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P300 cognitive assessment in patients with first-episode psychosis: a prospective case-control study

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Abstract

Background: Several studies using event-related potential (ERP) methods have reported a relationship between the cognitive dysfunction of patients with psychosis and P300 latency and amplitude. P300 follow-up studies in patients with schizophrenia receiving antipsychotic treatment revealed that the P300 amplitudes were increased while other studies showed limited changes in the P300 amplitude even after antipsychotics use.

Results: We found that at the first presentation, all patients' groups have significantly lower amplitude and more prolonged latency of P300 than controls. All the first-episode psychosis patients showed a significant improvement of P300 amplitude mean scores after 1 year, but with no significant change in the P300 latency. There was an inverse correlation between the patients' PANSS scores and their P300 latency and amplitude values.

Conclusion: P300 amplitude and latency might be of clinical value in the evaluation of cognitive functions in the first-episode psychosis patients. The abnormalities in P300 may be improved with continuous control of psychotic symptoms with psychotropic medications.

Background

Event-related potentials (ERPs) are considered cerebral responses which are linked to various psychological events. They are objective measurements reflecting cognitive functions [1, 2]. The P300 ERP component is defined as a delayed cognitive-related ERP component associated with attention and memory processes [2]. The P300 event-related brain potential is an index of endogenous cognitive processes that include directed attention and the contextual updating of working memory [3]. One of the measurements of the central nervous system activity is the P300 amplitude which happens when stimulus memory representations are generated. The P300 latency is considered to be a measure of stimulus classification speed. It has no obvious relation to response

selection processes and independent of behavioral response time [4].

P300 aberrations have been found in many mental disorders, such as Alzheimer's disease [5], bipolar disorder [6], depression [7], personality disorder [8], and schizophrenia. Many studies reported aberrations in both the P300 wave amplitude and latency in psychotic patients. For example, Jeon and Polich reported P300 abnormality of schizophrenia in a meta-analysis research, containing literature published from 1966 to 1999 [9]. Moreover, there are two meta-analyses conducted by Bramon et al. about P300 abnormalities in schizophrenia patients [10] and in patients' relatives [11], respectively. Although P300 amplitude decrease and latency prolongation were reported in schizophrenia patients and their relatives, the subjects included in former meta-analyses were medicated schizophrenia patients, whose P300 probably has been changed by the effect of antipsychotics. The presence of similar abnormalities in medication-free first-

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episode schizophrenia (FES) patients remains unconfirmed. Until now, the effect of medication on P300 amplitude and latency is still a debated issue. Some studies suggested that antipsychotics, especially the second-generation agents, could partially improve the performance of P300 amplitude and latency [12], and Jeon and Polich did not find any correlation between medication and P300 amplitude effect size in his meta-analysis [9]. Another factor that impacted P300 latency effect size was the disease duration [9]. Delayed P300 latency found in chronic schizophrenia patient may be in conformity with that in FES patients. So far, there has been no agreement on P300 latency changes in patients with FES. Although some studies reported significantly delayed P300 latency in patients [12, 13], others reported inconsistent results [14–16].

The aim of this study is to evaluate P300 abnormalities in first-episode psychosis patients on the first presentation and after 1 year of treatment and follow-up and to study the correlation between P300 abnormalities and the severity of psychopathology

Methods

Study design

This prospective study evaluated P300 abnormalities in first-episode psychosis patients on the first presentation and after 1 year of treatment and follow-up. All participants signed informed consent after understanding the nature of the research, their voluntary participation, and the right to withdraw at any time without giving reasons, and the withdrawal would not affect any management privileges. The study protocol was approved by the research ethics committee of the Faculty of Medicine, Assiut University.

Participants

The study was performed at Assiut University Hospitals between the 1st of January and the 31st of December 2013. The study included 108 patients who fulfilled the criteria for the diagnosis of first-episode psychotic disorders including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and psychotic disorder not otherwise specified. Additionally, mood disorders with psychotic features such as bipolar disorder with psychotic features and depressive disorder with psychotic features were included.

The diagnosis was made according to DSM-IV criteria with no history of substance abuse during the last 12 months which was also confirmed by urine screen. They did not previously receive antipsychotic treatment before admission to the hospital. Their age was 18 years and older. We excluded all cases with mental retardation, substance use disorders, or psychosis due to organic causes. A control group of 50 subjects was recruited

from the patients' relatives or the staff of the same institution. They were matched for age, gender, educational level, and other demographic variables as far as possible. None of the controls had any history of illegal or opioid drug abuse. The controls were screened by psychiatric interview for having no history of significant psychiatric morbidity or substance abuse. Follow-up assessment was scheduled for each patient at the end of the 3-month, 6-month, and 12-month follow-up intervals.

Instruments

Initial sheet

It was applied to all patients on the first interview, and another follow-up sheet completed on a further follow-up visit. It was developed by the researcher to collect demographic and clinical data specially prepared for the study and the duration of untreated psychosis (DUP), mode of onset, treatment (if any), diagnostic shifts, and other variables.

Psychiatric interview

Each participant was individually assessed through a standardized psychiatric interview for the participants and the family members/informants. The diagnosis was made based on the DSM-IV-TR (Diagnostic Statistical Manual of Mental Disorders 4th edition, text revised) [17].

Arabic version of Mini International Neuropsychiatric Interview (MINI Plus)

It is a brief structured diagnostic interview used to screen for major DSM-IV and ICD-10 psychiatric disorders, with an administration time of approximately 15 min. It was designed to meet the need for a short but accurate structured psychiatric interview. The MINI Plus scale is a widely used structured scale that was translated into 43 languages and used by mental health professionals and health organizations in more than 100 countries [18].

The Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS), developed by Kay et al. in 1987, is one of the most commonly used instruments for evaluating symptomatology in schizophrenic patients and other psychotic disorders. This is a 30-item test, and each item is rated from one (no evidence) to seven (extreme). In addition to the total score for overall psychopathology (sum of all 30 items), PANSS has subscales that yield data on positive symptoms of psychosis (7 items), negative symptoms of psychosis (7 items), and general psychopathology (16 items) [19].

P300 audio-evoked potential

Audio-evoked potential is an objective measure of cognitive processing recorded through an array of scalp electrodes, and it is used for measuring brain functions as

memory, attention, and concentration. The test was done using surpass EMS biomedical and quantitative EMG/EP workstation. The test was done through applying an odd-ball paradigm as the subject has to detect an occasional target stimulus in a train of regular “frequent” stimuli. The evoked potential waves were recorded from scalp electrodes placed in CZ, FZ, and PZ points with reference electrode place on the ear lobule and a ground electrode placed on the hand. A headphone was used for applying the auditory stimuli and completely covered the ears. The waves were marked as N1, P2, N2, P3, and N3 [20]. The recorded variables were the P300 latency which is related to the speed of cognitive processing and amplitude of wave which is related to memory consolidation [21]. The test was first explained to the patient before starting the examination. The test was repeated several times before the wave was recorded to ensure the patient understands the procedure. If the patient was not cooperative or exhausted, a test was performed on another day. Most of the patients were able to understand the test after 2 or 3 trials, and each trial would approximately take 30 min.

Procedure

Three hundred fifty first-episode psychosis patients were admitted to the psychiatry unit, Assiut University Hospital, along the year 2013. Two hundred thirty-five patients were excluded (due to mental subnormality, chronic medical illness, substance use disorder comorbidity, or substance-induced psychosis). One hundred fifteen patients were eligible for the research, out of which 108 agreed to participate. The participants were given clear and comprehensive information about the study and were completely free to participate or not with no consequences if they disagreed to participate. For those who agreed to participate, a written consent was obtained from them and their caregivers.

There was no interference whatsoever with the treatment prescribed by colleagues, the duration of hospitalization, or the time of discharge. Follow-up dates were written and explained to the patient and family on the back of the discharge card, to be 3 months, 6 months, and 12 months after discharge. Phone calls for further questioning and specific times to call were offered to the patients and caregivers, and reference phone numbers to reach the patients were taken in order to remind patients ahead from follow-up date by 1 week to attend the follow-up. At the end of 1 year, only 72 patients completed the study with a drop rate of 30.5% which is expected in similar studies. Controls were recruited from hospital workers and employees who volunteered and not from patients’ relatives. All the clinical assessment

and psychometric tools were applied immediately after admission and on follow-up dates. And it was done by the specialized psychiatrists and psychologists. The neurophysiologic aspect which included the P300 wave study was performed in the neurophysiology unit.

Statistical analysis

Data were analyzed using SPSS version 20 software package [22]. Descriptive statistics for quantitative variables were expressed as numbers, percentages, means, and standard deviations. Student *t* test was used to compare quantitative data of 2 groups. Comparison among diagnostic groups was performed using analysis of variance (ANOVA) when ANOVAs yielded a significant result, Newman-Keuls post hoc tests were used to identify significant pairwise group analysis.

Results

Clinical characteristics of the participants

Table 1 shows that patients with schizophrenia spectrum disorders (SSD) constituted (43.5%) of the study group, followed by bipolar disorder with psychotic feature patients (38%) and depressive disorder with psychotic feature patients (18.5%). Among the subgroups’ diagnoses, bipolar disorder with psychotic features was the most frequent diagnosis (38%), followed by brief psychotic disorder (21.30%), a depressive disorder with psychotic features (18.5%), schizophreniform disorder (9.25%), schizophrenia (7.4%), psychotic disorder not otherwise specified (PNOS) (3.70%), and schizoaffective disorder (1.85%). Male patients represented (53%) of the total sample. Bipolar disorder is the most frequent diagnosis among males (42.10%) and females (33.35%). However, depressive disorder and brief psychotic disorder are higher in frequency in females (27.4%, 25.5%) than males (10.5%, 17.5%), respectively. Schizophrenia and schizophreniform disorders are more frequently diagnosed in males (12.3%, 10.5%) than in females (1.95%, 7.85%), respectively. There was no statistically significant difference between males and females in terms of frequency of diagnoses.

Socio-demographic characteristics

Table 2 shows that the mean age of SSD patients was 27.49 ± 10.7 years, for bipolar patients with psychotic features was 24.68 ± 7.3 years, and was 25.50 ± 6.7 years for major depression with psychotic features patients. It was found that 57.45% SSD patients were males, 63.82% were single, 65.95% lived in rural areas, 53.20% were illiterate, read and write, and 44.69% were not working/housewife. 58.54% of BP patients were males, 70.73% were single, 73.17% lived in rural areas, 58.54% had basic

Table 1 Frequency and percentage of different diagnoses among study group at first presentation

Diagnosis	Total (N = 108)		Male (n = 57)		Female (n = 51)	
	No.	%	53%		47%	
	No.	%	No.	%	No.	%
Schizophrenia spectrum disorders	47	43.5	27	47.4	20	39.2
Brief psychotic disorder	23	21.30	10	17.55	13	25.50
Schizophreniform disorder	10	9.25	6	10.52	4	7.85
Schizophrenia	8	7.40	7	12.30	1	1.95
Schizoaffective disorder	2	1.85	1	1.75	1	1.95
Psychotic disorder not otherwise specified (PNOS)	4	3.70	3	5.26	1	1.95
Bipolar disorder with psychotic features	41	38	24	42.10	17	33.35
Depressive disorder with psychotic features	20	18.5	6	10.52	14	27.45
P value	0.125					

N.B P value in comparison of males and females

education, 34.14% were not working/housewife, and 36.59% were non-skilled workers. Seventy percent of MDD patients were females, 50% were single, 85% were living in urban areas, 60% had basic education, 75% were not working/housewife, 20% were non-

skilled workers, and none of them were students or employees. There was no significant difference among first-episode psychosis patients in different groups and control group as regards all demographic variables.

Table 2 Demographic characteristics of first-episode psychosis patients and control groups

Demographic characteristics	SSD (n = 47)		BP (n = 41)		MDD (n = 20)		Control (n = 50)		P value
	No	%	No	%	No	%	No	%	
Sex									
Male	27	57.45	24	58.54	6	30	25	50.0	.745
Female	20	42.55	17	41.46	14	70	25	50.0	
Marital status									
Single	30	63.82	29	70.73	10	50	18	36	
Married	17	36.18	10	24.39	10	50	32	64%	.002
Divorced, widowed	0	0	2	4.88	0	0	0	0	
Residence									
Rural	31	65.95	30	73.17	3	15	34	68	.587
Urban	16	34.05	11	26.83	17	85	16	32	
Education									
Illiterate, read and write	25	53.20	12	29.26	8	40	17	34	.001
Basic education	20	42.55	24	58.54	12	60	21	42	
University/higher education	2	4.25	5	12.20	0	0	12	24	
Occupation									
Not working and house wife	21	44.69	14	34.14	15	75	2	4	
Non-skilled worker	10	21.27	15	36.59	4	20	18	36	.331
Skilled worker	8	17.02	7	17.07	1	5	15	30	
Student	4	8.51	5	12.20	0	0	10	20	
Employee	4	8.51	0	0	0	0	5	10	
Mean age	27.49 ± 10.7		24.68 ± 7.3		25.50 ± 6.7		32.10 ± 7.8		.176
	Range 17.4–37.6		Range 17.5–31.6		Range 19.2–31.4		Range 25.5–39.4		

N.B non-skilled, manual worker/farmer. Basic education, from primary to secondary school

P300 at first presentation

Patients were grouped according to diagnosis at first presentation into schizophrenia spectrum disorder (SSD), bipolar disorder (BP), and major depressive disorder (MDD). We found significantly lower mean scores of P300 amplitude in all groups in comparison to the control group in comparison to healthy controls (SSD group, $p = 0.006$; BP, $p = 0.001$; MDD, $p = 0.003$ respectively) (Table 3). SSD patients have the lowest P300 amplitude in comparison to other groups (BP, MDD, and control groups). On the other hand, there was significant P300 latency prolongation in SSD, BP, and MDD groups in comparison to the control group (SSD group, $p = 0.001$; BP, $p = 0.001$; MDD, $p = 0.003$, respectively). Once again, the SSD group has the largest P300 latency prolongation in comparison to the other groups (Table 3).

P300 after 1 year

We measured the P300 latency and amplitude in all the studied groups (SSD, BP, and MDD) again after 1 year. We found that there is a significant increase in mean scores of P300 amplitude in comparison to the mean scores at the first presentation in all groups ($p < 0.05$). On the other hand, there was no significant change in latency in all the study groups in comparison to the mean scores at the first presentation (Table 4).

Correlation between PANSS and P300

The mean scores of PANSS subscales for SSD, BP, and MDD patients were significantly lower after a 1-year follow-up in comparison to the mean scores at first presentation except for the negative subscales in the SSD group and MDD group which showed no statistically significant change after 1 year (Table 5). Pearson correlational analyses were used to examine the relationship between the PANSS scores on the one hand and the P300 amplitude and latency on the other hand. Results indicated an inverse relationship between PANSS scores and P300 amplitude and latency both at first presentation ($r =$

-0.539 , $p = 0.007$; $r = -0.460$, $p = 0.024$) and after 1 year ($r = -0.326$, $p = 0.014$; $r = -0.267$, $p = 0.032$). This suggests that the more symptoms the patient has the lower P300 values he scores, and the reverse is true (Table 6).

Discussion

Clinically, schizophrenic patients often present with attention, verbal memory, and working memory dysfunctions [23]. Previous studies suggested that aberrations of P300 amplitude in schizophrenia patients were indicators of these dysfunctions [24], which might be further related to structural and functional changes in the schizophrenia patient's temporal lobe and parietal lobe [25].

The present study used the auditory P300 ERP as a cognitive measurement to compare between patients with first-episode psychosis and unrelated matched healthy controls. This study included 1-year follow-up and P300 reevaluation for the participants for the purpose of elucidating the long-term effect of treatment on P300 scores. In addition, we tried to find a correlation between the severity of psychopathology and the P300 latency and amplitude scores.

We found that the P300 amplitude was significantly reduced compared to controls in all patient groups in comparison to the control group and that schizophrenia spectrum disorders (SSD) patients had a significantly lower score compared to both bipolar and depressive psychosis. Similarly, the P300 latency was prolonged in all patient groups compared to the control group, with the latency in SSD significantly delayed more than in bipolar and depressive psychoses groups. On the other hand, we found that the more psychopathology the patients had according to PANSS, the worse was their performance on P300 examination.

Some studies suggested that P300 originated from a broad cerebral cortex network, such as parietal lobe [26], cingulate gyrus, and frontal lobe [27]. Our results may suggest that cognitive impairment is present even in the early days of the illness, and therefore, our findings suggest that the dysfunction of the corresponding brain area may take place in FES patients. Additionally, the results

Table 3 Comparison of P300 variables among first-episode psychosis diagnostic groups and control

P300 variables	SSD (n = 47)		BP (n = 41)		MDD (n = 20)		Controls (n = 50)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	
P300 amplitude	6.32 [#]	± 2.6	8.97 [#]	± 3.36	12.59 [#]	± 5.41	21.57	± 5.87	1 = 0.006* 2 = 0.001* 3 = 0.003*
P300 latency	367.77 [#]	± 22.4	343.14 [#]	± 22.21	340.97 [#]	± 22.54	326.11	± 15.78	1 = 0.001* 2 = 0.001* 3 = 0.699

*P value by one-way ANOVA, post hoc tests were used to compare pairwise group difference when $P < 0.05$, post hoc in between groups (1 = SSD and BP, 2 = SSD and MDD, 3 = BP and MDD)

[#]Significant difference among patient diagnostic groups and control

Table 4 Comparison of the P300 variables, at first presentation and after 1 year among first-episode psychosis diagnostic groups

P300 Variables	SSD				BP				MDD			
	First presentation		After 1 year		First presentation		After 1 year		First presentation		After 1 year	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
P300 amplitude	6.32	±2.61	12.53*	3.77	8.97	±3.36	12.72*	3.65	12.59	±5.41	17.04*	3.89
P300 latency	367.7	±22.4	475.7	±53.5	343.1	±22.2	355.2	±37.3	340.9	±22.54	354.8	28.92

*P < 0.05

demonstrated prolonged P300 latency in FEP patients relative to healthy controls, which indicated a decline in patients’ brain processing speed of external information.

Contrary to schizophrenia P300 amplitude reduction which is replicated in many studies, the presence of P300 amplitude reduction in affective disorder is somewhat controversial. Some studies have shown a reduction in amplitude [28, 29] which are consistent with the present study, but others did not find a reduced P300 amplitude [30–32].

Several studies examined P300 in psychotic versus nonpsychotic affective disorder. For example, Muir et al. reported that P300 amplitude was reduced in bipolar psychotic disorder, but not in the unipolar depression [33]. Similarly, Santosh et al. reported that P300 was reduced only in those depressed patients with hallucinations or delusions [34]. Thus, P300 reduction in affective disorder may reflect underlying psychosis in contrast to

an underlying abnormal affective process which is consistent with this study.

In the present study, only the P300 amplitude had improved in all first-episode patients significantly after 1 year which was consistent with the findings in other literatures [35–37]. These findings revealed that psychotropic medications could bring a partial recovery in P300 amplitude in previously unmedicated or drug-naïve schizophrenic patients. These findings reflect the fact that cognitive functions, for those who remain in treatment, may not deteriorate early in the course of illness, or may even improve, as previously explained in some neuropsychological studies [38].

The inverse correlation we found between P300 parameters and the severity of the psychopathology was obvious either in drug-naïve patients with psychosis or after 1 year of treatment. This kind of correlation is not totally confirmed in previous studies [39, 40]. A possible explanation of the inconsistent results may be related to the “state or trait” hypothesis, which could be inferred that P300 may be a biological marker in the acute stage [41]. Some studies have shown that the P300 amplitudes may increase after psychotic symptoms improve, with or without medical treatment [25, 42], which could be regarded as being in support of the above explanation.

Conclusion

FES patients demonstrate obvious abnormalities of P300 amplitude and latency. P300 amplitude and latency might be of clinical value in the evaluation of cognitive functions in first-episode psychosis patients. The abnormalities in P300 may show improvement with continuous control of psychotic symptoms with psychotropic medications. Patients with severe psychopathology from the start are more prone to cognitive impairment as evidenced by P300 abnormalities and its association with PASS scores.

Limitations of this study

(1) Hospitalized patient-based sampling limited generalization through excluding patients with disorders that are less severe to require hospitalization. (2) Thirty-

Table 5 Comparison of PANSS mean scores at first presentation and after 1 year follow-up

PANSS subscale	SSD				P-value
	Mean	±SD	Mean	±SD	
Positive	27.27	±5.6	17.03	±7.15	.000*
Negative	26.91	±8	21.84	±10.23	.059
General psychopathology	55.34	±9.45	37.12	±14.54	.000*
Total score	110.23	±17.2	76.56	±29.67	.000*
	MDD				
Positive	8.7	±1.2	7.32	±1.15	.038*
Negative	17.10	±3.30	16.71	±5.41	.358
General psychopathology	45.2	±8.03	25.85	±7.10	.000*
Total score	71.05	9.70	49.21	±12.27	.001*
	BP				
Positive	32.58	±7.45	10.92	±5.74	.000*
Negative	15.92	±7.25	11.65	±4.05	.006*
General psychopathology	49.63	±8.2	23.73	±9.98	.000*
Total score	98.14	±12.54	46.30	±17.58	.000*

SSD schizophrenia spectrum disorder, BP bipolar disorder, MDD major depressive disorder. *P < 0.05

Table 6 Correlation between PANSS scores and P300 amplitude and latency

	PANSS score at presentation		PANSS score after one year	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
P300 amplitude	– .539	0.007	– .326	0.014
P300 latency	– .460	0.024	– .267	0.032

three percent of patients were lost in follow-up which is expected in similar studies, but still, there is a potential risk of bias due to attrition resulting from drop out. (3) Different patient's diagnoses had different treatment regimens, including antipsychotics, mood stabilizers, and antidepressants. (4) We depended only on P300 as a cognitive assessment tool.

Abbreviations

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, text revised; ERPs: Event-related potentials; FES: First-episode schizophrenia; ICD-10: The 10th Revision of the International Statistical Classification of Diseases and Related Health Problems; MINI Plus: Arabic version of Mini International Neuropsychiatric Interview; PANSS: The Positive and Negative Syndrome Scale

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Authors' contributions

W. Abdelnaser, A. Darweesh, H. Khalifa, and S. Hassaan designed the research, shared in the application of the cognitive tests, and analyzed data. A. Abdel-Rahman and I. F. Fahmy shared in the application of the neuropsychological and neurophysiological assessment tests. A. Darweesh, H. Khalifa, S. Hassaan, and I. Fahmy performed biostatistical analyses. W. Abdelnaser and I. Fahmy supervised the research and shared in data collection. A. Darweesh, H. Khalifa, and S. Hassaan interpreted data and wrote the draft paper. The authors have read and approved the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethical committee of the Faculty of Medicine, Assiut University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. The reference number is not available.

Consent for publication

Not applicable

Competing interests

All authors declare no actual or potential conflict of interest whether financial, personal, or otherwise related to this manuscript

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