duration 50 ms, rise and fall time 10 ms, and intensity 90 dB). A total of 200 tones (80% at 1000 Hz and 20% at 2000 Hz) were presented, and subjects were instructed to mentally count the number of infrequent 2000 Hz tones, considered as targets.

Records were obtained from P3, P4, F3 and F4 electrodes according to the International 10–20 System.

The electrodes selected here appear to be the most appropriate to obtain substantial P300 values and group differences. Classically, the P300 component peaks maximally over parieto-central regions, and this is the reason why either Pz or Cz leads are used most often and are the electrodes recommended to record P300 (Polich, 1991). Paradoxically, however, main neural generators for this component are located within the temporal regions, maybe within the

hippocampi, but also within other areas of the temporal lobes (Frodl-Bauch et al., 1999a, b). As has been mentioned, frontal areas also contribute to P300 latency and amplitude (Courchesne et al., 1987; Tarkka and Stokic, 1998). However, the orientation of the P300 generators within these areas determines the parietal maximum, since their positive poles are oriented towards parietal regions (Frodl-Bauch et al., 1999b; Tarkka and Stokic, 1998). As a consequence of this orientation, the P300 signal is usually weaker at temporal electrodes than that at parietal electrodes. Accordingly, when temporal regions are affected (as is the case in schizophrenia), a parietal location of the electrodes seems appropriate to explore this damage by means of P300.

The reference was algebraically linked earlobes. Vertical electro-oculogram (EOG) was obtained in the right eye (bottom to top) and horizontal EOG in the lateral orbital rim (left to right). Sampling rate was 250 Hz, and the band-pass was 0.3–50 Hz. Epochs of 1-s duration were recorded, starting 200 ms before stimulus onset. To eliminate defective records, each epoch was visually checked. Separate averages were calculated for target and non-target stimuli, after correcting EOG artifacts by means of the Semlitsch et al. (1986) method. P300 was defined as the most positive peak at each electrode between 250 and 500 ms after target stimulus onset. Two parameters, P300 amplitude and latency, were calculated for each electrode.

2.3. Magnetic resonance imaging

Image measurements were performed on MRI studies acquired on a Philips Gyroscan 1.5T scanner using a gradient echo T1-weighted 3D sequence, with the following parameters: matrix size 256×256, pixel size 0.9×0.9 mm (FOV about 256 mm), flip angle 30°, echo time 4.6 ms, slice thickness ranging from 1.1 to 1.5 mm. T2-weighted sequences were also acquired for verification and other clinical purposes (Turbo-Spin Echo, turbo factor 15, echo time 120 ms, matrix size 256×256, slice thickness 5.5 mm.)

A slight effect of field inhomogeneity was observed in the MRI images. This problem was not corrected, since no measurable alterations of the estimated volumes were observed and there is no algorithm universally accepted to fix the problem without biasing image contrast.

MR images were processed in the Imaging Laboratory of the Hospital General 'Gregorio Marañón', using locally developed software that incorporates a variety of image processing and quantification tools (Benito et al., 1999; Desco et al., 1999). To perform the volumetric measurements of the different structures, a two-step procedure was adopted, as follows.

In the first stage, cerebral tissue was segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) by using an automatic method (Ashburner and Friston, 1997) that has been widely tested and is currently included as a standard processing tool in the SPM (Statistical Parametric Mapping) program. The algorithm classifies all MR pixels into four tissue types: 'gray matter', 'white matter', 'CSF' and 'other tissues' according to a clustering algorithm that starts from a priori probability templates. This automatic tissue segmentation produces a set of three 3D volume masks, one for each tissue type, for each patient. All these automatically generated 3D masks were checked for inconsistencies and corrected whenever necessary by an experienced radiologist, blind to the diagnosis.

The second stage defines the actual regions of interest to be measured by superimposing the CSF 3D mask onto each subject's Talairach coordinate system. Basically, Talairach normalization (Talairach and Tournoux, 1988) consists of a piecewise linear transformation and tessellation of each brain into a grid of 1056 cells. The image processing software is able to automatically calculate the 3D grid upon manual selection of the anterior and posterior commissures (AC and PC) and the mid-sagittal plane, on MR images where scalp and cerebellum had been previously removed. Once the grid is calculated and adjusted to each particular brain, the regions of interest are defined as sets of cells, according to the Talairach Atlas. ROI volume is then calculated as the portion of the CSF mask contained in the set of cells that define the ROI (Benito et al., 1999; Desco et al., 1999).

'Prefrontal lobe' ROI was defined as the part of the frontal lobe above the AC–PC plane and anterior to an imaginary plane orthogonal to the AC–PC plane through the AC. 'Whole hemisphere' ROI was defined as the total brain volume above the AC–PC

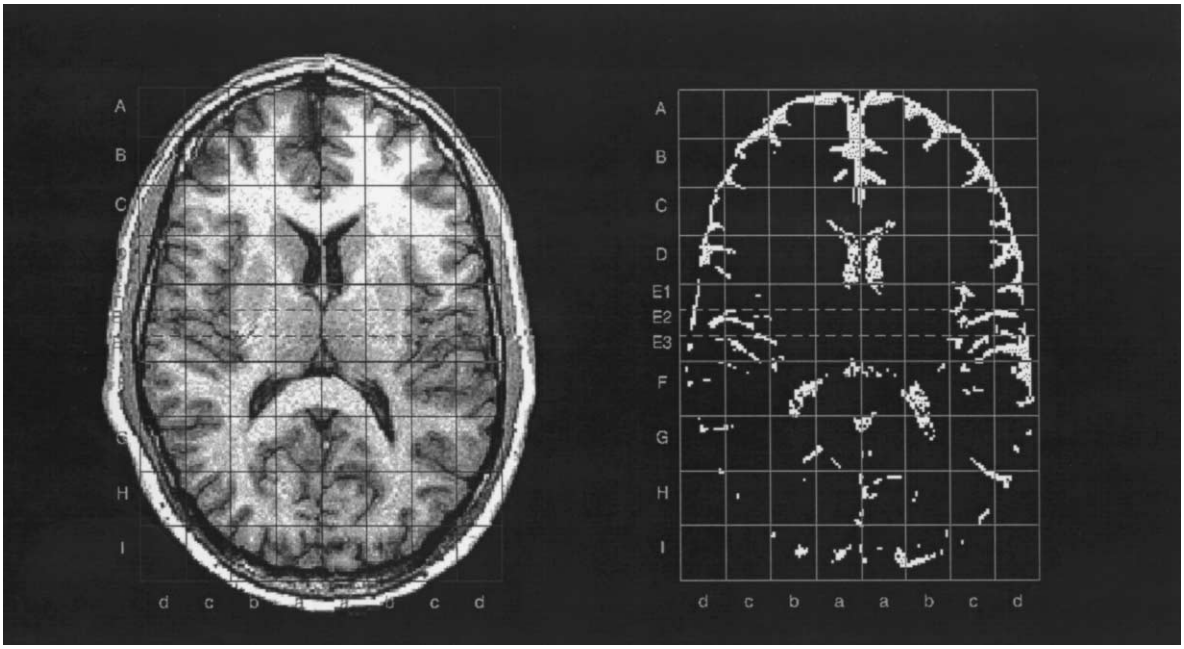

Fig. 1. Left: axial view of an MRI showing its adjusted Talairach grid. Right: the LCR mask resulting from the automatic segmentation method. Registration of the LCR mask with its corresponding Talairach grid enables regional volumetric estimations (see text for more details).

plane. The hemispheric region below the AC–PC plane was not considered since CSF in that area is mainly associated to other encephalic structures, such as the cerebellum. All ROIs were studied separately for the left and right sides.

Reliability of the segmentation procedure was assessed by using two repeated scans of two subjects selected at random. SPM segmentation and Talairach normalization (Fig. 1) were performed on each study, recording the percent difference between repetitions for each volume variable. Mean error values ranged from 1.1% to 9.3% for left and right prefrontal and hemispheric CSF, and from 4.7% to 8.4% for GM tissue.

Validity of the Talairach-based procedure as an automatic segmentation tool suitable for schizophrenia research has been also shown by Andreasen et al. (1996). Interobserver repeatability is excellent, since minimal operator intervention is required.

2.4. Statistics

Relationship between variables was assessed by calculating partial correlation coefficients controlling for the effect of age and sex. Pairwise comparisons, performed separately for each group, were as follows:

1. P300 parameters vs illness duration.
2. P300 parameters vs relative volumes of CSF, white and gray matter.
3. Illness duration vs relative volumes of CSF, white and gray matter.

Student's *t* tests were used to assess the significance of the differences between patient and control groups. Variable distribution was normalized through logarithmic transformation when the Kolmogorov–Smirnov test showed deviation from normality.

3. Results

P300 amplitude, measured over the right parietal electrode, showed a significant negative correlation with duration of illness ($r = -0.65$; $P < 0.01$). Age of onset was also significantly related to P300 amplitude at the right parietal electrode ($r = 0.498$; $P = 0.04$).

Table 1
Significant correlations between P300 parameters and volume measurements

P300 parameter	Structure[a]	*r* value	*P* <
Amplitude at P3	Right PFCSF	−0.63	0.05
Amplitude at P3	Right PFGM	0.62	0.05
Amplitude at P3	Right WHGM	0.70	0.005
Amplitude at P4	Right PFCSF	−0.73	0.005
Amplitude at P4	Right WHCSF	−0.68	0.005
Amplitude at P4	Left WHCSF	−0.57	0.05
Amplitude at P4	Right PFGM	0.57	0.05
Amplitude at P4	Right WHGM	0.66	0.01
Amplitude at P4	Left WHGM	0.54	0.05

[a] PF = prefrontal; WH = whole hemisphere; CSF = sulcal cerebrospinal fluid; GM = gray matter.

In the patient group, left and right P300 amplitude at parietal sites (P3 and P4) showed a consistent number of significant correlations or trends with measurements of CSF volumes (Table 1). This correlation pattern is consistent with the hypothesis that higher degrees of neurodegeneration (measured by the CSF volume) may correspond to smaller P300 amplitudes (Fig. 2). The same hypothesis is supported by the fact that all significant correlations between P300 parameters and relative volume of gray matter were positive (Table 2).

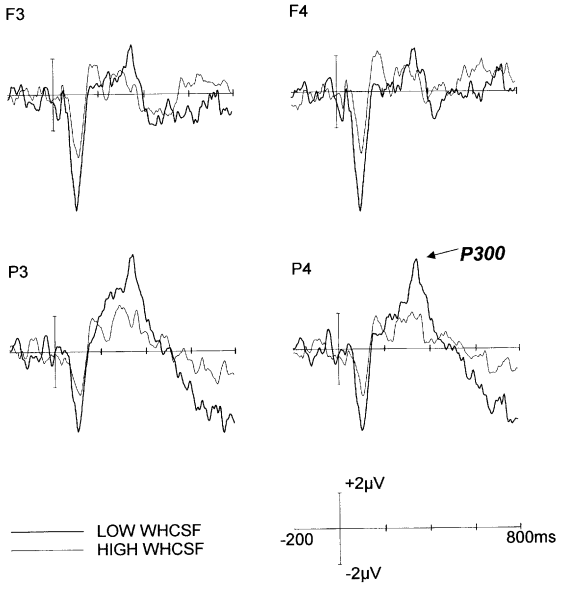

Fig. 2. ERPs representing P300 values for the subjects with high whole-hemisphere CSF values (high WHCSF, dotted line) and the subjects with low WHCSF values (plain line). The former group, which presents a higher degree of neurodegeneration as compared with the latter, also presents a notably reduced P300 amplitude.

Table 2
Significant correlations between volume measurements and duration of illness

Structure[a]	*r* value	*P* <
Right PFCSF	0.57	0.05
Right WHCSF	0.54	0.05
Right PFGM	−0.61	0.05
Left PFGM	−0.59	0.05
Right WHGM	−0.59	0.05
Right PFGM	−0.55	0.05

[a] PF = prefrontal; WH = whole hemisphere; CSF = sulcal cerebrospinal fluid; GM = gray matter.

No significant correlations were found between P300 amplitude or latency and relative volume of white matter.

On the other hand, all measurements of CSF volumes, particularly those concerning prefrontal lobes, were correlated with illness duration (Table 2).

In the control group, no significant correlations were obtained between neurodegeneration indicators (gray matter and CSF volumes) and P300 parameters.

Prefrontal and whole hemisphere CSF volumes were significantly larger in the schizophrenic group than in the control group, whereas prefrontal and whole hemisphere gray matter volumes were significantly smaller in the schizophrenic than in the control group (Table 3). P300 amplitude was also signifi-

Table 3
Significant differences in volume measurements of CSF and gray matter between schizophrenic and control groups

Structure[a]	*t* value	*P* <
Left PFCSF	4.29	0.000
Right PFCSF	4.73	0.000
Left WHCSF	2.72	0.01
Right WHCSF	3.38	0.005
Left PFGM	−4.11	0.000
Right PFGM	−3.02	0.005
Left WHGM	−4.61	0.000
Right WHGM	−5.71	0.000

[a] PF = prefrontal; WH = whole hemisphere; CSF = sulcal cerebrospinal fluid; GM = gray matter.

Table 4
Significant differences in P300 amplitude measures between schizophrenic and control groups

P300 amplitude at	*t* value	*P*<
F3	−4.6	0.000
F4	−4.46	0.000
P3	−5.6	0.000
P4	−7.3	0.000

cantly smaller in the schizophrenic than in the control group at all the electrode sites, whereas P300 latency was not significantly different between groups (Table 4).

4. Discussion

We have found evidence of an association between P300 amplitude and sulcal CSF volumes, mainly on the right side. This result supports the initial hypothesis relating the decrease in P300 amplitude with the existence of degenerative process in schizophrenic patients as suggested by the increase in cortical CSF.

It should be emphasized that a decrease in P300 amplitude in schizophrenia is not necessarily caused by neurodegeneration. Other mechanisms, such as neurodevelopmental factors (Hegerl et al., 1995; Murray et al., 1992), might also be involved in the reduction of P300 amplitude. The finding of significant correlations with duration of illness, even when controlling for age, may derive from the relationship between the progression of relative sulcal CSF and the P300 amplitude decrease.

We observed a reduction of the gray matter as well an increase of the CSF volume in schizophrenic patients with respect to control subjects. This increase has been previously reported in first-break patients (Nopoulos et al., 1995) and related to neurodegeneration in the brain of schizophrenics (Woods 1998). This process may continue after illness onset (DeLisi, 1999). Our results are thus in accordance with the hypothesis of a neurodegenerative progression in at least a subgroup of patients (Nair et al., 1997; DeLisi et al., 1997; Gur et al., 1998; Rapoport et al., 1999).

On the other hand, our results do not necessarily imply that all schizophrenic patients undergo a progressive loss of tissue reflected by an increase of relative CSF volume. Rather, our study suggests that whenever this progression in CSF volume occurs, it is associated with a progressive decrease in P300 amplitude.

The weak correlation observed between illness duration and P300 amplitude, contrasts with the strong relationships between P300 and sulcal CSF. This contrast may reflect the pooling of patients showing recent cerebral degeneration and patients with a static defect (probably developmental). Following this argument, patients with larger age-corrected CSF values could be those with higher probability of cerebral degeneration (Woods, 1998). Of course, this speculative possibility should be explored in studies with larger sample sizes.

Among the factors that could interact with duration of illness producing a differential degree of neurodegeneration, we should mention age at the onset of illness. Olichney et al. (1998) reported smaller P300 amplitudes in a group of early-onset patients when compared with patients with late onset. Our results also support the existence of a relationship between age of onset and P300 amplitude. Conceivably, this may indicate that early-onset patients would undergo more severe degeneration than the late-onset group.

Our sample included previously treated and drug-naive patients. It has been reported that medication does not play a determinant role in the reduction of P300 amplitude in schizophrenia. Pfefferbaum et al. (1989) reported reduced amplitudes in both medicated and non-medicated patients, although the latencies were more prolonged in medicated patients. In a follow-up study, Coburn et al. (1998) reported that previously reduced amplitudes of P300 increased after treatment with neuroleptics, therefore disregarding a neuroleptic-induced P300 amplitude decrease in schizophrenia. Hirayasu et al. (1998) reported significant decreases in P300 amplitude with respect to healthy controls in both neuroleptic-naïve and drug free patients, thus providing for additional support to the finding of reduced amplitude of P300 in schizophrenia, regardless of medication. Therefore, medication may be reasonably discarded as a distorting factor of our findings.

Other evidence that P300 parameters could be interpreted as an index of neurodegeneration has been previously reported. For instance, Hegerl et al. (1995) found a higher risk for tardive dyskinesia (TD)

in patients with smaller P300 amplitudes. These authors pointed out that TD has been related to structural brain abnormalities such as cortical atrophy (i.e. neurodegeneration).

On the other hand, the studies of Egan et al. (1994) and McCarley et al. (1993) pointed to a relationship between cortical atrophy on temporal lobe structures and P300 parameters. A more recent report by Havermans et al. (1999), focusing only on temporal structures, failed to confirm such a relationship between P300 amplitude and temporal lobe cortical atrophy in schizophrenia, although a lack of resolution prevented the segmentation of gray and white matter in this study. However, these studies did not consider the progression of cortical atrophy.

The lack of association between white matter volume and P300, together with the significant correlation between gray matter and CSF volumes with P300, strongly suggest that the possible neurodegeneration is due to a selective loss of gray matter.

In the control group, no correlations were obtained between neurodegeneration indicators (gray matter and CSF volumes) and P300 parameters. This finding also bears out our interpretation of the relationship between P300 amplitude and neurodegeneration as a specific finding in schizophrenia, therefore reflecting pathological features of the illness.

It is also interesting to note that only a relationship between P300 amplitude and neurodegeneration was detected in the patients group, disregarding latency as a main factor. It has been stated that P300 amplitude reduction is the most replicable biological marker of schizophrenia (Ford, 1999), even considering other more complex techniques such as functional MRI.

If P300 amplitude reduction is so consistent in schizophrenia and could also be considered a good marker of neurodegeneration, this event-related potential (ERP) may play an important role in future research on schizophrenia.

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