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Auditory P300 event related potential and serotonin reuptake inhibitor treatment in obsessive-compulsive disorder patients

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Abstract

Neuropsychological findings in obsessive-compulsive disorder (OCD) have been explained in terms of reduced cognitive shifting ability as a result of low levels of frontal inhibitory activity. This deficit could be reflected in an abnormal P300 component of the event-related potential. The improvement in cognitive processing due to pharmacological treatment would modify the P300 component, bringing it close to that of normal controls. Nineteen patients suffering from OCD and 19 normal controls were recorded. We used a computerized version of the auditory 'odd-ball paradigm' to obtain the P300 component at the Pz electrode. Patients were tested twice, drug-free and under treatment with clomipramine in 250–300 mg doses. We observed the P300 component to have lower amplitude and longer latency in drug-free OCD patients when compared with controls. P300 amplitude in OCD increased after treatment, although this was supported only by a statistical trend. There was no modification in P300 latency after treatment. It is possible that inhibitory activity improves with treatment and allows patients to answer with more confidence, which results in an increase in P300 amplitude. This study suggests that cognitive dysfunction in OCD fluctuates with changes in the clinical associated with treatment, probably in relationship to central serotoninergic transmission.

Keywords: Neurophysiology; Electroencephalography; Cognitive shifting; Neuropsychological functioning

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1. Introduction

There is no clear evidence on the nature of cognitive dysfunction in obsessive-compulsive disorder (OCD) patients (Insel and Winslow, 1992; Beers et al., 1999; Fitzgerald et al., 1999; Mataix et al., 1999). Conflicting neuropsychological findings in this disorder have been reviewed and explained in terms of reduced cognitive shifting ability (Lucey et al., 1997; Cavedini et al., 1998; Schmidtke et al., 1998). Previously, Head et al. (1989) had interpreted this cognitive deficit in terms of a loss of normal inhibitory processes associated with the dominant frontal area, and suggested that this may account for what they regard as the fundamental aspect of obsessions: the inability to inhibit verbal representations. This deficit in cognitive shifting ability could be related to attentional abnormalities in OCD, for which there is a growing body of evidence, and to the dysfunction in frontal inhibitory process necessary for the maintenance of working memory (Schmidtke et al., 1998). This cognitive dysfunction may be reflected in P300 abnormalities (Mourault et al., 1997).

The involvement of the serotoninergic system and frontal functioning in inhibiting behavioral response has been reported in animal models (Soubrié, 1986; Pitman, 1989; Rauch and Jenike, 1993); it is also well known that central serotoninergic neurotransmission is involved in the pathophysiology of OCD (Lopez-Ibor, 1988; Hollander, 1998). Hegerl and Juckel (1993) published a very interesting study in which they proposed the intensity-dependence of auditory evoked potentials as an indicator of the central serotoninergic system. Studies on the influence of serotoninergic function on brain ERPs in OCD patients are contradictory: Mourault et al. (1997) found significantly reduced N2 and enhanced P3 amplitudes before treatment in patients whose OC symptoms improved after treatment when compared with those who failed to show improvement; on the contrary, the findings of Towey et al. (1994) of greater N2 amplitudes correlated to better responses to serotonin re-uptake blockers in a quite similar treatment protocol. These contradictory findings, even for the effects of serotoninergic agents on ERPs, still represent an argument for a dysfunction of the processes underlying auditory evoked potentials rather than a static impairment. The results are not conclusive for the consideration of a specific index for predicting treatment efficacy.

We propose the hypothesis that an abnormal P300 wave indicates that a subject is not cognitively processing the evoking stimulus appropriately. In OCD patients a difficulty in paying attention only to target stimuli because of problems in frontal inhibitory control may result in an abnormal P300 wave. Treatment with serotoninergic agents may improve cognitive processing resulting in a P300 wave similar to that of normal controls.

2. Methods

2.1. Sample

Nineteen healthy volunteers (nine females, mean age 20.5 years) and 19 OCD patients (10 females, mean age 25.8 years) took part in the study. Patients were diagnosed in accordance with DSM III-R criteria. Patients with obvious brain disease or other psychiatric illness were excluded. A total score on the Hamilton Depression Scale > 10 was the exclusion criterion. No subjects had a history of alcohol or drug abuse. One hundred percent of the controls had completed at least 1 year at the university whereas this was the case for 70% of the patients. The rest of the patients had undertaken primary and secondary school education. All subjects were right-handed and had normal or corrected-to-normal vision. OCD patients were selected from the outpatient clinic. They received detailed information about the study protocol and gave written consent. Ten of the participants were psychotropic-naïve, and this was their first acute episode.

2.2. Assessment

Patients were diagnosed using the structured clinical interview for DSM III-R (SCID; Spitzer et al., 1987).

We assessed psychopathology with the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b), the Hamilton Depression Scale (Hamilton, 1960) and the Hamilton Anxiety Scale (HAS).

Patients were interviewed and studied twice, drug-free and under treatment with clomipramine in 250–300 mg doses. Eight patients were under treatment when they were included in the study and without acute symptoms and were, therefore, tested first under treatment. They subsequently stopped taking medication, and after at least 1 month, and when acute symptomatology appeared again, they were given the second interview and the electroencephalographic study was carried out. This permitted us to minimize the learning effect in the P300 component obtained under treatment. Four of the 19 patients dropped out of the study before their second ERP session, after treatment.

2.3. Recording system

EEG activity was recorded from the scalp through 20 tin electrodes inserted in a pre-configured cap (Electrocap International). Recording systems included Pz of the International 10–20 system (Pivik et al., 1993). Linked mastoids were used as the reference and Fpz as ground. The electro-oculogram (EOG) was recorded bipolarly from electrodes placed above and adjacent to the outer canthi of the right eye. Electrode impedances were kept below 5 kΩ. All EEG and EOG channels were amplified with a SYNAMP (NeuroScan Inc.) DC coupled amplifier system. Recordings were made from DC with a low pass filter set at 50 Hz (12 dB/octave roll-off). Single-trials epochs were digitized at 4 ms/sample and stored on magneto-optical disk for off-line analysis, together with event markers and response latencies. Each epoch was of 600-ms duration, including a 200-ms pre-stimulus baseline.

2.4. Stimuli

We used the computerized version of the auditory 'odd-ball paradigm' incorporated with the NeuroStim Inc. package. Two tones were presented binaurally in a random fashion while the subjects looked at a fixation point. Subjects were told to press a response button with their right hand whenever they heard a different tone (80% trials, 1500 Hz, 100 ms with 10 ms rise/fall times and 80 dB SPL) from the background tones (20% trials, 800 Hz). They were told to answer as soon as they heard the different tone.

2.5. ERP analyses

Continuous EEG recordings were epoched from 200 ms prior to stimulus onset to 600 ms after it. Blinks and horizontal eye movements were corrected on a trial-by-trial basis using a standard linear correction procedure (Semlitsch et al., 1986). After EOG artifact correction, trials exceeding amplitudes of ± 75 μV at any of the active electrodes were automatically discarded from the averages. Any linear trend within the recording epoch was removed prior to averaging, and waveforms were aligned to a 200-ms pre-stimulus baseline.

The Pz P300 component for rare stimuli (minimum 30 trials for each subject) was assessed by calculating the mean value between 250 and 300 ms. We chose the Pz electrode following the review of Polich (1992), and the time interval following visual inspection of the mean waveform (Figs. 1 and 2).

3. Results

We used parametric comparisons (Student's *t*-test for independent samples) to analyze the mean differences between groups (normal controls/OCD). Although the sample was small ($n = 19$ in each group), we were able to use parametric comparisons because they complied with the application conditions. (Shapiro–Wilks test indicated that we could accept the normality distribution of the sample. We also applied Levene's test for Equality of Variances.) We made the following comparisons:

- We first compared the amplitudes of P300 waves between normal controls and OCD

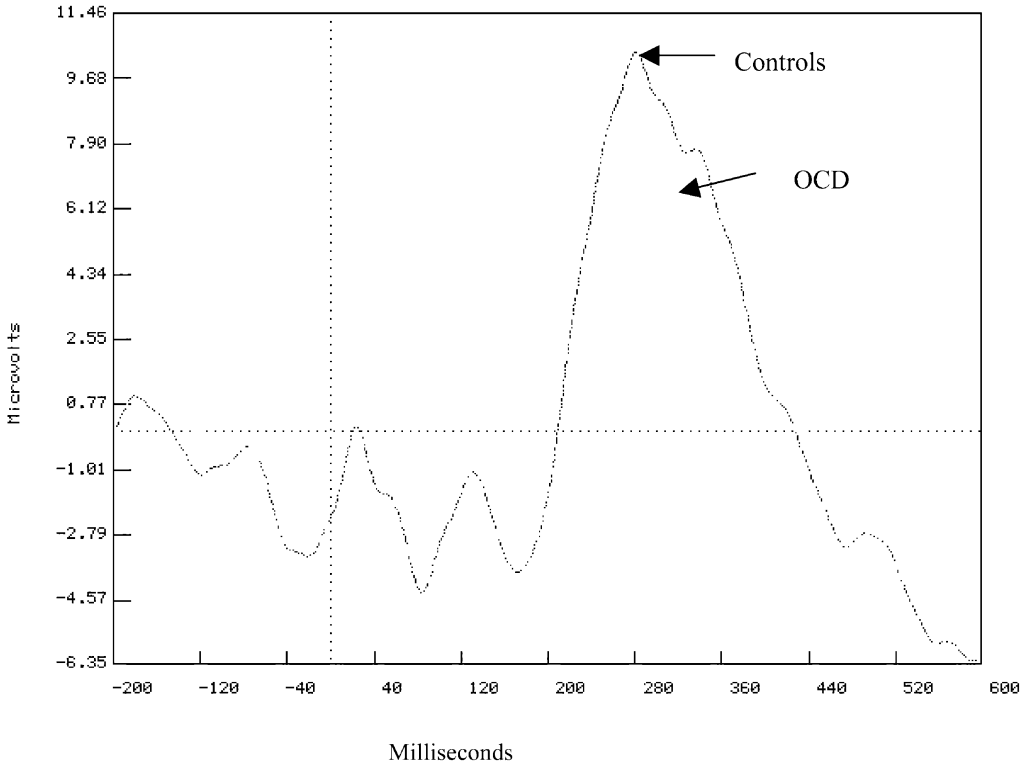

Fig. 1. P300 normal controls/OCD patients.

patients. Mean amplitude was significantly lower for OCD patients without pharmacological treatment (6.6 μV) as compared with controls (11.01 μV) (pooled t: 2.07, d.f.: 35, $P < 0.05$).

- The analysis of latency data revealed longer latency in OCD patients without treatment (308 ms) when compared with normal controls (288 ms) (pooled t: −2.67, d.f.: 33, $P < 0.05$) (Fig. 1). Latency showed a Pearson correlation coefficient of 0.5, close to significance: $P < 0.08$.

The mean global score on the Y-BOCS for the patients was 36.84 and that for the HAS was 11.8.

- We observed the effect of treatment in the P300 component by means of the parametric comparison for repeated measures. We only considered patients who finished the study. In spite of the small sample size ($n = 15$), we decided to used parametric comparison for repeated measures because it provides more statistical power. This was possible because the sample had a normal distribution, as confirmed by the Shapiro–Wilks test. We observed an increase in amplitude (4.3 μV in the OCD group without drugs and 7.4 μV in the OCD group with drugs) close to the level of significance (matched t: −1.99, d.f.: 14, $P = 0.066$) (Fig. 2).
- There was no difference in latency before/after treatment

The mean global score on the Y–BOCS before treatment was 41.9 (S.D. 10.6), and after treatment it changed to 27.2 (S.D. 10.9). Anxiety level was the same before and after treatment. The correlation between YBOCS change score (drug minus base line) and P300 change (drug minus

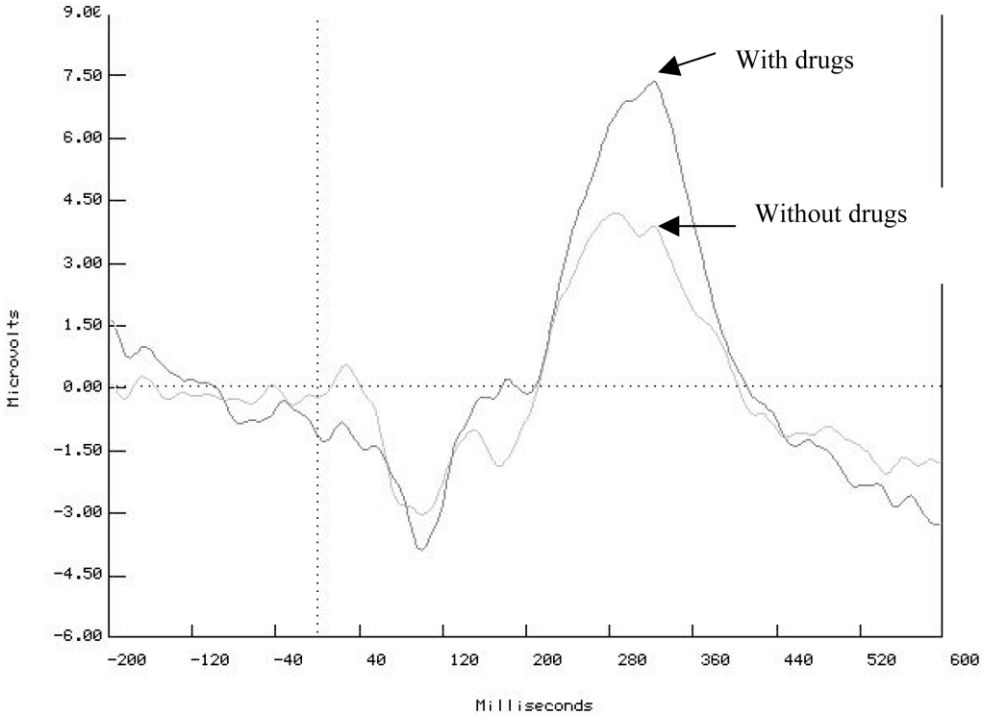

Fig. 2. P300 OCD patients with/without treatment.

base line) was a correlation coefficient: -0.4, without statistical significance ($P = 0.1$).

The control group performed with 99.8% accuracy and the OCD group with 99%.

4. Discussion

It is interesting to note the lower P300 amplitudes in OCD patients when compared with volumes in normal controls and changes in amplitude after treatment. As is well known, the P300 component has a very wide variability among subjects, even in normal people. In spite of this variability we found statistically significant differences in P300 amplitude between normal and OCD patients free of treatment. The increase in P300 amplitude we observed after treatment in OCD patients came close to statistical significance. There was no modification in P300 latency after treatment. It would be interesting, therefore, to perform further research using a larger sample to increase the statistical power of the trend found here.

The trend-level increase in P300 amplitude after treatment may lead us to suspect an influence of serotoninergic central function in the cognitive processes necessary for evoking the P300 component. Most studies have considered the P300 as a good general index of cognitive processing. In this regard, different cognitive deficits have been found across studies in OCD: memory for actions, frontal dysfunction, visuo-spatial inability (Tallis, 1995). Inconsistencies may be due to one or more sources of variability within samples, such as symptom severity, diagnostic heterogeneity and subtle brain abnormalities that are difficult to locate (neurological soft signs). The majority of authors are agreed on explaining cognitive deficits in terms of reduced cognitive shifting ability, and this deficit is the only one replicated across studies (Head et al., 1989; Tallis, 1995; Lucey et al., 1997; Cavedini et al., 1998; Schmidtke et al., 1998).

The inhibitory function implied in cognitive shifting ability seems necessary to correctly perform the auditory 'odd-ball paradigm'. One must inhibit the motor action to answer when one hears the frequent tone in order to answer only when the different tone is heard. The frontal lobe is directly related to this inhibitory process, and many authors have emphasized the participation of the frontal lobe in P300 generation (Alexander et al., 1986; Savage et al., 1994).

Low levels of inhibitory activity have constituted the most consistent dysfunction proposed in the pathophysiological features of OCD disorder (Beech et al., 1983; Mourault et al., 1997). The inability to inhibit responses probably makes the evaluation of the stimulus and its correct mnesic representation difficult. As mentioned above, the evaluation and mnesic representation of stimuli are in direct relationship to P300 generation, and their dysfunction modifies this component (Donchin and Coles, 1988).

It is worth mentioning the increase in P300 amplitude seen after clomipramine treatment. Our data suggest that when serotoninergic function improves, P300 amplitude comes closer to normal values, although it was only a statistical trend.

There are some studies on the implication of serotoninergic systems and frontal functioning in inhibiting the behavioral response reported in animal models (Soubrié, 1986; Pitman, 1989; Rauch and Jenike, 1993). Given the functional and morphological diversity of the frontal cortex and its interactions with other cerebral regions, a dysfunction in frontal function could be reflected in other areas. Although in the present study we only studied electrical activity at the Pz electrode, we can infer the participation of other areas in the generation of this ERP as a result of more global cognitive function. We have interpreted the diminished P300 amplitude in OCD patients as a reflection of low levels in inhibitory activity, and its increase after treatment supports the idea that cognitive dysfunction in OCD fluctuates with treatment-related changes in clinical state probably in relationship to central serotoninergic transmission.

We found a positive correlation between anxiety level and P300 latency. Several studies suggest the possibility that P300 latency may be related to stimuli evaluation, while P300 amplitude may be linked to the subject's certainty in answering (Squires et al., 1977a,b; Kutas et al., 1977; Donchin, 1981). It is possible that the ability to inhibit responses improves sufficiently with treatment for subjects to answer with more confidence, which leads in turn to an increase in P300 amplitude.

In the light of our findings, P300 latency and amplitude appear to be related to different cognitive processes.

In summary, a low level in inhibitory activity may make the evaluation and mental representation of the target stimuli difficult, leading OCD patients to feel less secure in their response. We think that the lower P300 amplitude in OCD patients may be related to uncertainty in answering. Uncertainty in making decisions is probably a fundamental aspect of OCD patients' psychopathology, and bears a direct relationship to the difficulty to inhibit.

The effect of treatment suggested that the cognitive function in OCD patients improved with pharmacological treatment because of a better serotonin function, and this was reflected in a P300 amplitude close to that of normal people. We can propose, then, that P300 amplitude probably fluctuates with changes in clinical state. Although this hypothesis is only supported by a statistical trend, we consider this finding quite interesting and suggestive, contributing new data about the effect of pharmacological treatment on cognitive functioning and demanding future research.

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