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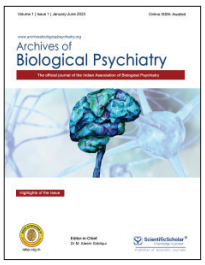

Original Article *Neurophysiology*

A family study assessing P300 as a probable electrophysiological endophenotype in obsessive-compulsive disorder

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ABSTRACT

Objectives: Endophenotype models of disease would help to clarify both diagnostic classification and etiological understanding of obsessive-compulsive disorder (OCD). The objective of the study is to investigate electrophysiological endophenotypes in OCD.

Material and Methods: We recorded P300 on an auditory oddball paradigm for 20 patients with OCD, their 20 first-degree relatives (FDRs), and 20 normal controls (matched with patients). Patients were assessed on the Yale-Brown Obsessive-Compulsive Scale, Hamilton Rating Scale for Anxiety, and Hamilton Rating Scale for Depression.

Results: Both patients and FDRs had significantly shorter P300 latencies as compared to normal controls in all regions assessed ($P < 0.01$). Significantly smaller centro-parietal ($P < 0.01$) P300 amplitude on auditory oddball paradigm was found in patients and FDRs as compared to normal controls.

Conclusion: Shorter P300 latency representing increased processing speed and smaller P300 amplitude reflective of dysfunctional response inhibition are suggested to mediate genetic risk for OCD and proposed as possible electrophysiological endophenotypes for OCD.

Keywords: Event-related potential, Auditory oddball paradigm, Trait marker

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronically debilitating neuropsychiatric disorder. Its prevalence in India is 0.8%, according to the National Mental Health Survey-2015–16.[1] OCD comprises two core symptom dimensions, obsessions and compulsions. OCD is not untouched by familial segregation often seen in other psychiatric disorders such as schizophrenia and bipolar affective disorder.[2] OCD has a genetic basis, with the levels of monozygotic twin concordance reported to be 63–87%, and first-degree relatives (FDRs) showing occurrence rates up to 10–22.5%.[3]

Behavior in psychiatric disorders is "phenotype" and phenotypes are products of genotype and environmental influences. Endophenotypes or hidden phenotypes mean internal phenotypes

discoverable by a "biochemical test or microscopic examination."[2] The endophenotype can be an attribute that is neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological. The argument in favor of studying endophenotypes is the number of genes representing an attribute which will definitely be less than the number of genes representing complex behavioral syndromes in psychiatric disorders.[2] On tests for cognition, not only OCD patients but also their FDRs show deficits in the various sub-domains.[4-7]

It is known that event-related potential (ERP) waveforms identify themselves with various cognitive processes; for example, P300 represents the processing speed of the information.[8] Studies have reported shorter latency of P300 in OCD patients with fair consistency,[9-14] but P300 amplitude is a matter of dispute with some of the studies,[12-15] reporting reduced amplitudes and the others[16,17] reporting larger amplitudes. A recent review, however, suggests decreased P300 amplitude in OCD patients.[18] More interestingly, some recent studies have shown that there is a lack of association between P300 measures and OCD symptom severity and suggest P300 in OCD to be a potential endophenotype.[19] If electrophysiological attributes have an endophenotypic value similar to their cognitive counterparts, it is worth investigating them. Although error-related negativity has been studied and also reviewed systematically for being a candidate endophenotype,[20] such studies using P300 are sparse for OCD. The present study was planned to do so.

MATERIAL AND METHODS

Study design

This study used a cross-sectional design with a comparator group and was conducted at a tertiary care mental health institute in Eastern India. This study included 20 OCD patients, their 20 FDRs and 20 normal controls matched for sex, age, and education with OCD patients. Individuals participating in the study were between 18 and 50 years of age and had received primary education. Written informed consent was obtained from all participants after explaining all the details of the experimentation. The study was approved by the Ethical Committee of the Institute. At the outset, all patient's diagnoses were reassessed against criteria laid down in the 10th edition of the International Classification of Diseases[21] through a detailed psychiatric interview. Patients with OCD having any comorbid psychiatric disorder were excluded from the study. All patients were drug naïve and or drug free for at least 2 weeks and not having received any other form of psychotherapeutic intervention. Furthermore, none of the patients received electroconvulsive therapy during the course of their illness until the assessment was done. Individuals with any substance use except nicotine or caffeine, or any significant neurological or medical illness were excluded from the study. FDR's and controls did not have any history of psychiatric illness. Patients with OCD were assessed for psychopathology on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[22] Hamilton Rating Scale for Depression (HAM-D),[23] and Hamilton Rating Scale for Anxiety (HAM-A).[24] FDR's and normal controls were screened using the General Health Questionnaire-12.[25] They were, additionally, screened for OCD or obsessive-compulsive (OC) symptoms. All the subjects selected for the study were right-handed, and screened by Sidedness Bias Schedule.[26]

P300 recording

The ERP recording of all the subjects was done using a 40-channel, evoked potential measuring system (Ebneuro Galileo Mizar 40) using Galileo NT ERP software. Electrodes were placed according to a 10–20 system of electrode placement over the scalp. "Oddball" paradigm in which subjects were instructed to respond to the infrequent or target stimulus and not to the frequently presented or standard stimulus was used. The frequency of the standard stimuli and target stimuli were 2000 Hz and 5000 Hz, respectively. Both stimuli occurred in a pseudorandom pattern. The total number of trials was 250, with a ratio of standard stimuli to target stimuli 4:1. The push button time for responding to the target stimuli ranged from 100 ms to 1000 ms, before and/or after which the response was rejected.

Wave selection

The P300 waves generated by the oddball paradigm application were subjected to automatic artifact rejection followed by a back-averaging procedure using Galileo NT software. Thus, an averaged P300 waveform was obtained for each of the channels. The P300 wave was identified by visual inspection method. The P300 wave was marked at a maximum point of positivity occurring between 250 ms and 400 ms post-stimulus for midline electrodes (FZ, FCZ, CZ, CPZ, and PZ). The choice of channel selection was chosen to be a more conventional one.[27] Trials, in which scalp muscle activity, blink, or eye movement artifacts have contaminated the recordings, were rejected by visual inspection of individual traces of the computer display.

Statistics

Statistical analysis is done using the Statistical Package for the Social Sciences (SPSS ver. 16.0). Categorical variables were compared between the three groups using the Chi-square test and the continuous variables using a one-way analysis of variance (*post hoc* Bonferroni). *P*-value was significant at <0.05. However, for the results of the comparison of P300 measures, they were also corrected for multiple comparisons

using the Bonferroni method. As there were five channels that were compared, statistical significance was determined as $P < 0.1$, that is, 0.5/5.

RESULTS

A comparison of sociodemographic profiles between groups [Table 1] showed that there was a significant difference with respect to gender and occupation ($P < 0.05$). The female gender had a poorer representation in the FDR group and 60% of patients were found to be unemployed as compared to 20% FDRs. Other variables were comparable across the three groups. The mean Y-BOCS obsession score was 10.15 (standard deviation [SD] = 2.30), the mean Y-BOCS compulsion score was 9.05 (SD = 2.48), and the mean total Y-BOCS was 19.20 (SD = 4.02). The mean HAM-D score was 4.45 (SD = 3.26) and the mean HAM-A score was found to be 6.50 (SD = 2.80).

A comparison between three groups for P300 latency in the auditory oddball paradigm is shown in [Table 2]. There was a significant difference between the three groups at all the scalp sites studied ($P < 0.01$). *Post hoc* Bonferroni revealed a pattern where P300 latency was significantly shorter in patients and FDRs as compared to controls at FCZ, CPZ, and PZ. P300 latency in FDRs at electrodes CZ and FZ was significantly longer than in patients and shorter than controls. The significance survived even after controlling for multiple comparisons.

[Table 3] shows a comparison between three groups for P300 amplitude in the auditory oddball paradigm. There was a significant difference between the three groups at electrodes CPZ ($P < 0.01$). *Post hoc* Bonferroni revealed that P300 amplitude was significantly smaller in patients and FDRs as compared to controls. The significance survived even after controlling for multiple comparisons.

DISCUSSION

The present study showed a significant difference between the three groups for P300 latencies at all the five midline electrodes (CPZ, CZ, FCZ, FZ, and PZ) over the scalp. P300 latencies on the auditory oddball paradigm for patients were found to be significantly shorter than controls. This finding was consistent with the findings of the previous studies done on OCD patients.[10-13,15,28] The shorter latency of the P300 wave is a measure of processing time required before response generation, that is, processing speed.[29] Studies have shown an association between higher processing speed and superior mental performance in OCD.[12,30] Immediate memory is reportedly associated with the latency of P300 waves.[29] Some of the studies have shown memory deficits in patients with OCD.[4] Moreover, recent studies have also reported memory deficits in FDRs of patients with OCD too.[7] P300 latency, according to current literature, seems to be the electrophysiological counterpart of cognitive processes such as processing speed and memory. Now interestingly, the present study reports an endophenotype pattern of significant difference for shorter latencies, that is, no significant difference between patients and FDRs and a pattern of significant difference where latencies in FDRs fell

Table 1: Comparison of sociodemographic profile (categorical) between the three groups.

Variables	Patients (*n*=20) *n* (%)/Mean±SD	Fdrs (*n*=20) *n* (%)/Mean±SD	Controls (*n*=20) *n* (%)/Mean±SD	χ^2/F	df	*P*
Sex						
Male	11 (55)	20 (100)	11 (55)	15.35‡	2	<0.01†
Female	9 (45)	0 (0)	9 (45)			
Marital status						
Married	11 (55)	11 (55)	11 (55)	0.00	2	1.00
Unmarried	9 (45)	9 (45)	9 (45)			
Occupation						
Employed	8 (40)	16 (80)	9 (45)	7.73‡	2	0.02*
Unemployed	12 (60)	4 (20)	11 (55)			
Socioeconomic status						
Upper	3 (15)	0 (0)	0 (0)	5.53‡	4	0.11
Middle	9 (45)	14 (70)	13 (65)			
Lower	8 (40)	6 (30)	7 (35)			
Habitat						
Rural	12 (60)	13 (65)	13 (65)	0.14	2	0.931
Urban	8 (40)	7 (35)	7 (35)			
Age (years)	27.15±6.00	26.10±2.95	27.20±5.94	0.29	2, 57	0.75
Education (years)	12.50±2.11	13.35±1.69	12.55±2.03	1.18	2, 57	0.31

*Significance at<0.05 levels (two-tailed), †Significance at<0.01 levels (two-tailed), ‡Fisher's exact test used. SD: Standard deviation

Table 2: P300 latency in auditory oddball paradigm in central leads.

Electrodes	Patients (a) (Mean±SD)	FDRs (b) (Mean±SD)	Controls (c) (Mean±SD)	F	*P*	*Post hoc* (Bonferroni)
CPZ	239.75±6.85	246.01±7.15	277.70±12.04	55.22	<0.01*	c > a, b
CZ	237.71±7.09	249.09±6.50	278.12±10.09	85.45	<0.01*	c > b > a
FCZ	240.85±12.49	246.16±5.71	274.38±9.66	42.58	<0.01*	c > a, b
FZ	237.87±8.76	247.03±6.58	272.15±9.55	63.38	<0.01*	c > b > a
PZ	243.29±5.94	244.95±6.75	272.10±8.41	45.83	<0.01*	c > a, b

*Significance at <0.01 levels (two-tailed). SD: Standard deviation

Table 3: P300 amplitude in oddball paradigm in central leads.

Electrodes	Patients (a) (Mean±SD)	FDRs (b) (Mean±SD)	Controls (c) (Mean±SD)	F	*P*	*Post hoc* (Bonferroni)
CPZ	2.04±0.97	2.38±0.86	3.64±1.10	7.63	<0.01*	c > a, b
CZ	3.22±2.23	2.52±1.01	3.04±1.25	0.53	0.59	-
FCZ	3.12±2.18	2.40±1.60	3.03±1.26	0.63	0.53	-
FZ	4.29±3.09	3.04±1.53	4.43±1.82	1.50	0.23	-
PZ	2.26±0.86	3.05±1.76	3.02±1.01	1.12	0.34	-

*Significance at <0.01 levels (two-tailed). SD: Standard deviation

in between patients and controls. We suggest that shorter P300 latency represents faster processing speed and superior mental performance as an endophenotype in OCD.

The pattern of *post hoc* differences has been used to determine two types/levels of endophenotype patterns.[31-33] According to the model suggested,[31] while P300 at CPZ, FCZ, and PZ follow level A endophenotype pattern, that is, both patient and FDR groups are similar, whereas P300 at CZ and FZ follow level B endophenotype pattern, that is, P300 is significantly lower in patients compared to FDRs. Our study, therefore, helps stratify familial risk in OCD.

The present study also came up with findings of reduced P300 amplitude in OCD patients than controls at the centro-parietal region (CPZ electrode). This finding was similar to the findings of the previous studies.[12-15] A recent review also supports the finding of lower P300 amplitudes.[18] However, most of the recent studies localize P300 to more frontal sources.[18,19] P300 amplitude is known to be proportional to the extent of attentional resources devoted to a given task[34-36] and has been associated with superior memory performance.[37] Impairment of inhibitory control is one of the frequently reported deficits in OCD and it has also been reported in their FDRs.[5,7] Moreover, the present study also reported an endophenotype pattern for the reduced amplitude of P300, specifically at the centro-parietal region (CPZ), as well. This pattern followed the level A pattern of endophenotype, which is more closer to the pattern in disease.

The inhibitory function plays an important role in cognitive shifting ability which seems necessary while performing on an auditory "oddball paradigm." One must be able to inhibit the motor action for the frequent tone to respond only when the different (odd) tone is heard. The frontal lobe is directly related to this inhibitory process, and many authors have stressed the role of the frontal lobe in P300 generation.[17,38,39] The inability to inhibit responses probably makes the evaluation of the stimulus and its correct amnesic representation difficult which would intern result into dysfunction in the P300 generation.[40] P300 amplitude has been linked to the subject's certainty in answering questions.[41] Moreover, the basic aspect of psychopathology in OCD is the patient's uncertainty in making decisions.[14] In our study, on the backdrop of the things discussed above, OCD patients along with their FDRs seem to have impaired response inhibition which can explain significantly reduced P300 amplitude in patients and FDRs as compared to normal controls.

CONCLUSION

Shorter P300 latency representing increased processing speed and smaller P300 amplitude reflective of dysfunctional response inhibition are suggested to mediate genetic risk for OCD and proposed as possible electrophysiological endophenotypes for OCD.

Strengths and limitations

The present study included patients who were drug naïve and or drug free for at least 2 weeks, nullifying the drug effect on ERP waves. This offers more validity to our findings as many of the previous studies included patients on medications,

which might have considerable influence on P300. Moreover, most of the patients were moderately symptomatic.

Among limitations, the present study did not assess subjects on tests for cognition which might have provided more information. Gender matching among FDRs could prove better generalizable. It has been shown that there are significant gender differences in the P300 elicited by auditory tasks with male subjects having relatively lower amplitudes.[42] Furthermore, the choice of channel selection for P300 was a more conventional one and not having measured P300 from other electrodes-temporal and/or parietal and or frontal remains a limitation and can be further studied.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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