Original Article

P300 IN OBSESSIVE COMPULSIVE DISORDER

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ABSTRACT

Objective : It has been hypothesized that an unstable arousal system exists in patients with obsessive-compulsive disorder (OCD) and P300 is commonly used to investigate for such information-processing abnormalities. However, studies of P300 in OCD have had inconclusive results, regarding both amplitudes and latencies, along with poor correlation with clinical variables. This study aimed to further investigate the suggested misallocation of cognitive resources and attentional disorder in OCD.

Methodology : Thirty patients of OCD, taken from the outpatient department of Central Institute of Psychiatry, and 27 age-, sex-, and education-matched normal volunteers were examined in this study. The psychopathology in the patients was evaluated using the Y-BOCS and HDRS scales; GHQ-5 was used to screen the normal controls. P300 was recorded by an auditory two-tone discrimination task in both groups using Neuropack Sigma-8 Nihon Kohden software. **Results :** P300 amplitude did not differ between patients and controls; neither was it correlated with most of the demographic and clinical variables. Patients had a significantly longer latency of P300 especially in frontal areas, those on medication also having a significantly longer latency than those off drugs. However, P300 latency did not vary significantly with sex, age, education, onset, duration, or course of illness, and severity of

depression or obsessions & compulsions.

Conclusion : This study replicated previous ones in showing no significant difference of P300 amplitude in OCD patients compared to controls. P300 latency was significantly increased ($p=0.035, 0.024$ & 0.044 , in Fz, F4 & F3, respectively) in frontal leads, suggesting an electrophysiological abnormality in this part of OCD brain, correlating well with other neuro-imaging and neuropsychological studies that have also implicated the frontal lobe in OCD.

INTRODUCTION

The last two decades have seen remarkable advances in the understanding of the neurobiology of Obsessive-compulsive disorder (OCD) in form of different structural (Behar et al., 1984), (Luxemberg et al., 1988) and functional abnormalities. The latter have been especially well documented as increased glucose metabolism and blood flow of orbito-frontal cortex, pointing to abnormal activation of an orbital frontal - basal ganglia - thalamic loop (Cohen et al., 1997). Neuropsychological tests have suggested impairment in executive functioning, as well as deficits in visual memory, with indication of lateralisation of neuropsychiatric dysfunction as visuo-constructional impairment is more than the verbal ones, suggesting left hemisphere hyperfunction with concomitant right hemisphere hypofunction (Schultz et al., 1999).

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It has been suggested that an unstable arousal system exists in OCD that makes the person vulnerable to rapid and fixed conditioning - implying that patients would show altered information processing in the central nervous system, the evidence of which is sought by examining evoked potential (EP) responses (Beech et al., 1983).

The most commonly used EP in neuropsychiatry is P300 (Barrett, 1993), whose amplitude is directly related to task relevance and difficulty (Altenmuller & Gerloff, 1999); longer P300 components are produced when more attentional resources are allocated to the task stimuli in a given experimental situation (Wickens et al., 1983). P300 amplitude is maximal over the midline central and parietal regions (Oken, 1997), with increased amplitude occurring during better memory performances (Fabiani et al., 1990; Smith et al., 1990). The latency of P300 reflects the speed of stimulus classification, is also related to task difficulty-- P300 latency increases as the task becomes harder, and shows a negative correlation with the level of attention and vigilance. Shorter P300 latency thus implies superior cognitive function in comparison to longer ones (Altenmuller & Gerloff, 1999; Polich, 1999).

The functional significance of P300 is often discussed as per a "context updating model" according to which, it is a manifestation of processes occurring when events necessitate a revision of the individual's internal representation of the outer world. P300 may be thus interpreted as indexing tasks that are required in the maintenance of 'working memory' (Altenmuller & Gerloff, 1999). An alternative approach is the interpretation of P300 as a deactivation consequent upon the closure of a perceptual epoch (Karlin, 1970).

Evoked potentials elicited by visual discrimination tasks in OCD have had inconclusive results, with the amplitudes ranging from being reduced (Ciesielski et al, 1981, Beech et al., 1983) to being larger (Di Russo et al., 2000) in comparison to normal controls. However, auditory oddball paradigm has shown either no significant difference (Okasha et al., 2000), or lessened P300 amplitude (Towey et al., 1994, Sanz et al., 2001) that also increased after treatment (Sanz et al., 2001).

Most studies have shown shorter latencies of EP in OCD using either visual stimuli (Ciesielski et al, 1981, Beech et al., 1983, De Groot et al., 1997) or auditory stimuli (Morault et al., 1997, Miyata et al., 1998). However, there are reports of no significant difference (Okasha et al., 2000), as well as longer latency of P300 in patients (Sanz et al., 2001) that persisted in spite of treatment (Sanz et al., 2001).

Increased tasks difficulty tended to lengthen latency and increase amplitude among normal persons, but not in OCD patients (Beech et al., 1983, Towey et al., 1990) and in fact the latter had significantly shorter latencies in the difficult task (Towey et al., 1990).

Efforts to correlate electrophysiological parameters with different clinical variables have been equivocal, in that some studies have shown no significant correlation of P300 values with severity of symptoms (Miyata et al., 1998), drug status (Ciesielski et al, 1981, Malloy et al., 1988), or age of onset and length of illness (Ciesielski et al, 1981). However, there are also contrary results of P300 amplitude varying with severity of symptoms (De Groot et al., 1997), and a positive shift of P300 amplitude in responders versus non-responders (Morault et al., 1997).

Thus, electrophysiological investigations have suggested misallocation of cognitive resources and attentional disorder in OCD (Di Russo et al., 2000); but most of the above dealt with small sample sizes, and further studies are clearly warranted in view of contradictory results.

METHODOLOGY

Consecutive patients of OCD diagnosed using the Diagnostic Criteria for Research of ICD-10, with age ranging from 18 to 50 years, were recruited from the Central Institute of Psychiatry, Ranchi, after giving informed consent for this cross-sectional and comparative study. Patients having any major medical illness, focal neurological deficits, history of any neurological disease, or any co-morbid psychiatric syndromes other than depression were excluded. However, in the depressed patients, efforts were made to ensure that depression is secondary to the OC-symptoms.

Staff and students of the Institute without any family or past history of psychiatric disorder were taken as normal controls, if they scored less than or equal to one on the General Health Questionnaire-5 (Shamsunder et al., 1986), after matching for age, sex and education. Tools of assessment included: 1) Socio-demographic & clinical data sheet, 2) Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989), 3) Hamilton Rating Scale For Depression (Hamilton, 1960), and 4) Handedness Preference Schedule (Mandal et al., 1992).

P300 was recorded using the Neuropack Sigma 8, Nihon Kohden software, the recording conditions and procedure as per standard guidelines suggested by Polich (1999). The subjects were asked to lie down

supine, to fixate both eyes at one point without moving eyeballs or eyelids, as immobile and relaxed as possible, and to press a button with the index finger in response to the infrequent target tones. The electrodes (silver / silver chloride discs) were positioned at the sites Fz, Cz, Pz, F4, F3, C4, C3 (recording), FP1 (electrooculogram / EOG), both mastoid (reference) and forehead (ground) on the basis of international 10-20 system of electrode placement, the impedance being kept at less than 2 Kohms.

ERP were elicited using the standard auditory odd ball paradigm - the stimulus being an auditory pure tone of 100 ms duration with a 10 ms rise and fall time, delivered binaurally through a head phone. The frequent stimulus was 1000 Hz (40 dB) and random infrequent stimuli 2000 Hz (55 dB) - their respective probabilities being 0.8 and 0.2. Triggered by the onset stimulus, 800 ms of the EEG epochs were collected for averaging, the record being band filtered between 0.1Hz and 100Hz. Trigger mode was recurrent. The on-line automated artifact rejection supplied by Neuropack sigma 8-Nihon Kohden was applied and trials continued till 10 artifact free registrations of such responses were obtained. Trials were automatically rejected if the voltage exceeded 100uv at any point in the averaging epoch in the EOG lead. Each recording session lasted approximately 30 minutes.

P300 was measured in form of peak amplitude relative to a pre-stimulus baseline and peak latency relative to the stimulus onset. Using the negative-up EEG convention as in most electrophysiological studies in psychiatric literature, the P300 waves were

identified visually as the most positive point in the waveform between 280-500ms-post stimulus, and marked by using the cursor provided by the computer.

The results were analyzed using the computer software program Statistical Package for Social Sciences-Version 7.5 (SPSS-7.5), with different parametric and non-parametric measures being used wherever applicable.

RESULTS

This study examined 30 patients of OCD selected as per inclusion and exclusion criteria and 27 healthy volunteers matched for age, sex and educational status.

Description of Subjects

The patient group included 14 males and 16 females, with ages ranging from 20 to 50 years (mean = 30.97 yrs., SD = ± 7.28), and a mean education of 10.83 years (range 0 to 16 years, SD = ± 4.03). Fourteen males and 13 females constituted the control group, their ages ranging from 18 to 45 years (mean=29.78 yr., SD= ± 7.73), with a mean duration of education of 13 years (SD= ± 4.92). There was no significant difference in age, sex, education, marital status, occupation or socioeconomic background between the two groups. All the patients were right handed, while one person among the controls was ambidextrous.

The age of onset of OC-symptoms varied from 11 to 40 years with a mean of 25.19 years (SD= ± 8.25). Onset of symptoms was significantly earlier ($p = 0.049$) in males (mean age of onset 22.05 years, SD= ± 8.39) than in females (mean age of onset 27.93 years, SD= ± 7.3). The course of illness was static in 14

patients (46.7%), fluctuating in 11 (36.7%) and deteriorating in 5 (16.7%). Duration of illness ranged from one month to 20 years, mean being 5.78 years (SD= ± 5.57), with no significant difference between the male and female patients.

Twenty patients (66.6%) were drug-naïve, while 10 (33.3%) were on medications that included SSRIs (Fluoxetine, Fluvoxamine), Clomipramine, or a combination of both.

Y-BOCS checklist showed the commonest symptoms to be the obsessions of contamination ($n=23$, 76.7%) and cleaning or washing compulsions ($n=19$, 63.3%); 9(30%) patients had mild, 18(60%) had moderate, and 3(10%) had severe OCD, as per the Y-BOCS ratings. Considering the HDRS cut-off levels, the number of patients having none, mild, moderate and severe depression, were 5 (16.7%), 14 (46.7%), 4 (13.3%) and 7 (23.3%), respectively.

Discriminant analysis taking P300 measurements, showed that 11 (36.7%) patients had been misclassified, while the corresponding number among the controls was eight (29.6%). Among the total subject population of 57, 66.7% of the original grouped cases had been classified correctly.

P300 Amplitude

There was no significant difference in P300 amplitude of patients and normal controls (**Table I**), in any of the channels measured (i.e., Fz, Cz, Pz, F4, F3, C4, and C3).

Subanalysis of P300 amplitude among the patients with different demographic and illness variables showed that amplitude at C4 channel had a significant negative correlation with years of education ($r = -$

0.291 at 0.028 significance level). C3 amplitude showed a trend to be negatively correlated with years of education ($r = -0.244$, significance=0.067), and positively correlated with illness duration ($r = 0.340$, significance=0.066) (**Table II**). There was no significant correlation between course of illness and

P300 amplitude. No significant difference was found in P300 amplitude among the patients, when subanalysis was done on the basis of sex or drug treatment.

Table I
Amplitude of P300 in OCD and controls

Channels	OCD (N=30) Mean $\pm$ SD	Controls (N=27) Mean $\pm$ SD	t	df	p
Fz	8.57 $\pm$ 13.62	10.71 $\pm$ 9.79	0.69	52.54	0.495
Cz	6.57 $\pm$ 7.83	10.26 $\pm$ 8.7	1.68	52.65	0.099
Pz	10.66 $\pm$ 7.23	12.34 $\pm$ 7.21	0.88	54.40	0.384
F4	7.34 $\pm$ 11.71	8.45 $\pm$ 7.67	0.43	50.43	0.672
F3	7.03 $\pm$ 12.32	8.88 $\pm$ 8.53	0.67	51.75	0.509
C4	5.0 $\pm$ 5.1	8.29 $\pm$ 5.65	1.6	52.68	0.116
C3	- 4.77 $\pm$ 6.05	- 7.94 $\pm$ 7.69	1.72	49.31	0.092

p = ns

Table II
Correlation of amplitude of P300 with patient variables

Patient Variables	Fz	Cz	Pz	F4	F3	C4	C3
Age in years	0.092	0.104	0.107	0.092	0.112	0.085	0.095
Years of education	- 0.133	0.158	- 0.158	- 0.153	- 0.175	- 0.291*	- 0.244
Duration of Illness	0.223	0.181	0.255	0.161	0.271	0.132	0.340
Onset of Illness	- 0.007	- 0.055	- 0.114	0.001	- 0.039	0.002	- 0.173
YBOCS-O	0.117	- 0.059	- 0.118	0.118	0.114	0.040	0.031
YBOCS-C	- 0.070	- 0.267	- 0.280	0.022	- 0.043	- 0.201	- 0.025
YBOCS-T	0.014	- 0.216	- 0.256	0.077	0.030	- 0.118	- 0.001
HDRS	0.249	0.177	0.219	0.201	0.239	0.253	0.198

* p < 0.05

P300 Latency

The latency of P300 was found to be longer in the patients in all leads, and the difference assumed significance in all frontal leads (F4, Fz, and F3). In the central leads, latency was significantly more in C4 & C3 and showed a statistical trend to be longer in Cz (**Table III**).

No significant correlation was seen between latency of P300 and the patient variables of gender, years of education, illness duration, or course of illness.

Comparison of who drug-naïve-patients with those on different antidepressants, showed that Fz latency was

Table III
Latency of P300 in OCD and controls

Channels	OCD (N=30) Mean $\pm$ SD	Controls (N=27) Mean $\pm$ SD	t	df	p
Fz	383.33 $\pm$ 79.17	350.52 $\pm$ 18.25	2.20	32.4	0.035*
Cz	371.07 $\pm$ 68.88	345.26 $\pm$ 20.12	1.96	34.42	0.058
Pz	373.53 $\pm$ 70.14	349.33 $\pm$ 17.02	1.83	32.76	0.076
F4	386.33 $\pm$ 82.00	349.63 $\pm$ 21.22	2.37	33.27	0.024*
F3	382.40 $\pm$ 75.35	352.59 $\pm$ 19.48	2.09	33.27	0.044*
C4	381.00 $\pm$ 72.01	348.74 $\pm$ 19.86	2.36	33.84	0.024*
C3	384.40 $\pm$ 80.22	350.07 $\pm$ 19.18	2.27	32.65	0.030*

* p < 0.05

Table IV
Subanalysis of P300 latency values in OCD patients
(Mann Whitney U Test)

Channels	Drug Naïve (n=20) Mean $\pm$ SD	On Drugs (n=10) Mean $\pm$ SD	z	p
Fz	398.5 $\pm$ 86.43	353.0 $\pm$ 53.78	- 1.915	0.055*
Cz	381.60 $\pm$ 74.68	350.0 $\pm$ 52.69	- 1.431	0.152
Pz	383.60 $\pm$ 76.45	353.4 $\pm$ 53.27	- 0.947	0.344
F4	401.0 $\pm$ 88.34	357.0 $\pm$ 62.3	- 1.739	0.082
F3	397.80 $\pm$ 81.02	351.60 $\pm$ 53.41	-1.784	0.074
C4	388.30 $\pm$ 77.72	366.40 $\pm$ 60.0	- 0.991	0.322
C3	394.30 $\pm$ 79.54	364.60 $\pm$ 82.03	- 1.894	0.058

* p < 0.05

significantly more in the former, with a trend for higher latency in F3 and C3 leads (**Table IV**).

Topographical Distribution of P300

The topographical distribution of maximum P300 amplitude and latency was examined in the patients and in controls. Parietal dominance was seen in both the groups, without any significant difference between them in either of the parameters.

DISCUSSION

The auditory oddball paradigm used to elicit the P300 has a distinct advantage over other sensory modalities for eliciting P300 as they are easily produced, they

capture the subject's attention easily without inducing excessive EOG artifacts and the effects of auditory stimulus parameters (tone frequency, duration, rise/fall time, and intensity) have been systematically evaluated (Polich, 1999). This paradigm to elicit P300 in a state-of-the-art machine was one of the strongest points in this study.

This study found no significant difference of P300 amplitude in OCD patients compared to controls, replicating previous ones that found either no difference (Okasha et al., 2000), or statistically insignificant difference (Ciesielski et al., 1981; Towey et al., 1993 & 1994). However, it contradicts

some findings of lower P300 amplitude especially with increasing task difficulty (Beech et al., 1983; Sanz et al., 2001) and greater P300 amplitude (Di Russo et al., 2000) in OCD patients. The significant negative correlation of P300 amplitude in some of the central leads with the years of education may be projected to a wider perspective: one may hypothesize that the difference in results of amplitude between the present study and previous western one actually portrays a difference in educational background of the samples. A replication of decreased P300 amplitude in OCD could perhaps have been possible if the sample population was not drawn from an educationally backward area. The preliminary and isolated finding of positive correlation of P300 amplitude at C4 channel with illness duration, has probably uncertain clinical significance at present, especially, considering that previously no relation was found between P300 amplitude and either medication or length of illness (Ciesielski et al., 1981; Malloy et al., 1988).

The statistically significant increased latency of P300 in all frontal leads suggests that whatever the abnormality in electrophysiology of OCD brain, it was occurring in the frontal area, correlating well with other neuroimaging and neuropsychological studies, that have also implicated the frontal lobe in OCD. Previous studies have shown longer latency in drug-free OCD patients in comparison to normal controls (Sanz et al., 2001) that persisted even after treatment. Contradictory reports exist, with some studies reporting no difference (Okasha et al., 2000) while others show decreased latency (Ciesielski et al., 1981; Oades et al., 1996; Morault et al., 1997; Miyata et al.,

1998) in OCD patients. The number of studies having contradictory results to the present one are no doubt more but each of them examined fewer number of patients ranging from 8 and 13 to 23; here the focus was 30 patients and the results do not seem unacceptable, in spite of obvious differences.

Electrophysiological studies have found an increasing latency of P300 with greater task difficulty in controls (Towey et al., 1993; Beech et al., 1983), and one may presume that the increased latency in this study is due to the OCD brain reacting to a task in a way that the normal brain would react only under difficult conditions. Latency of P300 reflects the speed of stimulus classification, resulting from discrimination of one event from another, and these results may show the ambivalence of the patients in deciding which really is the target stimulus. P300 latency is also found to show a negative correlation with the level of attention and vigilance (Altenmuller & Gerloff, 1999; Polich, 1999). Longer P300 latency thus implies inferior cognitive function and poorer attentional capacities in this sample of OCD patients; this may be compared to results of neuropsychological attentional tests where OCD patients performed as well as controls regarding the qualitative aspect in Trail making test-Form B and Stroop test, but took significantly more time to complete the tasks (Martinot et al., 1990).

The lack of correlation with HDRS with P300 latency is especially noteworthy, suggesting that depression per se, did not perhaps colour the results of P300 measurements.

A longer latency in frontal channels of unmedicated patients compared to those receiving antidepressants

showed that the difference between controls and patients is also replicated when the drug status of patients is considered- it appears that the medications(TCA,SSRI or combination)are, electrophysiologically and statistically speaking, bringing the patients closer to the status of normal controls. This was, of course a cross-sectional study, and cannot be used to confirm electrophysiological normalization in patients due to drugs.

The main drawback of this study lies in some of the OCD subjects having significant, albeit secondary depression, and inability to segregate depressive psychopathology from OCD may have coloured the results -- one cannot say confidently that whatever was shown in the study was only due to OC-symptoms and not due to depression. Also, it examined a heterogeneous group of unmedicated and on-treatment patients, with the former including those who were drug-naïve as well as those who had been treated previously but were currently drug-free. Inability to control drug status was a flaw here,

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- especially considering the fact that neurobiological correlates were being examined. Recording of P300 was mainly done using frontal and central electrodes, and absence of other electrodes may have made the topographical assessment unsatisfactory.

CONCLUSION

Patients with OCD had a longer latency of P300 in comparison to normal controls, suggesting a lower level of attentional resources that was unrelated to either demographic or clinical parameters, and may be suggestive of a marker of illness per se. The shorter latency in medicated patients compared to those off drugs, point to an electrophysiological evidence of improved cognitive functioning with pharmacological control of symptoms. Absence of difference in P300 amplitude, on the other hand, may reflect a heterogeneity of population being studied, or just an inability of efficient allocation of cognitive resources in the patients.

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