Event-Related Potentials in Major Depressive Disorder: The Relationship between P300 and Treatment Response

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SUMMARY

Objective: Although conflicting results have been obtained regarding P300 amplitude and latency in major depressive patients, most studies have reported that major depressive patients have smaller P300 amplitudes and longer latencies than healthy people. This study aimed to investigate the relationship between P300 and treatment response in major depressive disorder patients.

Methods: Twenty-eight patients suffering from major depression who completed 12 weeks of follow-up appointments and 28 healthy people, whose age and gender were matched with patients, were included in the study. Event-related potentials (P300) were recorded for patients before and after treatment with sertraline (50-200 mg/day) for 12 weeks. Treatment response was defined as a 50% or greater decrease in a given patient's total Hamilton Depression Rating Scale score. Pre-treatment and post-treatment P300 amplitude and latency values were compared for responders (n=18), non-responders (n=10) and healthy subjects.

Results: No significant difference was found between the P300 amplitude values of responders, non-responders and healthy subjects before or after treatment. Pre-treatment P300 latencies of non-responders were significantly longer than latencies of responders and healthy subjects. After treatment for depression, P300 latency values of responders were normalized, but non-responders still maintained longer P300 latencies than responders and healthy subjects.

Conclusion: These findings suggest that delayed P300 latency may be related to a non-response to sertraline treatment. No relation was found between P300 amplitude and treatment response.

Keywords: Major depressive disorder, P300, event-related potentials.

INTRODUCTION

Major depressive disorder is associated with inadequate cognitive function as well as with its effects on mood (Rogers et al. 1998). In studies evaluating information processing speeds and cognitive function in patients with depression, deficient information processing speeds, psychomotor speeds, attention, inhibition, and executive functions have been observed (Gualtieri et al. 2006, Marazziti et al. 2010). It is thought that these cognitive impairments in major depression patients stem from structural and functional disorders in the prefrontal cortex and fronto-striatal structures (Rogers et al. 1998, Rogers et al. 2004). Evaluation of event-related potentials is a commonly used method for investigating cognitive disorders (Hansenne et al. 2000).

Evoked potentials are waves that are formed when the brain is stimulated (by visual, auditory, somato-sensorial or cognitive stimuli) and that can be recorded from the surface of the skin. While the waves emerging first (<100 ms) reflect neuronal activity in the sensory nerves, brain stem and primary sensory cortex, waves emerging later reflect information processing, attention, decision processes, and short-term memory functions and are defined as "event-related potentials" (ERP; Sara et al. 1994, Polich and Kok. 1995). In the literature, latency (the time delay between stimulation and the appearance of the wave) and amplitude are criteria employed to determine

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the level of cognitive function. ERP are used to examine the physiology of the brain during cognitive function and to relay information about temporal function. P300, which emerges 300 ms after stimulation and is a 10-20 μV positive wave, is the most commonly investigated ERP component. P300 latency is associated with the duration of time spent in order to decide whether stimulant is important, and its amplitude is associated with psychological processes, such as expectation, attention and stimulus meaning (Vandoolaeghe et al. 1998).

In many clinical disorders leading to alterations in cognitive function, changes in P300 amplitude and latency have been detected. In addition to major depressive disorder, these disorders include diseases such as dementia (Goodwin et al. 1978, Polich et al. 1990), schizophrenia (Roth et al. 1995, Kidogami et al. 1991), obsessive compulsive disorder, Parkinson's disease, Huntington's disease, progressive supra-nuclear palsy, epilepsy and multiple sclerosis (Yaltkaya ve Nuzumlali 1994). It has been reported in various studies that P300 amplitude is generally lower in major depression patients when compared to a healthy control group (Gangadhar et al. 1993, Murthy et al. 1997, Kaustio et al. 2002, Urretavizcaya et al. 2003, Kemp et al. 2010, Karaaslan et al. 2003). In Murthy et al. (1997), it was demonstrated that, in both dysthymia and melancholic depression patients, P300 amplitude values returned to normal after treatment. While some studies of P300 latency report major depression patients have longer latency values than healthy control subjects (Vandoolaeghe et al. 1998), other studies find no significant difference between the two groups (Schlegel et al. 1991, Murthy et al. 1997, Karaaslan et al. 2003).

Some studies report that changes in P300 latency and amplitude are associated with different clinical forms of depression. While, in major depressive disorder, low P300 amplitude and prolonged P300 latency are found to be associated with affective and psychotic symptoms (Kaustio et al. 2002, Karaaslan et al. 2003, Santosh et al. 1994), as well as, with a melancholic type (Urretavizcaya et al. 2003, Gangadhar et al. 1993, Kemp et al. 2010), a history of suicide attempts was found to be associated with low P300 amplitude (Hansenne et al. 1994, Urcelay-Zaldua et al. 1995, Hansenne et al. 1996, Jandl et al. 2010) and with more rapid P300 habituation (Jandl et al. 2010).

In the literature, there are few studies which evaluate the relation between P300 and treatment response in MDD patients. In one study, P300 recordings were examined before and after five weeks of antidepressant treatment. Non-responders had longer pre-treatment P300 latency values than either a healthy control group or responders (Vandoolaeghe et al. 1998). In another study, comparing P300 recordings of 49 geriatric patients before and after six weeks of antidepressant treatment with recordings of healthy individuals, it was established that pre-treatment P300 latency values of patients not responding to treatment were longer than those of healthy individuals or responding patients (Kalayam and Alexopoulos 1999). In both of the aforementioned studies, no relation was found between treatment response and P300 amplitude. In another study investigating the relation between response to ECT (electroconvulsive treatment) and P300, it was determined that MDD patients who had normal P300 amplitudes before treatment responded more rapidly to ECT (Ancy et al. 1996).

Currently, no clinical or physiological marker of MDD treatment response exists of which there is general agreement. The aim of the present study is to investigate whether there is a relation between response to antidepressants and changes in the P300 wave, which is an objective indicator of cognitive function, in major depression patients.

METHODS

Forty-five consecutive patients diagnosed with MDD according to DSM-IV (American Psychiatry Association 1994) criteria were included in the study. All cases were between the ages of 18 and 50, and all had, at a minimum, completed primary school. All patients were informed of the study and gave their informed consent. The study was approved by the local ethics committee. Cases who were on psychotropic drugs during the previous month (including antidepressants, antipsychotics, benzodiazepine, antiepileptics, or antihistamines), had a neurological disease or audio-visual disorder, had different axis–I and axis-II diagnoses, or who had a history of alcohol or substance abuse were excluded from the study. The severity of depression was evaluated with the Hamilton Depression Rating Scale (HDRS). All cases included in the study were administered sertraline treatment flexibly at doses of 50-200 mg/day according to tolerability and response to treatment.

Each case was interviewed at weeks 0 (onset), 2, 4, 6, 8 and 12, for a total of six interviews. The first interview took place prior to treatment. In the first interview, the Axis-I MDD diagnosis, according to DSM-IV criteria, was confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I: First et al. 1997, Çorapçioglu et al. 1999). Afterwards, a socio-demographic data form was completed, and the HDRS questionnaire was administered. Following the initial evaluation, ERP recordings were made within the same day and antidepressant treatment was initiated. In the following interviews, the HDRS questionnaire was administered again in order to evaluate depression levels. After 12 weeks of treatment, ERP recordings were made again. A fifty percent or greater decrease in a patient's HDRS scores after 12 weeks was considered a treatment response.

Seventeen patients were excluded from the study: two cases whose P300 recordings could not be taken, one patient due

to hypomanic shift, three patients due to lack of regular antidepressant use, two patients due to drug side-effects and nine patients who failed to follow-up. Twenty-eight healthy volunteers, matched for age and sex with 28 patients who completed follow-up, were included in the control group.

ERP recordings were made in a room that was well-lit and isolated from noise when possible. Recordings were taken with the patient in a seated position and a four channel Esaote (Italy) EMG-EP device was used. Before placing electrodes, the subject's scalp was cleaned, and silver/silver chloride electrodes (CM52–422) were filled with conductive substance and placed tightly on the scalp. Active electrodes were placed in Cz regions according to the international 10-20 system, and recordings were made using mastoid regions as reference. Impedances were kept under 5 kΩ. The P300 potential was obtained using the oddball paradigm (sending a target stimulant at uncertain times between expected stimulants). Auditory stimulants were relayed to both ears at a loudness of 60 dB over the threshold hearing value. The frequency of the non-target stimulant was determined as 1000 Hz and that of the target stimulant as 2000 Hz. The frequency of stimulation was determined as 0.7/s (Vandoolaeghe et al. 1998, Tascilar et al. 2011) and the sweep time as 500 ms. After patients were informed about the test protocol, patients listened to the target and non-target voices one by one. They were asked to count target stimulants appearing randomly at a frequency of 20% among non-target stimulants appearing at a frequency of 80%. Recording was continued until 40 target stimulants were given, then the average value of obtained potentials was calculated. Recordings were repeated twice. Infraorbital (IO) recordings were taken for eye blinking artifacts. Recordings of those with eye blinking artifacts and/or whose stimulant counts differed by more than 10% from the actual number of target stimulants were repeated. In analysing the data recordings of the Cz, the area which generates the best recordings, were taken into consideration. The highest positive wave between 200-500 ms after stimulation was evaluated as the P300 response. The point at which the wave deviated from baseline was evaluated as the onset of P300 latency, while P300 amplitude was evaluated as the height between the baseline and the peak of the potential. Measurements were made using the programs in the Esaote EMG-EP device.

Statistical analysis

Statistical analysis of the data was made on the computer using SPSS (Statistical Package for Social Sciences for Windows, version 15.0). For descriptive statistics, frequency distributions, and continuous variables, arithmetic means and standard deviation values were used. Groups were compared using the chi-square test for discontinuous variables. To compare the mean values of two groups with normal distributions, Student's t-Test was used. To compare the mean values of three or more groups, one-way variance analysis (ANOVA) was used and to evaluate repeated measurements in dependent groups, t-tests were used. An alpha value of 0.05 was designated and p values less than or equal to this value were considered statistically significant.

RESULTS

No significant difference was found between responder (n=18) and non-responder (n=10) groups in terms of age, sex or education level (Table 1). When clinical variables were examined, no significant difference was found between groups with regard to the severity of depression, the number of episodes, the age of onset, family history of MDD, or the duration of disease (Table 1). In cases responding to treatment, the baseline HDRS score was found to be 25.83 ± 2.93, and in those not responding, 28.70 ± 4.52, with no statistically significant difference between groups (p=0.052). After 12 weeks of treatment, mean HDRS scores decreased to 5.77 ± 3.29 for the responding group and 20.20 ± 3.15 for the non-responding group.

ERP recordings of all groups before and after treatment are shown in Figure 1. Mean P300 amplitude values for all patients pre-treatment (9.89 ± 5.67 μV) were significantly lower than those of the healthy control group (13.26 ± 4.38 μV; p=0.016; Table 2). No significant difference was found between pre-treatment P300 amplitude values of responders (10.19 ± 6.59 μV) and of the healthy control group (p=0.125). Similarly, pre-treatment P300 amplitude values were not significantly different between the non-responding group (9.36 ± 3.73 μV) and either the healthy control group (p=0.105) or the responding group (p=0.910; Table 3).

Regarding post-treatment P300 amplitude values, no significant difference was found between the three groups. P300 amplitude values increased significantly in the responding group after treatment (p=0.014), while no statistically significant difference was found in P300 amplitude values for the non-responding group (Table 3).

In comparing P300 latencies, all cases had significantly longer mean P300 latencies (334.57 ± 30.82 ms) compared to the healthy control group (301.03 ± 18.62 ms; p=0.001; Table 2). Pre-treatment P300 latency values of responding cases (322.33 ± 29.24 ms) were found to be significantly longer than those of the healthy control group (p=0.009; Table 3). Pre-treatment P300 latency values of the non-responding group (356.60 ± 19.88 ms) were found to be significantly longer than those of both the healthy control group (p=0.001) and the responding group (p=0.001; Table 3).

When latency values were examined after treatment, no significant difference was found between the values of the group responding to treatment and those of the healthy control

Table 1. Socio-demographic and clinical features of responder and non-responder groups

	Responders (n=18)		Non-responders (n=10)		
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	P
Gender					
Female	14	77.8	7	70.0	0.649
Male	4	22.2	3	30.0	
Severe depression					
Yes (HAM-D ≥25)	11	61.1	8	80.0	0.305
No (HAM-D <25)	7	38.9	2	20.0	
Index episode					
First episode	7	38.9	4	40.0	0.954
Recurrent episode	11	61.1	6	60.0	
Age of onset					
Early (≤25)	6	33.3	2	20.0	0.454
Adult (>25)	12	66.7	8	80.0	
Family history					
Yes	5	27.8	2	20.0	0.649
No	13	72.2	8	80	
	Mean ± SD		Mean ± SD		
Episode duration (weeks)	4.16 ± 1.94		5.20 ± 3.11		0.289
Age of onset (years)	29.72 ± 9.41		31.70 ± 6.29		0.559

Table 2. Comparison of patients' pre-treatment P300 amplitudes and latencies with those of the control group

P300 (Cz)	Patients (n=28)	Control (n=28)	P
Amplitude (μV)	9.89 ± 5.67	13.26 ± 4.38	0.016
Latency (ms)	334.57 ± 30.82	301.03 ± 18.62	0.001

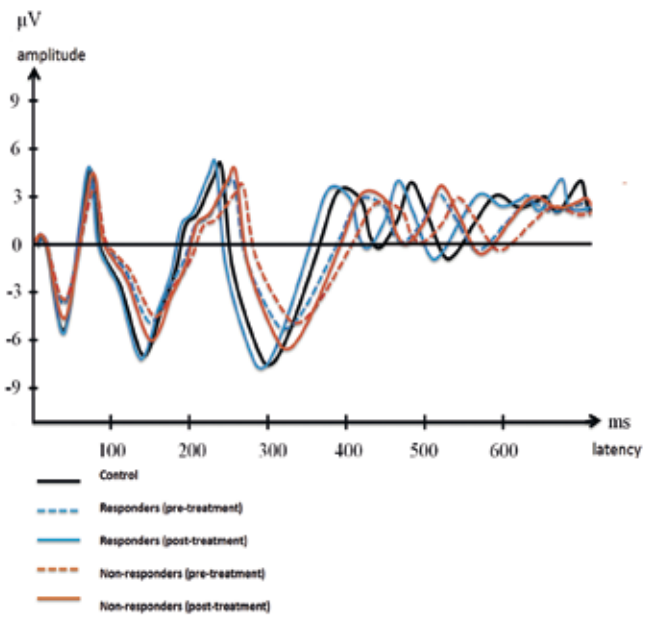

Figure 1. ERP recordings of subjects before and after treatment.

group (p=0.561). Post-treatment latency values of the non-responding group were found to be significantly longer than either the healthy control group (p=0.001) or the responding group (p=0.001; Table 3). In the responders group P300 latency values were significantly shortened after treatment (p=0.002). Similarly, in non-responders group P300 latency values were also significantly shortened (p=0.046; Table 3).

DISCUSSION

No statistically significant difference was found between groups responding and not responding to treatment with respect to age, sex or education level. In addition, there were no significant differences between the responding and the non-responding groups in terms of clinical characteristics (severity of depression, the number of episodes, the age of onset, family history and duration of disease), which suggests that two groups are homogenous for clinical features. The age range of the patients was between 19 and 50 years and the mean age was 34.03 ± 8.01 years. Patient age is an important factor which may impact P300 amplitude and latency values. At advanced ages, the amplitude of P300 decreases and its latency is prolonged (Goodwin et al. 1978, Geal-Dor et al. 2006, Elwan et al. 2003). In the present study, there were no elderly patients, removing age as a factor.

In the present study, P300 amplitudes of MDD patients were found to be significantly lower than those of the healthy control group and their latency values significantly longer. The

Table 3. Comparison of responders' and non-responders' pre-treatment and post-treatment P300 amplitudes and latencies with those of the healthy control group

		Patients		Control*	ANOVA
P300 (Cz)		Responders (*n*=18)	Non-responders (*n*=10)	(*n*=28)	
Latency (ms) (mean±SD)	Before treatment	322.33±29.24[a]	356.60±19.88[a,b]	301.03±18.62	*F*=22.47 df=2,53 *P*<0.001
	After treatment	295.00±20.71[c]	339.00±18.97[a,b,c]	301.03±18.62	*F*=18.31 df=2,53 *P*<0.001
Amplitude (μV) (mean±SD)	Before treatment	10.19±6.59	9.36±3.73	13.26±4.38	*F*=3.12 df=2,53 *P*=0.052
	After treatment	13.37±4.16[c]	12.21±4.81	13.26±4.38	*F*=0.26 df=2,53 *P*=0.772

*Control group was tested only once and same values were used for ANOVA. [a]Significantly different from control group as determined by one-way ANOVA (post hoc Tukey test). [b]Significantly different from responder group as determined by one-way ANOVA (post hoc Tukey test). [c]Significantly different from pre-treatment values (t-test for dependent groups, p<0.05).

results of the related studies are contradictory. Some studies have stated that there is no difference between P300 latency and amplitude values of MDD patients and those of healthy individuals, whilst there are studies reporting differences in amplitudes or latencies or in both (Vandoolaeghe et al. 1998, Urretavizcaya et al. 2003, Gangadhar et al. 1993, Kemp et al. 2010, Karaaslan et al. 2003, Houston et al. 2004). Debates on the cause of these discrepancies focus on the differences between the methods of the studies. In order to resolve these contradictions, non-psychotic, unipolar major depression patients who are not advanced in age (>50 years) were included in this study. As serotonergic drugs exert acute effects on P300 (d'Ardhuy et al. 1999), all patients were drug-free at the time of their first P300 recordings. Findings of the present study are congruent with other studies reporting that, in major depression patients, P300 amplitude is low and its latency is prolonged. A decrease in P300 amplitude and prolongation of latency point to the impairment of information processing observed during depressive episodes.

No statistically significant difference was found between the two treatment groups (responding and non-responding) and the healthy control group in terms of pre-treatment P300 amplitude values. When evaluating all depression patients as a single group, P300 amplitude values were found to be lower for depression patients than for the healthy control group. However, when patients were grouped according to treatment response, no statistically significant difference was found between treatment groups and the healthy group, a result which may be due to smaller sample size or to a lack of separation and evaluation of depression subtypes.

Pre-treatment P300 latency values of patients responding to treatment were longer than those of the healthy control group. For patients not responding to treatment, pre-treatment P300 latency values were found to be longer than those of either the healthy control group or the group responding to treatment. P300 latency is related to the time to determine whether stimulant is important and reflects the speed of cognitive processes (Vandoolaeghe et al. 1998). Therefore, longer P300 latencies among cases not responding to treatment indicate a slowing of cognitive function in these patients. This finding is consistent with studies which have reported that depression patients with impairment in cognitive function respond less to Selective Serotonin Reuptake Inhibitor (SSRI) treatment (Kampf-Sherf et al. 2004, Dunkin et al. 2000, Taylor et al. 2006). In addition, findings obtained in the present study are compatible with those of two previous studies which found a relation between lack of treatment response and prolonged P300 latency (Vandoolaeghe et al. 1998, Kalayam and Alexopoulos 1999).

Initial P300 latency values of patients responding to treatment are shorter than those of the non-responding group and longer than those of the healthy control group, indicating that cognitive functions are affected also in the group responding to treatment. However, P300 latencies of responding patients shortened significantly after 12 weeks of treatment, becoming comparable to the values of healthy individuals. The findings of the present study are in keeping with Karaaslan et al. (2003) which reported that P300 latencies of MDD patients returned to normal with treatment. Although P300 latency values shortened significantly for the non-responding group, their values continued to be longer than those of the other groups. That P300 latency prolongation in non-responders was maintained post-treatment suggests that impairment of cognitive function continued to affect this patient group.

In conclusion, in MDD patients, no relation was found between P300 amplitude values and response to treatment. However, P300 latencies were found to be longer among cases not responding to treatment than among either those who responded or the healthy control group. The relation between prolongation of P300 latency and lack of response to treatment seems to be an important issue and thus requires further investigation.

The small sample size and our decision to not evaluate depression subtypes may be considered limitations of this study. In

order to better clarify the relation between P300 and treatment response in MDD patients, further studies with larger samples which evaluate depression subtypes separately and which compare different antidepressants are required.

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