

# Long-Term Olanzapine Treatment and P300 Parameters in Schizophrenia

Vicente Molina<sup>a</sup> Francisco Muñoz<sup>b</sup> Manuel Martín-Loeches<sup>b</sup> Pilar Casado<sup>b</sup>  
José A. Hinojosa<sup>b</sup> Alfonso Iglesias<sup>b</sup>

<sup>a</sup>Hospital Clínico Universitario de Salamanca, Salamanca, y <sup>b</sup>Universidad Complutense, Madrid, Spain

## Key Words

P300 · Olanzapine · Schizophrenia

## Abstract

The well-known amplitude reduction of the P300 appears to be unaffected by the treatment with classical antipsychotics in schizophrenia, whereas the effects of atypical neuroleptics on this event-related potential are less understood. The study of these changes could help in deciding whether the P300 amplitude reduction in schizophrenia is a trait or state marker of that illness and in better describing the effect of atypical antipsychotics on altered cognitive functions. We present a prospective longitudinal study of P300 amplitude and latency before and after 6 months' treatment with olanzapine in 11 patients with schizophrenia. A healthy control group (n = 30) was also studied. Overall, no significant changes, either in amplitude or in latency as measured at Pz and Fz electrodes, were found when comparing the pre- and postolanzapine conditions, despite the overall improvement in positive and negative symptoms. Nevertheless a direct specific association was observed between a P300 amplitude increase with olanzapine and the improvement in negative symptoms. These data would suggest that P300 amplitude reduction in schizophrenia may be relatively independent from clinical state and treatment,

thus constituting a trait marker of schizophrenia. Our data also suggest that, in addition to this, some further changes in P300 amplitude might depend on the clinical state of the patients.

Copyright © 2004 S. Karger AG, Basel

## Introduction

Amplitude reduction of the P300 event-related potential (ERP) is a consistent finding in schizophrenia. This finding may be independent from the treatment with classical antipsychotics [1], and might constitute a trait marker.

The effects of atypical drugs on P300 are, however, less understood. On the one hand, available data support no significant changes in P300 parameters with risperidone, despite some latency decrease [2]. Similarly no changes in either P300 amplitude or latency were observed after 4-week olanzapine therapy in schizophrenia by Gallinat et al. [3], or in healthy controls after a single dose by Hubl et al. [4], whereas Gonul et al. [5] have recently reported in unmedicated patients a P300 normalization at frontal leads but not at parietal leads after 6 weeks of olanzapine treatment. On the other hand, olanzapine enhances neuropsychological performance in schizophrenia [6], P300 being related to neuropsychological performance in that

**KARGER**

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

© 2004 S. Karger AG, Basel  
0302-282X/04/0502-0182\$21.00/0

Accessible online at:  
[www.karger.com/nps](http://www.karger.com/nps)

V. Molina, PhD  
Department of Psychiatry, Hospital Clínico Universitario  
Servicio de Psiquiatría, Paseo de San Vicente, 58–182  
ES–37007 Salamanca (Spain)  
Tel. +34 923291102, Fax +34 923291383, E-Mail [vmolinarod@wanadoo.es](mailto:vmolinarod@wanadoo.es)

illness [7, 8]. Furthermore, atypical (clozapine, olanzapine and risperidone) but not typical antipsychotics may normalize ERP indices of information processing other than the P300, such as the P50 suppression [9].

Accordingly, it appears pertinent to further explore the effects of atypical drugs on P300. Electrophysiological changes with these treatments might be more evident after long (over 6 months) treatment periods, as neuronal changes induced by antipsychotics may take longer periods, particularly those underlying cognitive enhancement [10].

For these purposes we performed a longitudinal study in a group of patients with schizophrenia, assessing the P300 event-related potential both before and after a 6-month trial with olanzapine.

## Subjects and Methods

Eleven patients (9 males, age  $32.8 \pm 10.8$  years, duration of illness  $8.3 \pm 7.9$  years) diagnosed as having paranoid schizophrenia (DSM-IV) were studied with P300 ERP before and after a 6-month trial of olanzapine. Their symptoms were assessed using the PANSS by only one and the same trained rater. Their socioeconomic status was evaluated with the Hollingshead index [11].

By the time of inclusion, patients had been receiving haloperidol at doses between 9 and 20 mg/day for a period longer than the preceding month. All cases were outpatients and were treated in a mental health community center. No other antipsychotics, benzodiazepines on a regular basis, antidepressants or mood stabilizers were used during this period. No depot neuroleptics were used during the 6 months preceding the inclusion. After inclusion, the first electrophysiological recording was performed and then treatment was progressively switched to olanzapine. A dose of 20 mg/day was reached and maintained during the follow-up period in all cases but one, that (due to tolerance problems) was treated with 15 mg/day. No other psychoactive drugs were given during the follow-up. A magnetic resonance image (MRI) of the brain was available in all cases, acquired in the month following the inclusion in the study, to avoid the inclusion of patients with central nervous system lesions.

After full written information, written informed consent was obtained from patients and their families. The ethical board endorsed the study.

Thirty healthy controls (18 males, age  $29.5 \pm 7.8$  years) were also studied without significant differences in socioeconomic status when compared to the patients ( $2.0 \pm 1.1$  years in patients and  $2.1 \pm 0.9$  years in controls). Differences in age or sex distribution between patients and controls were not significant.

Exclusion criteria for patients and controls were: neurological illness, MRI findings judged clinically relevant by a radiologist blind to diagnosis, history of cranial trauma with loss of consciousness, substance abuse criteria during the last 3 years (except for caffeine or nicotine), antecedents of axis I psychiatric processes or treatment (except schizophrenia in the case of patients), or any current treatment with known central nervous system action. Urinalysis was used to rule out current use of toxic substances.

### *Electrophysiological Recordings*

P300 was recorded using a standard auditory odd-ball paradigm in which brief tones (50-ms plateau, 10-ms rise/fall, 90 dB) of 1,000 Hz (80%) and 2,000 Hz (20%) were presented in random order by means of loudspeakers. Subjects were instructed not to move their eyes and to ignore the low (1,000-Hz) tones and mentally count the high (2,000-Hz,  $n = 40$ ) target tones.

Electroencephalograms were recorded from midline parietal (Pz) and frontal (Fz) sites referenced to linked earlobes. All impedances were maintained below 5 k $\Omega$ . The electro-oculogram (EOG) was obtained from below versus above the right eye (vertical EOG) and the left versus right lateral orbital rim (horizontal EOG). Sampling rate was set at 250 Hz, and EEG was band-pass-filtered at 0.3–50 Hz. Epochs of 1 s duration were recorded, starting 200 ms prior to stimulus onset. To eliminate epochs with artifacts, each epoch was visually checked. Separate averages were calculated for the target and the nontarget stimuli, after correction of EOG artifacts by means of the method proposed by Semlitsch et al. [12]. A minimum number of 20 artifact-free epochs was required per subject before averaging. P300 was the most positive peak between 250 and 500 ms after target stimulus onset. Two parameters, the P300 amplitude and latency, were measured.

### *Statistics*

Given the sample sizes, normality could not be assumed and non-parametric tests were used.

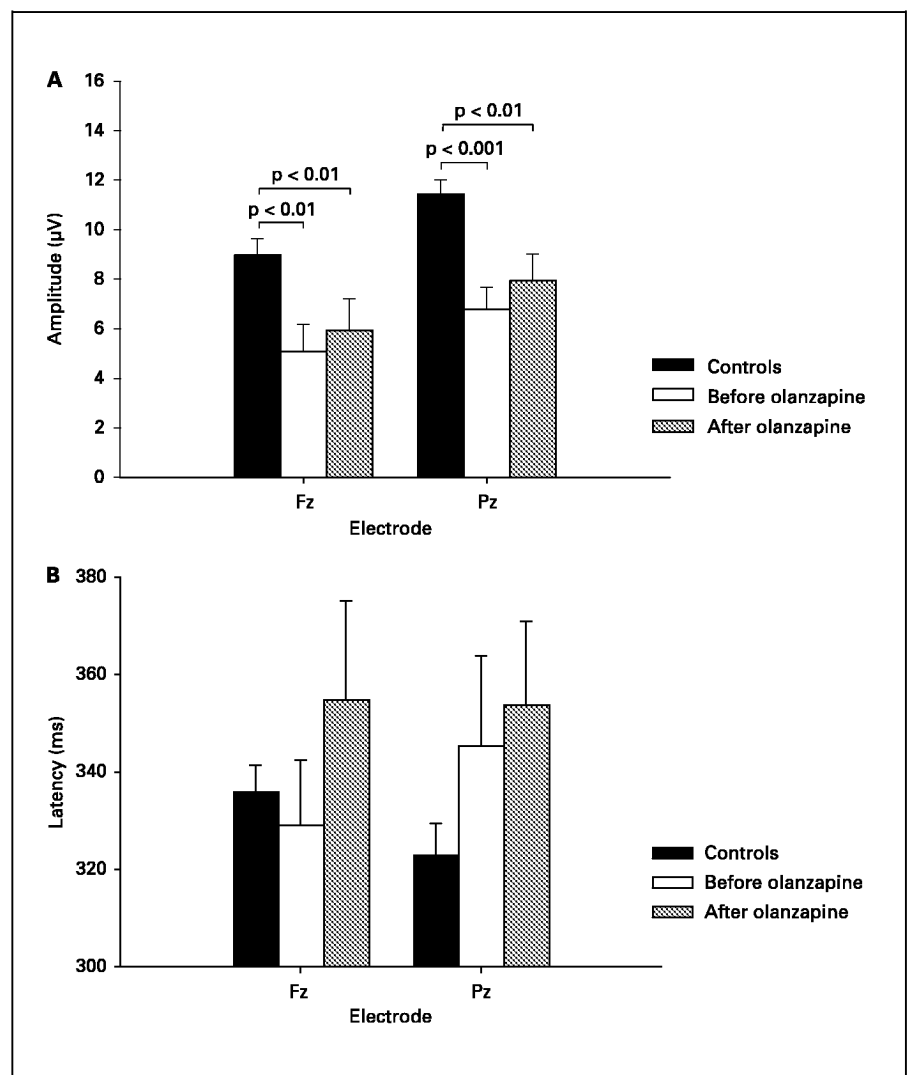
Amplitude and latency comparisons were respectively conducted between patients on haloperidol ('baseline') and after treatment with olanzapine, and controls on the other hand, using Mann-Whitney U tests. Pairwise changes in these parameters were compared in the patients before and after the olanzapine trial using Wilcoxon tests. The association in patients between the changes in positive and negative symptoms and, on the other hand, electrophysiological changes was assessed using Spearman's rho tests. For these comparisons, we considered the rank-transformed percent of change in positive and negative symptoms between the pre- and postolanzapine conditions. Lower ranks correspond to the cases with less improvement.

## Results

Positive (before treatment with olanzapine,  $20.8 \pm 7.0$ ; after,  $14.4 \pm 7.0$ ;  $z = 2.66$ ,  $p = 0.008$ ) and negative (before,  $25.7 \pm 10.0$ ; after,  $22.3 \pm 10.0$ ;  $z = 2.37$ ,  $p = 0.01$ ) symptoms improved with olanzapine.

The number of tones correctly identified did not significantly differ between before- and after-treatment conditions (before,  $34.1 \pm 17.0$ ; after,  $39.5 \pm 5.3$ ;  $z = 0.42$ ,  $p = \text{NS}$ ).

Figure 1 shows the amplitude measures at Fz and Pz electrodes in controls, patients on haloperidol (baseline) and patients after olanzapine treatment. These values were  $9.0 \pm 3.5$ ,  $5.10 \pm 3.5$  and  $5.95 \pm 4.12$   $\mu\text{V}$ , respectively, at Fz, whereas at Pz they were  $11.4 \pm 3.3$ ,  $6.81 \pm 2.9$  and  $7.95 \pm 3.5$   $\mu\text{V}$ , respectively. Latency measures at Fz were  $336.1 \pm 29.6$ ,  $329.1 \pm 44.0$  and  $354.9 \pm$



**Fig. 1.** Bar diagram representing both amplitude (A) and latency (B) in controls and pre- and postolanzapine conditions.

67.0 ms, respectively. Latency measures at Pz were  $323.1 \pm 34.9$ ,  $345.4 \pm 61.1$  and  $353.8 \pm 56.5$  ms, respectively.

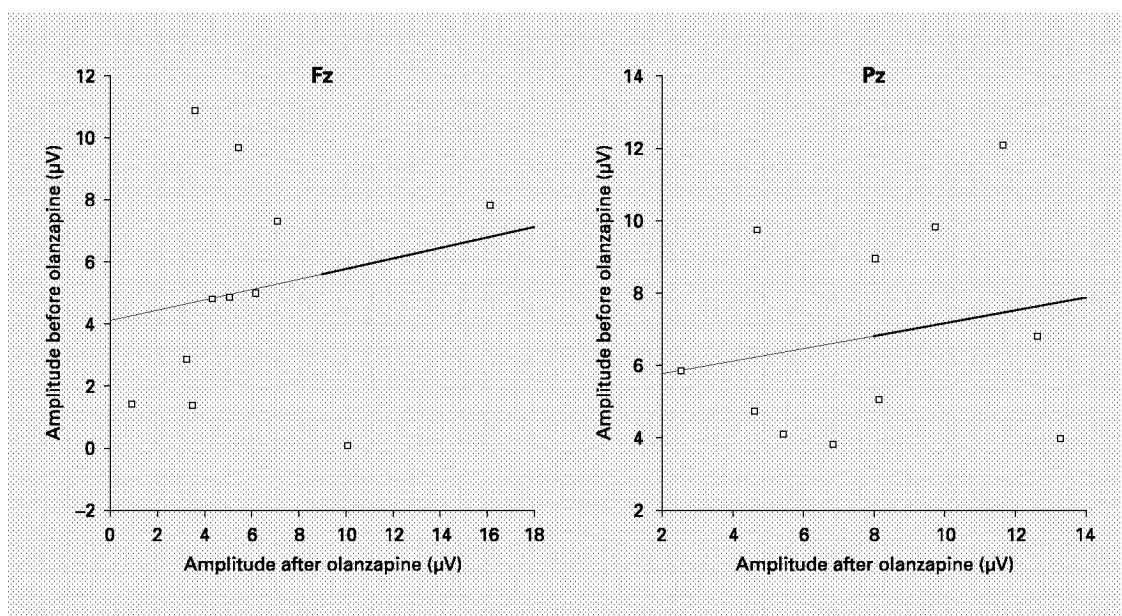
When compared to controls, patients on haloperidol (baseline) showed a significantly lower amplitude at Fz ( $U = 73.0$ ;  $p < 0.01$ ) and at Pz ( $U = 45.0$ ;  $p < 0.001$ ). However, the group of patients did not significantly differ in latency either at Fz ( $U = 162.0$ ;  $p = 0.9$ ) or at Pz ( $U = 119.5$ ;  $p = 0.18$ ) with respect to controls.

After 6 months on olanzapine, the amplitude at both Fz and Pz electrodes in the patients is still significantly lower than in controls ( $U = 78.0$ ;  $p = 0.01$  and  $U = 82.0$ ;  $p = 0.01$ , respectively). Again, the group of patients did not significantly differ in latency either at Fz ( $U = 144.0$ ;  $p = \text{NS}$ ) or at Pz ( $U = 118.0$ ;  $p = \text{NS}$ ) when compared to controls. Also, there were no significant differences in the

group of patients between before and after treatment with olanzapine for either the amplitude (at Fz,  $z = 0.44$ ;  $p = \text{NS}$ ; at Pz,  $z = 0.53$ ;  $p = \text{NS}$ ) or the latency (at Fz,  $z = 0.44$ ;  $p = \text{NS}$ ; at Pz,  $z = -0.80$ ;  $p = \text{NS}$ ). Individual changes are shown in table 1.

There was no association between pre- and postolanzapine amplitude values, neither at Fz ( $\rho = 0.15$ ;  $p = \text{NS}$ ) nor at Pz ( $\rho = 0.22$ ;  $p = \text{NS}$ ). This is shown in figure 2.

There was, however, a significant association between the change in negative symptoms and the amplitude change at Pz between pre- and postolanzapine conditions (at Fz,  $\rho = 0.07$ ;  $p = \text{NS}$  and at Pz,  $\rho = 0.80$ ;  $p = 0.003$ ) (fig. 3). In other words, the more decreased the negative symptoms, the more increased the P300 amplitude with olanzapine. There was no significant correlation between



**Fig. 2.** Scatterplot representing the lack of association between pre- and postolanzapine P300 amplitude values (case by case) measured at Fz and Pz.

**Table 1.** Individual and mean clinical, demographic, behavioral and electrophysiological values

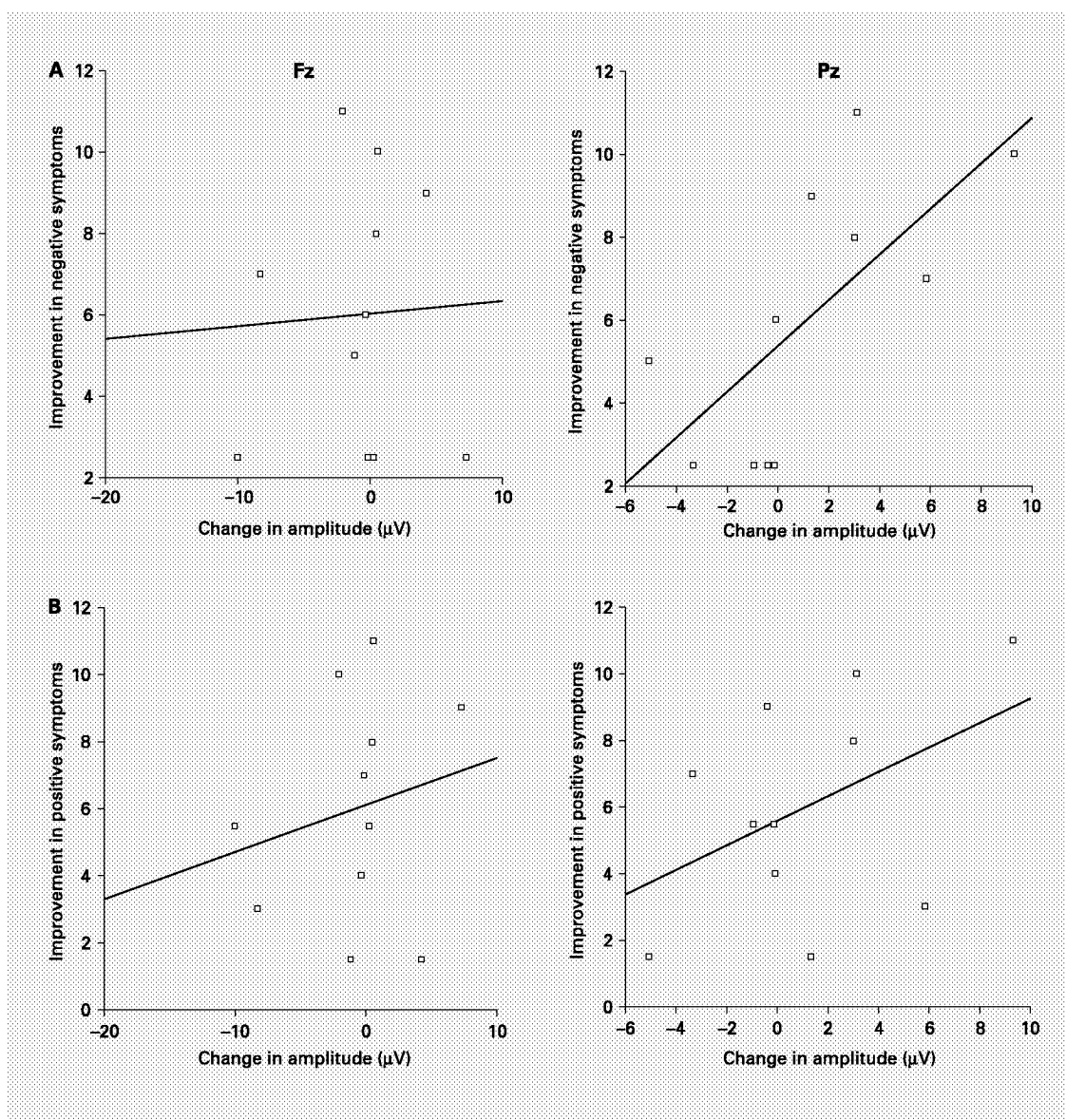
No.	Subject		Haloperidol <sup>1</sup>		Positive symptoms		Negative symptoms		Amplitude at Fz		Amplitude at Pz		Latency at Fz		Latency at Pz		Targets detected	
	age	sex	time	dose	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1	42	M	2	10	18	15	45	45	7.33	7.08	8.96	8.03	324	280	328	284	0	40
2	32	M	3	10	23	13	38	30	4.80	4.36	3.82	6.83	260	468	256	468	40	40
3	25	M	9	9	29	8	32	20	0.09	10.07	3.97	13.27	348	328	336	340	39	40
4	24	M	2	15	14	12	14	12	7.84	16.14	6.81	12.61	300	308	340	320	42	40
5	41	F	2	10	11	11	23	18	2.87	3.21	4.12	5.42	252	392	376	392	41	40
6	23	F	4	20	33	33	25	24	5.01	6.18	9.74	4.69	372	344	336	352	40	40
7	41	M	3	10	25	21	28	26	9.67	5.44	9.84	9.74	352	344	376	420	40	40
8	56	M	1	9	20	15	28	28	4.84	5.05	5.86	2.53	396	476	496	304	47	28
9	25	M	5	12	12	10	21	21	1.44	0.89	4.73	4.60	324	356	284	292	42	38
10	30	M	3	20	25	11	18	11	1.39	3.51	5.05	8.16	348	272	348	376	0	40
11	22	M	4	10	19	100	11	11	10.90	3.62	12.08	11.65	344	336	324	344	45	49
Mean					20.8	14.4	25.7	22.3	5.10	5.95	6.81	7.95	329.1	354.9	345.4	353.8	34.1	39.5
SD					6.9	7.0	10.0	10.0	3.54	4.12	2.87	3.54	44.03	66.95	61.06	56.55	17.0	4.7

<sup>1</sup> Time on haloperidol in months; dose of haloperidol in milligrams per day.

the changes in negative symptoms and latency (Fz,  $\rho = 0.08$ ;  $p = \text{NS}$  and at Pz,  $\rho = 0.40$ ;  $p = \text{NS}$ ). A decrease in positive symptoms, on the other hand, did not correlate with amplitude (at Fz,  $\rho = 0.26$ ;  $p = \text{NS}$ , and at Pz,  $\rho = 0.35$ ;  $p = \text{NS}$ ) or latency (at Fz,  $\rho = 0.22$ ;  $p = \text{NS}$ , and at Pz,  $\rho = 0.11$ ;  $p = \text{NS}$ ) changes.

## Discussion

Our data suggest that long-term administration of olanzapine produces no significant overall changes in the P300 parameters (amplitude and latency) of schizophrenic patients as compared to the treatment with haloperidol



**Fig. 3.** Scatterplot reflecting the case-by-case association between changes in P300 amplitude and the improvement in negative (**A**) and positive (**B**) symptoms. Significant results were only obtained at Pz and for negative symptoms. On the x axis, the more positive change reflects the more increased amplitude, and on the y axis higher ranks correspond to patients with more improvement after treatment.

in spite of significant clinical improvement. This is similar to an earlier report for a shorter treatment period with olanzapine [3] and adds evidence supporting the relative independence of P300 amplitude from the pharmacological state [1, 2, 13]. Accordingly, the well-known P300 amplitude reduction in schizophrenia would be a trait marker [14] rather than a state marker or a consequence of other variables such as treatment in agreement with the

reported reduction of P300 amplitude in neuroleptic-naïve schizophrenic patients [15]. Thus, reduction of P300 amplitude may rather depend on other stable factors, such as structural defects, as supported by the association found between P300 amplitude reduction and increase in cortical frontal CSF volumes [16].

However, in spite of the lack of any significant change between the haloperidol and olanzapine conditions, some

patients showed an increase of P300 amplitude, and that increase was significantly related to the improvement in negative symptoms. This is in agreement with a previous proposal by Mathalon et al. [14] that the auditory P300 reduction in schizophrenia is a trait marker over which clinical state may induce further fluctuations. These authors reported an inverse association between negative symptoms and P300 amplitude, which is in line with our results (but at variance with those of Turetsky et al. [15]). It seems to us conceivable that a state effect imposed over a trait better characterizes P300 reduction in schizophrenia, which could on the other hand account for the lack of a significant association between pre- and postolanzapine P300 amplitudes.

It could be argued that the reduction in negative symptom scores observed in our patients could reflect a lower incidence of extrapyramidal side effects with olanzapine. Indeed, we did not distinguish between primary and secondary negative symptoms, and our patients had been treated with haloperidol prior to the olanzapine trial. Although we cannot rule out side effects to explain the increase of P300 amplitude in some patients, this seems unlikely considering that classical drugs seem to lack any effect on this potential [1].

The lack of significant changes in P300 parameters with olanzapine together with a significant correlation with symptom improvement resembles the results of Gallinat et al. [3]. However, these authors found a correlation with positive symptom changes, although differences in methods may account for such discrepancy (these authors used dipole analyses to disentangle factors contributing to P300). In any case, the results of Gallinat et al. [3] seem to be consistent with a P300 reduction as a trait marker of schizophrenia over which clinical state induces fluctuations.

We cannot rule out that a type II error could explain the lack of change in amplitude of our cases. This would be consistent with both the slight amplitude increase observed in the patient group and the correlation with improvement in negative symptoms. Previous studies have reported relatively small P300 changes with treatment in broader sample sizes [14]. Thus, our sample may have lacked statistical power to detect such small changes. Nevertheless, P300 amplitude was still reduced in patients after olanzapine, even if P300 amplitude increased with treatment.

Another possible limitation is that our patients were not drug-naïve at baseline. It may be presumed that olanzapine might be more effective in this respect in that kind of patients, as suggested by the results of Gonul et al. [5] in

unmedicated patients. However, against that possibility is the fact that both at baseline and after treatment our patients showed a significantly decreased amplitude in comparison to normals. It is also possible that olanzapine could be more effective in normalizing neurophysiological parameters in earlier stages of illness. This is suggested by the significant association between excess of cerebrospinal fluid (a possible neurodegenerative marker) and P300 amplitude previously reported [16].

It remains to be studied whether other atypical drugs, in particular clozapine [9, 17], give similar results with respect to P300, although available data suggest no differences between clozapine and olanzapine [3].

In conclusion, in our study only small, nonsignificant, overall amplitude changes were detected after long-term olanzapine administration in schizophrenic subjects after switching from haloperidol, in spite of clinical improvement. Both before and after olanzapine, P300 amplitude was decreased in our sample in comparison to healthy controls. This argues for a role of P300 amplitude decrease as a trait marker of schizophrenia. However, a subgroup of patients may show a P300 increase with olanzapine in association with a decrease of negative symptoms, whereas pre- and postolanzapine amplitudes were unrelated. These facts would argue for some state dependency of the P300 component on a trait-related decrease of amplitude.

### Acknowledgments

This work has been partially supported by grants from the Fondo de Investigaciones Sanitarias (FIS 00/0036), Fundación La Caixa (99/042-00) and a grant from Eli-Lilly.

## References

- 1 Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A: ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 1994;36:153–170.
- 2 Iwanami A, Okajima Y, Isono H, Shinoda J, Kasai K, Hata A, Fukuda M, Nakagome K, Kamijima K: Effects of risperidone on event-related potentials in schizophrenic patients. *Pharmacopsychiatry* 2001;34:73–79.
- 3 Gallinat J, Riedel M, Juckel G, Sokullu S, Frodl T, Moukhtieva R, Mavrogiorgou P, Nisse S, Muller N, Danker-Hopfe H, Hegerl U: P300 and symptom improvement in schizophrenia. *Psychopharmacology (Berl)* 2001;158:55–65.
- 4 Hubl D, Kleinlogel H, Frolich L, Weinandi T, Maurer K, Holstein W, Czekalla J, Dierks T: Multilead quantitative electroencephalogram profile and cognitive evoked potentials (P300) in healthy subjects after a single dose of olanzapine. *Psychopharmacology (Berl)* 2001;158:281–288.
- 5 Gonul AS, Suer C, Coburn K, Ozesmi C, Oguz A, Yilmaz A: Effects of olanzapine on auditory P300 in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:173–177.
- 6 Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Breier A, Tollefson GD: Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for Research in Schizophrenia. *Arch Gen Psychiatry* 2000;57:249–258.
- 7 Donchin E, Karis D, Bashore TR, Coles MGH, Gratton G: Cognitive psychophysiology and human information processing; in Coles MGH, Donchin E, Porges SW (eds): *Psychophysiology: Systems Processes, and Applications*. New York, Guilford Press, 1988, pp 244–267.
- 8 Ford JM: Schizophrenia: The broken P300 and beyond. *Psychophysiology* 1999;36:667–682.
- 9 Light GA, Geyer MA, Clementz BA, Cadenhead KS, Braff DL: Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. *Am J Psychiatry* 2000;157:767–771.
- 10 Gur RE, Kohler C, Ragland JD, Siegel SJ, Bilker WB, Loughhead J, Phend N, Gur RC: Neurocognitive performance and clinical changes in olanzapine-treated patients with schizophrenia. *Neuropsychopharmacology* 2003;28:2029–2036.
- 11 Hollingshead A, Frederick R: Social stratification and psychiatric disorders. *Am Soc Rev* 1953;18:163–189.
- 12 Semlitsch H, Anderer P, Schuster P, Presslich O: A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 1986;23:695–703.
- 13 Schall U, Catts SV, Chaturvedi S, Liebert B, Redenbach J, Karayanidis F, Ward PB: The effect of clozapine therapy on frontal lobe dysfunction in schizophrenia: Neuropsychology and event-related potential measures. *Int J Neuropsychopharmacol* 1998;1:19–29.
- 14 Mathalon DH, Ford JM, Pfefferbaum A: Trait and state aspects of P300 amplitude reduction in schizophrenia: A retrospective longitudinal study. *Biol Psychiatry* 2000;47:434–449.
- 15 Turetsky B, Colbath EA, Gur RE: P300 sub-component abnormalities in schizophrenia. II. Longitudinal stability and relationship to symptom change. *Biol Psychiatry* 1998;43:31–39.
- 16 Martin-Loeches M, Molina V, Munoz F, Hinojosa JA, Reig S, Desco M, Benito C, Sanz J, Gabiri A, Sarramea F, Santos A, Palomo T: P300 amplitude as a possible correlate of frontal degeneration in schizophrenia. *Schizophr Res* 2001;49:121–128.
- 17 Kumari V, Soni W, Sharma T: Normalization of information processing deficits in schizophrenia with clozapine. *Am J Psychiatry* 1999;156:1046–1051.