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Dorsolateral prefrontal cortex contribution to abnormalities of the P300 component of the event-related potential in schizophrenia

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Abstract

Abnormalities of the P300 component of the event-related potential are a common finding in schizophrenia. It seems possible that the dysfunction in the dorsolateral prefrontal (DLPF) region that has been reported in schizophrenia contributes to this finding. To explore this possibility, we calculated the relationship between, on the one hand, P300 latency and amplitude and, on the other hand, the degree of DLPF atrophy (as measured by magnetic resonance imaging) and metabolic activity during an attentional task (as measured by positron emission tomography). Seventeen schizophrenia patients with a brief duration of illness and minimal exposition to treatment and 25 healthy controls were studied. Patients exhibited significantly lower metabolic activity in the DLPF region, but they did not show cortical atrophy. P300 amplitude was also significantly reduced in the schizophrenia patients compared with the controls. Right DLPF region metabolic activity correlated significantly with P300 amplitude. This pattern remained after partialling out the influence of activity in the hippocampus, superior temporal gyrus and parietal lobe. It is therefore suggested that the prefrontal cortex could be implicated in the P300 amplitude reduction in schizophrenia.

Keywords: Schizophrenia; Evoked potentials; Dorsolateral prefrontal cortex; Magnetic resonance imaging; Positron emission tomography

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1. Introduction

Among the most prominent abnormalities of the event-related potential (ERP) that have been reported in schizophrenia are a reduction of the amplitude of the P300 component (Ford, 1999) and increased P300 latency (Coburn et al., 1998; Weir et al., 1998). The regional brain correlates of these ERP abnormalities in schizophrenia are not yet completely understood.

A distributed network including frontal, parietal and temporal structures has been related to the generation of P300 in normal subjects (Pae et al., 2003; Soltani et al., 2000; Winterer et al., 2001). Of particular interest in schizophrenia research is the contribution of the prefrontal region to this component. Evidence comes from activation studies (Winterer et al., 2001; Linden et al., 1999) and from studies in patients with frontal brain injuries (Knight and Chao, 1984; Wirsen et al., 1992). It is conceivable that a prefrontal dysfunction could contribute to P300 abnormalities in schizophrenia, since both alterations have been reported in the literature. Both functional (Rubin et al., 1991; Andreasen et al., 1992; Volz et al., 1999) and anatomical (Shenton et al., 2001) prefrontal alterations have been widely reported in schizophrenia. A possible relationship between prefrontal alterations and the P300 component is suggested by the inverse correlation between inferior left prefrontal perfusion and P300 amplitude in schizophrenia that was reported by Blackwood et al. (1999). Furthermore, diminished verbal fluency—a possible index of prefrontal dysfunction—predicts a lower P300 amplitude in schizophrenia (Souza et al., 1995).

Consequently, it could be hypothesized that there is a relationship between P300 abnormalities and prefrontal dysfunction in schizophrenia. To test this possibility, it would be critical to study a population free of the confounders of chronicity and medication because P300 amplitude may decrease as a consequence of progressive structural changes in schizophrenia (O'Donnell et al., 1995; Mathalon et al., 2000b; Martin-Loeches et al., 2001). An effect of antipsychotic medication on prefrontal activity has also been reported by some investigators (Bartlett et al., 1994; Holcomb et al., 1996).

Accordingly, we studied dorsolateral prefrontal (DLPF) anatomy and activity together with P300 amplitude and latency in a sample of patients with a short duration of illness who received limited exposure to psychotropic medication. Their data have been compared with those from a group of controls. The hypothesized association between DLPF alterations and P300 parameters does not indicate that other regions could not also contribute to the amplitude decrease or latency delay of the P300 in schizophrenia. Indeed, it seems likely that other regions are implicated, since temporal (McCarley et al., 1993; Winterer et al., 2001) and limbic (Egan et al., 1994) abnormalities have been linked to P300 abnormalities in schizophrenia. Thus, our hypothesis was not that single dysfunction (i.e., a DLPF deficit) would explain the expected reduction in P300 amplitude in schizophrenia. Rather, our aim was to study the functional consequences of DLPF dysfunction in schizophrenia through an examination of the relation of that dysfunction with P300 parameters, which are linked to attention and short-term memory—prefrontal-based functions.

2. Methods

2.1. Subjects

Electrophysiological recordings were obtained in 17 schizophrenia patients (7 women) and 25 healthy controls (10 women). All patients and 16 controls (7 women; mean age 27.2 years, S.D. 5.4) were also studied with positron emission tomography (PET) and magnetic resonance imaging (MRI). All of the patients and control subjects were right-handed. As a requirement for patients to be included in the study, illness duration was always less than 5 years. The group of patients included nine "neuroleptic-naïve" first episode cases with duration of illness of less than 6 months, and five other cases with no previous treatment, together with three previously treated cases with illness duration shorter than 5 years.

Clinical data were available in the follow-up period to confirm (or disconfirm) the diagnosis of schizophrenia. Two psychiatrists (VM and JS) prospectively confirmed the diagnosis using a semi-structured interview (Structured Clinical Interview for DSM-IV, clinical version) as well as information obtained from relatives and clinical staff. Accordingly, it was confirmed that all the patients included in the study met the criteria for schizophrenia, despite their short duration of illness. Six other cases were eliminated and

are not included with the 17 patients whose data are reported here because their first psychotic episodes did not evolve into schizophrenia. Table 1 presents clinical information derived from the Positive and Negative Syndrome Scale, which was administered at the time of admission.

The 14 previously untreated patients received brief treatment with antipsychotic medication 2 days before the PET study. This procedure enabled us to include a representative sample of subjects and to avoid the selection bias of selecting only those cases able to cooperate in neuroimaging procedures in an unmedicated state. All of the patients received the same treatment (haloperidol, 10 mg/day); the same medication was given to the three previously medicated patients. No medication was given for the 12 h that preceded the PET study, in order to minimize the possible influence on metabolic measurements.

Table 1
Mean values in patients and controls

	Patients	Controls
Number	17	25
Age, mean (S.D.)	24.73 years (4.06)	30.48 years (8.29)
Illness duration, mean (S.D.)	2.26 years (2.11)	
Socioeconomic status, mean (S.D.)	2.2 (1.5)	2.3 (0.9)
Education, mean (S.D.)	11.4 years (4.3)	12.0 years (4.9)
Positive symptoms, mean (S.D.)	22.77 (7.75)	
Negative symptoms, mean (S.D.)	18.00 (10.77)	
Total symptoms, mean (S.D.)	89.1 (26.62)	
P300 amplitude, mean (S.D.)[#]	8.94 μV (6.60)	11.67 μV (2.66)
P300 latency, mean (S.D.)	312.47 ms (40.81)	321.44 ms (42.43)
Left DLPF volume, mean (S.D.)	32.82 cc (5.30)	34.56 cc (3.94)
Right DLPF volume, mean (S.D.)	32.96 cc (5.63)	35.66 cc (4.28)

Volumetric residuals correspond to the deviation from expected values in controls. Activity values correspond to measurements relative to total cortex (see text). Data on metabolic activity and anatomical volumes for controls were obtained in a subgroup of 18 subjects (see text).
[#]$P=0.06$.

After full information was provided about the study, written informed consent was obtained from the control subjects and from the patients and their families. The investigational boards of the participating centers approved the study protocol. Exclusion criteria were neurological illness, MRI findings judged to have neurological relevance by a radiologist blind to diagnosis, history of cranial trauma with loss of consciousness, substance abuse during the last 3 years (except for caffeine or nicotine), other Axis I psychiatric diagnoses or psychiatric treatment, or any current treatment with CNS-active medications. Current substance abuse was ruled out by urine analysis.

2.2. Electrophysiological recordings

To elicit the P300 component, the standard oddball paradigm was used. Accordingly, subjects heard 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 the subjects were instructed to silently count the number of 2000-Hz tones, which were designated as targets. Electroencephalographic activity was recorded from 16 scalp sites, according to the 10/20 International System. We planned to use P300 data obtained at the mid-line parietal (Pz) site, as P300 is usually larger at this location (Courchesne et al., 1987). It was also planned to use P3, P4, F3 and F4 to corroborate the findings obtained at Pz. The reference was algebraically linked earlobes; that is, the original left earlobe recording reference was re-referenced based on the arithmetic mean of the left and right earlobes. The electrooculogram (EOG) was obtained from below versus above the right eye (vertical EOG) and the left versus right lateral orbital rim (horizontal EOG). The sampling rate was 250 Hz, and the band-pass filter was 0.3–50 Hz. Recorded epochs were 1 s in duration, starting 200 ms before stimulus onset. To eliminate epochs with artifacts, each epoch was visually checked. Separate averages were performed for the target and the non-target stimuli, after correction of EOG artifacts by means of the method proposed by Semlitsch et al. (1986). The minimum number of sweeps per subject accepted for averaging was 20 for the target stimuli (maximum = 40). The P300 was defined as the most positive peak at each electrode between 250 and 500 ms after target stimulus onset.

Two parameters, the P300 amplitude and latency, were calculated. The P300 study was done on the same day as the PET study.

2.3. Imaging procedures

2.3.1. MRI acquisition

Magnetic resonance studies were acquired on a Philips Gyroscan 1.5-Tesla scanner using a gradient echo T1-weighted 3D sequence (matrix size = 256 × 256, pixel size = 0.9 × 0.9 mm, flip angle = 30°, echo time = 4.6 ms, slice thickness ranging from 1.1 to 1.5 mm) and a T2-weighted sequence (Turbo-Spin Echo, turbo factor = 15, echo time = 120 ms, matrix size = 256 × 256, slice thickness = 5.5 mm).

2.3.2. PET acquisition

PET studies were obtained in a Siemens Ecat 47 tomograph, 20 min after the injection of 370 MBq of ^{18}F-deoxyglucose (FDG). Matrix size was 256 × 256 × 61; slice thickness was 2.6 mm. During tracer uptake, the patients performed a contingent Continuous Performance Test (Rosvold et al., 1956). Subjects were instructed to push a button if 'T' immediately followed the letter 'L', as presented on a computer screen. The interstimulus interval was 1 s. After the placement of an intravenous line for FDG administration, the subject began the task, which was divided into four blocks of 5 min each, with 1 min of rest between the two blocks. The FDG was administered 1 min after the initiation of the task.

2.3.3. Segmentation

To perform the metabolic and volumetric measurements of the different brain structures, a two-step procedure was adopted (Desco et al., 2001). The first step involved editing the MRI to remove skull and extracranial tissue, registration of PET and MRI, and initial segmentation of cerebral tissues into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). In a second stage, we applied the Talairach method to define regions of interest (ROIs) and to obtain volume and metabolic activity data. The software used is part of a Multimodality Workstation that incorporates a variety of image-processing and quantification tools (Benito et al., 1999; Desco et al., 1999). We have described the method elsewhere (Molina et al., 2003a,b).

The edited MRI without extracranial tissue was co-registered with the PET image using the AIR algorithm (Woods et al., 1993), which optimizes volume matching between two images. Fusion results were visually checked in all cases, and the observed fit was always optimal. Initial segmentation of cerebral tissue into GM and WM was performed 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 MRI pixels into four tissue types: GM, WM, CSF and "other tissue" according to a clustering algorithm derived from a priori probability templates. The algorithm also removes the effect of radiofrequency field inhomogeneities (Ashburner and Friston, 2000). The automatically generated three-dimensional (3D) masks were checked for inconsistencies and corrected whenever necessary by an experienced radiologist who was blind to diagnosis. These inconsistencies consisted of the misidentification as GM of tissue belonging to extracerebral structures (i.e., bone, muscle or fat). The second stage defined the actual regions of interest (ROIs) to be measured by superimposing WM and GM 3D tissue masks 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, after manual selection of the anterior and posterior commissures (AC and PC) and the mid-sagittal plane, on MR images from which scalp and cerebellum have been previously removed. Once the grid had been calculated and adjusted to each particular brain, the ROIs were defined as sets of cells, according to the Talairach atlas. ROI volume and activity were then calculated as the portion of the tissue mask contained in the set of grid cells that defined the ROI (Benito et al., 1999; Desco et al., 1999). On each grid cell, volume and count rate activity data from the superimposed PET image were collected. The validity of the Talairach-based procedure as an automatic segmentation tool suitable for schizophrenia research has been previously demonstrated (Andreasen et al., 1996). Only one operator segmented all the data.

The volume and activity of the dorsolateral prefrontal region were analyzed and defined as the set of

cells including Brodmann areas 8, 9 and 10 (Talairach and Tournoux, 1988) (Fig. 1). Activity values are expressed as relative to the mean total cortical values.

2.4. Statistical analyses

The effect of age and total cranial volume was statistically removed before data analysis because these factors are major determinants of variations in regional cerebral volume. Data transformation was performed using regression parameters obtained from a normative group of healthy individuals ($n=42$, 22 males) following the procedure of Pfefferbaum et al. (1992). The normative group includes the healthy controls in the present study. At the end of this age-correction transformation, patient volumes were expressed as deviations from the expected volumes of healthy individuals of the same age as the patient (Pfefferbaum et al., 1992). Negative residuals are therefore a quantitative measure of atrophy in the corresponding tissues.

We also assessed the significance of the differences between patients and controls in functional and anatomical variables by means of Student's t test, since there were no differences in age or gender proportion between the patients and the subgroup of controls studied with PET and MRI ($n=16$). Concerning the electrophysiological data, the statistical significance of differences was assessed with analysis of covariance (ANCOVA, with age as covariate and group as factor).

The hypothesis of a significant relationship between electrophysiological values and prefrontal parameters was studied with correlation coefficients calculated between P300 amplitude and latency at the Pz electrode and, on the other side, gray matter volume residues and relative activity in DLPF in each side. After verification of the normality of the data (Kolmogorov–Smirnoff test), Pearson coefficients were calculated.

3. Results

Compared with controls, schizophrenia patients displayed a lower P300 amplitude in the ANCOVA, although at a trend level (mean differences: -3.07 μV, S.D.=1.59, $P=0.06$). On the other hand, the two groups did not differ with regard to P300 latency (mean difference: -6.34, S.D.=21.3, $P>0.5$). Patients exhibited reduced metabolic activity in the DLPF region, both on the left ($t=-3.19$, $df=32$, $P<0.01$) and right ($t=-2.23$, $df=32$, $P<0.05$) sides. This difference remained even after the previously treated patients

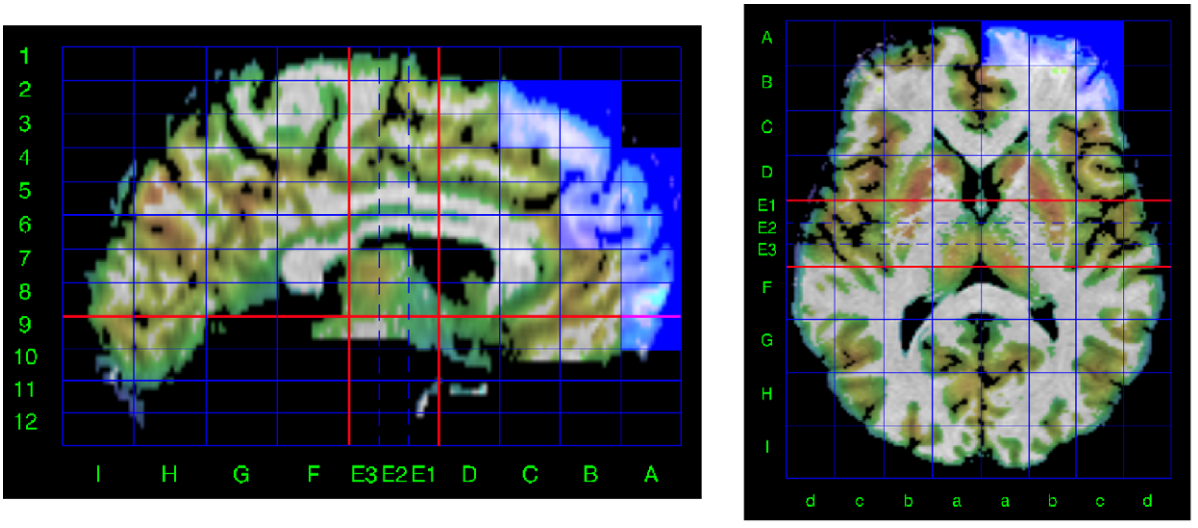

Fig. 1. Sagittal and axial views illustrating a Talairach grid built upon an edited MRI and fused with the GM segmentation of the PET scan. The Talairach grid cells describing the dorsolateral prefrontal region (DLPF) are highlighted in blue. This region of interest is defined as the cortex, encompassed in Brodmann areas 8, 9, 10, and 46, according to the Talairach atlas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were excluded from the analysis. However, there were no significant differences on anatomical residuals (that is, patients did not show significant atrophy) on either side (left: $t=0.65$, $df=27$, $P>0.5$; right: $t=-0.47$, $df=27$, $P>0.5$). We reanalyzed metabolic activity data by multivariate analysis of variance, after adding activity data for parietal lobe, hippocampus and superior temporal gyrus (STG) regions that have been linked to P300 abnormalities in schizophrenia. These regions were also defined according to the Talairach atlas (Talairach and Tournoux, 1988). In this analysis, group (patients versus controls) and gender were included as factors and age as a covariable. Multivariate results showed that the effect of group was significant ($F=3.54$; $df=6,23$; $P=0.01$), and post hoc analyses revealed that patients had less activity in both the left (difference between adjusted means $=-5.3\pm1.7$, 95% confidence interval [CI] $=-8.8$ to -1.7, $P=0.005$) and the right (difference between adjusted means $=3.4\pm1.4$, 95% CI $=-6.4$ to -0.4, $P<0.05$) DLPF regions. In addition, patients showed higher metabolic activity in the left (difference between adjusted means $=5.3\pm1.5$, 95% CI $=2.2$ to 8.3, $P=0.001$) and right (difference between adjusted means $=4.0\pm1.8$, 95% CI $=0.3$ to 7.8, $P<0.05$) hippocampus and in the right STG (difference between adjusted means $=3.0\pm1.0$, 95% CI $=1$ to -5.1, $P=0.005$). No differences were found concerning parietal lobe activity between patients and controls. These results are shown in Table 2 and illustrated in Fig. 2.

Table 2
Metabolic values in patient and controls groups (normalized to total mean cortical value)

	Patients		Controls
	Activity	Anatomical residuals	Activity
Left DLPF	96.25 (3.98)**	1.3 (2.5)	101.72 (5.90)
Right DLPF	101.39 (3.16)*	−0.32 (2.8)	104.64 (5.16)
Left STG	97.6 (3.3)	−0.2 (0.8)	97.3 (2.5)
Right STG	99.8 (3.4)**	−0.4 (0.7)	97.0 (3.1)
Left hippocampus	88.7 (3.8)**	−0.1 (0.2)	83.0 (4.8)
Right hippocampus	89.6 (6.0)*	−0.1 (0.2)	85.2 (4.3)
Left parietal	103.1 (3.6)	−1.5 (4.1)	102.2 (1.8)
Right parietal	102.9 (3.4)	−2.1 (4.8)	104.0 (3.8)

We also show the anatomical residuals for the patient group (see text) to illustrate structural differences between groups.
**$P<0.01$; *$P<0.05$ for the differences in activity.

In the patients, a significant correlation was found between the activity in right DLPF cortex and P300 amplitude measured at the Pz electrode. This finding is displayed in Fig. 3 and Table 3. Since it could not be

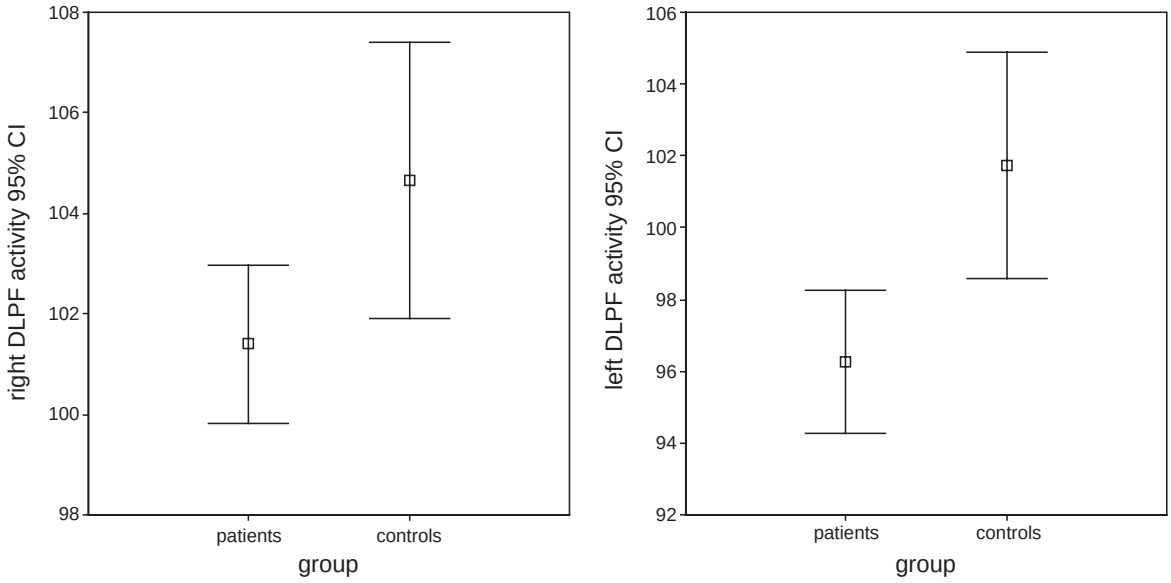

Fig. 2. Error bar diagram depicting the differences in dorsolateral prefrontal (DLPF) activity between patients and controls.

ruled out that P300 recorded on different scalp sites could reflect different cognitive processes, we decided to assess correlation coefficients with P300 amplitude measured at the F3, F4, P3 and P4 electrode sites. We found that the correlation pattern was the same in all these electrode sites as that observed at the Pz electrode site; that is, the lower the DLPF activity, the lower the P300 amplitude ($r>0.60$, $P<0.01$ in all cases). In the healthy controls, no significant association was detected between DLPF activity in either hemisphere and P300 amplitude ($r<0.20$, $P>0.5$). No significant correlations were found between left DLPF activity and P300 latency measured at these sites.

On the other hand, there was a trend for a significant correlation between P300 latency and DLPF gray matter atrophy (the larger the atrophy, the larger the latency; Table 3).

To eliminate the contribution of other regions to the decrease in P300 amplitude, we calculated partial correlation coefficients between P300 amplitude and DLPF activity, after partialling out activity at parietal lobe, hippocampus and STG regions. Even after these values had been partialled out, the association between right DLPF activity and P300 amplitude was still significant ($r=0.62$, $df=9$, $P<0.05$). The partial correlation coefficient between left DLPF activity and P300 amplitude was not significant ($r=0.13$, $P>0.5$).

Previous studies (cf. Mathalon et al., 2000a) have demonstrated that P300 may partly reflect symptomatic

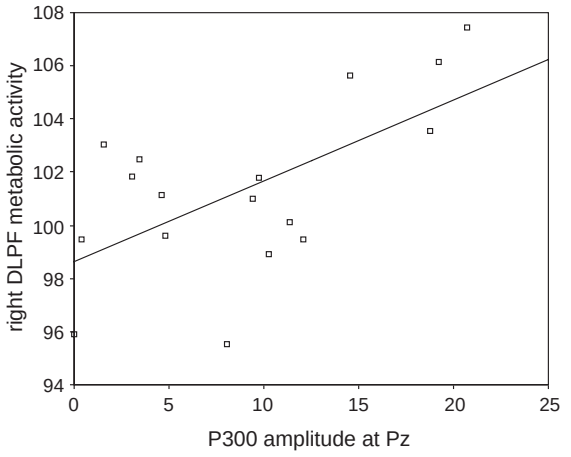

Fig. 3. P300 amplitude (in μV) as a function of dorsolateral prefrontal (DLPF) metabolic activity in the right hemisphere ($r=0.614$); see text.

Table 3
Pearson correlation coefficients between electrophysiological parameters at Pz and dorsolateral prefrontal (DLPF) measurements (atrophy and metabolic activity during activation conditions) in patients with schizophrenia

	Left DLPF residual	Right DLPF residual	Left DLPF activity	Right DLPF activity
P300 amplitude	−0.202	−0.188	0.116	0.614**
P300 latency	−0.234	−0.408*	0.038	0.279

**$P<0.01$; *$P=0.1$. Correlation coefficients between activity and amplitude measured over other electrode placements are shown in the text.

state, and other studies have suggested that hypofrontality might also be associated with the symptomatic profile (cf. Andreasen et al., 1992; Wolkin et al., 1992). To test the idea that the relation found in our study between DLPF activity and P300 was merely mediated by symptoms, we assessed the correlation coefficients between P300 amplitude (measured at the Pz electrode) and positive and negative symptom scores. These correlations were not significant (for positive symptoms, $r=0.27$; for negative symptoms, $r=0.34$).

4. Discussion

Our data in schizophrenia patients with a brief duration of illness support a significant relationship between P300 abnormalities and DLPF hypoactivation during a cognitive task. The patients did not, however, exhibit a significant degree of DLPF atrophy relative to controls. They also did not show a significant P300 latency increase. The observed correlation between metabolic activity (significantly lower than in controls) and P300 amplitude supports the hypothesis that a prefrontal dysfunction contributes to the impairment in information processing in schizophrenic patients. This finding is in accordance with the report of Shajahan et al. (1997), who found that patients with schizophrenia did not significantly activate prefrontal regions during an oddball paradigm that elicited the P300 waveform, whereas controls activated the prefrontal region.

Other possibilities may be relevant to the observed association between hypofrontality and reduced P300 amplitude in our patients. For example, it has been shown that human frontal lesions decrease auditory discrimination through an impairment in inhibitory

control over attention to irrelevant stimuli (Chao and Knight, 1995). This is an interesting possibility, given the amount of data coherent with a decreased inhibitory function in the prefrontal cortex in schizophrenia (Simpson et al., 1989; Akbarian et al., 1995; Pierri et al., 1999; Volk et al., 2000, 2002).

The absence of significant DLPF atrophy in our patients may relate to their short duration of illness. This is consistent with the findings of other groups in the DLPF (Gilbert et al., 2001) or frontal (Bilder et al., 1994) regions. Within this framework, the fact that the decrease in P300 amplitude relative to control values was only a statistical trend may again relate to the short duration of illness in our patients. An inverse relationship between P300 amplitude and illness duration has been reported (Martin-Loeches et al., 2001; Mathalon et al., 2000b). Additional data further suggest that P300 amplitude reduction may reflect a neurodegenerative process (O'Donnell et al., 1995). In this line, our results would be compatible with the idea that those patients displaying the largest P300 amplitude reduction and latency decrease would be those with the highest prefrontal affectation, even in very early periods of illness. In other words, it is conceivable that if our sample went on to show significant cortical atrophy over the course of illness, P300 amplitude might also decrease significantly.

The significant relationship between P300 amplitude and DLPF activity implicated the right but not the left DLPF region, presumably related to the higher right hemisphere implication during the task performed by the patients (CPT test). Our results are discrepant concerning localization with those of Blackwood et al. (1999), who reported a significant association between left inferior prefrontal activity and P300 amplitude. Methodological reasons might account for such a discrepancy. First, the method used in that study was single photon emission tomography while ours was PET. Second, while most of our cases were previously untreated, those of Blackwood et al. (1999) showed an increased subcortical activity, which might suggest a persisting influence of previous neuroleptic treatment (Bartlett et al., 1994; Buchsbaum et al., 1987; Holcomb et al., 1996). Finally, it cannot be ruled out that different groups of patients had functionally different forms of hypofrontality.

It can be argued that the short-term medication given to our patients is a limitation. However, there are data indicating that the influence of acute medication on brain activity disappears after 12 h (Holcomb et al., 1999), the wash-out period in our patients after a short treatment. Moreover, treatment with neuroleptics does not seem to determine P300 parameters in schizophrenia. Hirayasu et al. (1998) reported significant decreases in P300 amplitude in both neuroleptic-naïve and drug-free patients, and other authors even reported P300 amplitude increase to be produced by neuroleptics (Coburn et al., 1998). Iwanami et al. (2001) reported no significant changes with risperidone in P300 amplitude. On the other hand, the advantage of giving very brief treatment is the possibility to include patients more representative of schizophrenia in general.

The fact that P300 amplitude was related to DLPF activity in patients but not in controls support the hypothesis of an involvement of prefrontal alterations in the reduction of P300 in schizophrenia. This suggests that the influence of the DLPF deficit reflected by hypofrontality in schizophrenia could determine a reduction of P300 amplitude in spite of the DLPF region's not being its main generator. The amount of variance explained by DLPF alterations on P300 amplitude is relatively low, suggesting that dysfunctions in other brain are also associated with P300 changes in schizophrenia. This is supported by the involvement of the temporal lobes (Winterer et al., 2001), parietal lobes (Linden et al., 1999) or hippocampus (Altenmüller and Gerloff, 1999) as P300 generators. The recognized implication of these regions in schizophrenia should also be considered (Shenton et al., 2001). Particularly, the STG could have a relevant role in P300 amplitude reduction, according to the previous results (McCarley et al., 2002, 1993). Data are not unanimous in this regard, since Kawasaki et al. (1997) did not find a correlation between P300 amplitude and STG volume, although they found such an association between P300 amplitude and medial anterior temporal lobe. In any case, the fact that partial correlation analysis did not eliminate the association between DLPF activity and P300 amplitude suggests that this association is not mediated by other regions.

In conclusion, our data support a relevant role of prefrontal dysfunction (particularly, its hypoactivation during a cognitive task) in P300 abnormalities in early schizophrenia. This association seems to be relatively independent from anatomical alterations.

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