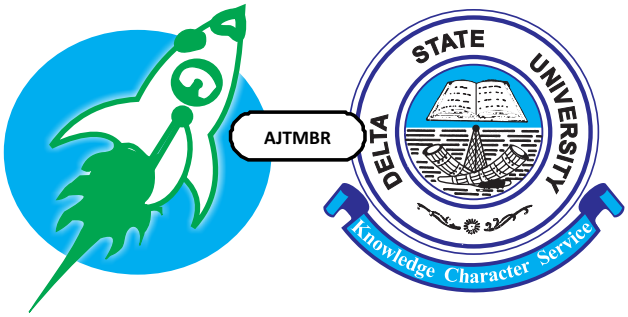
African Journal of Tropical Medicine and Biomedical Research (AJTMBR)



The Journal is the Official Publication of the College of Health Sciences, Delta State University, Abraka, Nigeria.

ISSN: 2141-6397

Vol. 7, No. 2, December 2024

Focus and Scope

The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

Editorial Notices

The journal will be published biannually in the months of March and September. Annual subscription fee in Nigeria is two thousand naira (N2,000) per volume (2issues); One-thousand-naira single copy (N1000). The annual subscription rate for other parts of the world is as follows: United Kingdom £60 (post free). West Africa $60 (post free). The rest of the World and the United States of America $120 (post free). A charge of $60 is made for reprints inclusive of postage. Cheques should made payable to the African Journal of Tropical Medicine and Biomedical Research and addressed to the Editor-in-Chief.

Journal Contact

All correspondence, including manuscripts for publication (in triplicate) should be addressed to:

Professor P.S. Igbigbi
The Editor-in-Chief,
Department of Anatomy,
Faculty of Basic Medical Sciences,
College of Health Sciences,
Delta State University, Abraka,
Delta State, Nigeria.

Or:
Professor Lawrence Omo-Aghoja
Editor
Department of Obstetrics and Gynecology,
Faculty of Clinical Medicine,
Delta State University, Abraka, Nigeria.
Email: journalajtmbr@yahoo.com
Cc: all email to
eguono_2000@yahoo.com
Tel: 08039377043

All authors are advised to submit an electronic copy in CD-ROM along with a hard copy of their manuscript, as this will spare remarkable time in the reviewing and typesetting processes.

In the alternative, authors can submit their articles and covering letter by email attachments. A covering letter (signed by all authors) accompanying the manuscript should certify that the article has not been previously published and is not being considered for publication elsewhere.

Information for Authors

All manuscript are peer-reviewed and accepted with the understanding that the work has not been published or being considered for publication elsewhere. Indeed, the authors would be requested

to sign a copyright form transferring the ownership of the paper to the African Journal of Tropical Medicine and Biomedical Research. All articles must include the correct names and addresses of author(s) including e-mail addresses and telephone numbers. Articles will be subjected to a thorough peer review process before any decision is made to publish or not. Authors should note that the African Journal of Tropical Medicine and Biomedical Research is not under any obligation to publish articles submitted, as decision to publish will be based on recommendations of reviewers and the editorial advisory board.

Manuscripts

Articles submitted for publication should be typed double-spaced with 2.5cm margins with accompanying CD-ROM in Microsoft Word format for easy and quick peer review and typesetting. Each of the following sections should begin in a new page: title page, abstract, introduction, materials and methods, results, discussion, acknowledgment (s), references, tables, legends to figures and illustrations. The manuscript should include:

Title Page

The title page should include the following information: 1. the title and sub-title; 2. the name(s) of the author(s); 3. the affiliation(s) of the author(s); 4. name and address of the corresponding author and 5. three to six key words for indexing and retrieval purposes.

Abstract

The abstract should be structured and not more than 250 words. It should carry the following headings: Introduction, Materials and Methods, Results and Conclusion.

Original Research- The journal welcomes articles reporting on original research, including both quantitative and qualitative studies. Full-length articles should generally not exceed 3000 words, excluding abstract, tables, figures, and references. The subject matter should be organised under appropriate headings and sub-headings as itemized above.

Review Articles- Comprehensive review articles on all aspects of tropical medicine and biomedical sciences will also be considered for publication in the journal. Reviews should provide a thorough overview of the topic and should incorporate the most current research. The length of review articles must not exceed 3,000 words and the organisational headings and sub-headings used are at the author's discretion.

Short Reports - Brief descriptions of preliminary research findings or interesting case studies will be considered for publication as short reports. The length of the abstract and article should be restricted to 150 and 2,000 words respectively and organisation of short reports are left to the author's discretion.

Commentaries or Editorials- Commentaries or editorials on any aspect of tropical medicine and biomedical sciences in Africa will be considered for publication in the journal. Opinion pieces need not reference previous research, but rather reflect the opinions of the author(s). The length should not exceed 2,000 words.

Tables and Figures

All tables and figures should be submitted on separate sheets of paper and should be clearly labelled. Coloured tables and figures may be reprinted in black and white. Authors should especially take care that all tables are clear and understandable by themselves, independent of

the text. A reader should be able to read only the tables and easily grasp all information without the text.

Acknowledgments

Acknowledgments should be included on a separate sheet of paper and should not exceed 100words. Funding sources should be noted here.

References

References should be in the Vancouver style and numbered consecutively in the order in which they are mentioned in the text. Titles of journals should be abbreviated according to the Index Medicus style. Authors must cross-check and make sure that all information provided in the reference list is complete and correctly written. Reference numbers should be inserted above the line on each occasion a reference is cited in the text, e.g., … as 1-3 reported in other studies. Numbered references should appear at the end of the article and should include the names and initials of all authors. The format of references should be as published by the International Committee of Medical Journal Editors in the British Medical Journal 1988, volume 296, pages 401-405. The following are sample references for an article published in a journal and for a book: Ahmed Y, Mwaba P, Chintu C, Grange JM, Ustianowski A, Zumla A. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. Int J Tuberc Lung Dis 1999; 3: 675-680. Whitby LG, Smith AF, Beckett GJ. Enzyme Tests in Diagnosis. In: Lecture Notes on Clinical Chemistry. Whitby LG, Smith AF & Beckett GJth (eds). 4 editions. Blackwell Scientific Publications. 1988. 103-127.

Units of Measurement

All measurements should be expressed in SI (Systeme International) Units.

Galley proofs

Corrections of galley proofs should be strictly restricted to Printer's error only. Orders for offprints should be made when the corrected proofs are being returned by the authors. Articles accepted for publication remain the property of the journal and can only be reproduced elsewhere in line with section 5 of the copyright agreement.

Table of Contents

Original Articles

Determination of Neurophysiological P300 and P50 in Patients with Schizophrenia at a Tertiary Hospital in Sokoto, Nigeria

Adebisi AS[1], Onwuchekwa C[2], Usman UZ[2], Shiitu BS[3]

Abstract

Introduction: Schizophrenia is a severe and complex mental disorder. It currently lacks an objective biological diagnostic test. Neurophysiological markers like P300 and P50 event-related potentials have shown some diagnostic usefulness in previous studies. However, very few of these studies have been done among Africans. The objective of the study was to evaluate neurophysiological P300 and P50 event-related potentials in 70 schizophrenia patients and 70 healthy controls at a tertiary psychiatric hospital in Sokoto, Nigeria.

Materials and Methods: The instruments used were the Electroencephalogram (EEG) machine, laptop with installed auditory P300 and P50 tones, headphones, Positive and Negative Syndrome Scale (PANSS).

Results: Schizophrenia patients were significantly associated with higher amplitude of P300 and prolonged P300 peak latency auditory event-related potential compared to healthy controls (U= 1077.000, P=<0.001 and U= 1191.000, P=<0.001) respectively. Schizophrenia patients were also significantly more associated with higher P50 amplitude ratio (U= 1342.500, P=<0.001). The P300 event-related amplitude had the highest area under the curve of 0.78. P300 peak latency was the most specific (Specificity=0.93) while P50 ratio was most sensitive (Sensitivity=0.76). The determined cut-off points for P300 amplitude, P300 peak latency, and P50 ratio were 6.84μv, 445ms, and 0.89 respectively. There was a significant positive correlation between P50 ratio and age of participants among schizophrenia patients (rs=0.29, P=0.02).

Conclusion: The study has determined the cut-off points for P300 and P50 neurophysiological markers in patients with schizophrenia. These will serve as an adjunct for diagnosis and for forensic purposes in these patients. Further studies including neuroimaging, biochemical, and genetic aspects are recommended in African countries.

1Federal Neuropsychiatric Hospital, Kware, Sokoto, Nigeria
2Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.
3Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.

Corresponding author: Adebayo Sunday Adebisi, Federal Neuropsychiatric Hospital, Kware, Sokoto, Nigeria.
Email: docotufodunrin@yahoo.com

INTRODUCTION

Schizophrenia is a chronic, severe and debilitating mental disorder characterized by disordered thought, abnormal perceptions and behaviours.[1] The symptoms usually emerge in late teens and early 30's[1]. Early detection is therefore crucial in the management of the disorder. Assessment of neurophysiological markers in schizophrenia patients are current methods that will serve as an adjunct in early diagnosis.[2] This will also help in predicting the risk and outcome of the disorder.

The Neurophysiological markers are laboratory-based measurements and intermediates between phenotypes and genetic predisposition.[3] The polygenic nature of schizophrenia and the current lack of a candidate gene for the disorder necessitates the assessment of these intermediates or allied phenotype markers. This

will conceptualize the complex genetic predisposition into quantitative measurements.[4] Cortical evoked-response potentials can be averaged into event-related potentials (ERPs) recorded using encephalography.[5] These waveforms have been reported by several studies to be genetically-linked markers.[6] The P300 and P50 event-related potentials in schizophrenia have been extensively studied and all previous studies were carried out predominantly among Caucasians.[7-9] The generalization of the findings of these studies poses a challenge among Africans. It is therefore, important to consider how these markers are expressed in the African population considering the varied genetic make-up between Africans and Caucasians. This will provide a more robust evidence-based data and a broader view of these neurophysiological markers and their diagnostic accuracy across races.

The determination of a cut-off point for these neurophysiological markers will also be necessary considering the fact that similar findings on P300 and P50 event-related potential have been reported in other disorders like Alzheimer's disease, bipolar disorder and panic disorder apart from schizophrenia.[10-12] There is a dearth of studies that have determined a cut-off point for P300 and P50 event-related potential measurements. This present study has provided a comprehensive evidenced-based assessment of the pattern and utility of P300 and P50 event-related potential among schizophrenia patients in Nigeria. The findings have implications as regards the genetic underpinnings of schizophrenia in this region.

METHODOLOGY

The study was conducted at the Federal Neuropsychiatric Hospital, Kware (FNPHK), Sokoto State. The hospital is a tertiary specialist health care facility situated in Kware Local Government, Sokoto Nigeria.

This is a cross-sectional, descriptive study.

(1). Schizophrenia patients attending follow-up clinic at the out-patient department of Federal Neuropsychiatric Hospital Kware, Sokoto.

(2). Non psychiatric healthy controls were staff of Federal Neuropsychiatric Hospital Kware, Sokoto.

Materials

(A**) Electroencephalography (EEG) machine** (Model: NIHON KOHDEN 1200K). The digital EEG machine was used to monitor and record the event related potentials of the brain. It was non-invasive, with the electrodes placed along the scalp. The electrode locations and names were as specified by the International 10–20 system which ensures that the naming of electrodes is consistent across laboratories for clinical and research applications.

The digital EEG signal was kept electronically and filtered for display. The high-pass filter was set at 150Hz and the low-pass filter filters at 15Hz.The impedance threshold was set at 10kΩ. The measurement of the amplitude of the evoked potential was done manually based on the scale ratio of the EEG tracing.[13]

(B) **A Laptop** with installed oddball (target) tone that is randomly interspersed within an ongoing train of a standard (non-target) tone, presented every 2 seconds for the P300 assessment. with installed tone of clicks at 500ms interval and frequency of 1500Hz for P50 assessment

(C) **A headphone stereo sound Headset** was used to transmit the sounds to participant ears from the laptop. This was to reduce the external sound interference and to enhance the concentration of participants when listening to the tones from the laptop.

(D) **ICD-10 Diagnostic Criteria for Research**

This diagnostic instrument was used to diagnose schizophrenia based on patients recall of morbid symptoms and documented symptoms in the case notes.

(E) **Positive and Negative Syndrome Scale** (PANSS)
It is a 30-item rating scale specifically developed for assessing individuals with schizophrenia especially in research settings. It is an adaptation from earlier psychopathology scales such as the Brief Psychiatric Rating Scale (BPRS). It is based on the grounds that schizophrenia has two distinct syndromes, a positive and a negative syndrome. The positive symptoms refer to an excess or distortion of normal functions (e.g., delusions and hallucinations) while the negative syndrome represent a diminution or loss of normal functions and comprise things like social withdrawal and flattened or blunted affect.

PANSS is applicable only to schizophrenia patients and takes 45 to 50 minutes to administer. The main indication for its use is to determine the presence of symptoms, their influence on activities, functions of the individual and the frequency of symptoms. The patient is rated from 1 to 7 on 3 scales consisting of 30 different symptoms.[14]

(F) **A proforma questionnaire** designed by the authours was used to record socio-demographic data and other relevant clinical variables of participants. reference

Sample size
This was calculated using the lower effect size in an Event-related Potential study for P300 latency which was 0.48 in a previous study.[15]The P50 event -related potential studies generally had higher effect sizes. The effect size of the P50 event-related study was selected to achieve sufficient sample size.
Formula for sample size using effect size for two independent samples=$2(Z_{1-\alpha/2}+Z_{1-\beta})^2/ES^2$. [16]
$Z_{1-\alpha/2} = 1.96$.
$Z_{1-\beta}$-=0.84
ES = Effect size
Sample size approximately =70
That is, 70 Schizophrenia patients were recruited for the study and also 70 Healthy controls.

Inclusion criteria
- Participants must be 18 years and above
- Schizophrenia patient must fulfill the ICD-10 diagnostic criteria for research and collaborated with diagnosis of the psychiatrist.
- Schizophrenia patients must be clinically stable.
- Healthy controls having no family history of mental disorder.

Exclusion criteria
- Those with co-morbid medical/physical illness.
- Those with co-morbid substance use.
- Individuals with hearing difficulties.

Ethical considerations
The ethical approval was obtained from the health research ethics committee of Federal Neuropsychiatric Hospital Kware, Sokoto with reference code was FNPHK/ADM/SUB/809. Informed consent for the research was obtained from all participants.

Procedure
The 10-20 system electrode placement was applied on grease free scalp and all jewelries removed while sitting down.

The Headset was fitted without interfering with the electrodes. P50 tones and P300 auditory tones were presented to the ears through the headset from the laptop installed with these tones. There were 150 presentations per participant for P300 at ratio of 1:2 (i.e., 50 oddball tones to 100 standard

tones).

The 50 paired auditory clicks presented 500ms apart were used to elicit the P50 evoked potentials. The inter-trial interval for the paired clicks was 7seconds.

The P300 standard and oddball tones were set at 1000Hz and 1500Hz respectively. The P50 tone was set at 1500Hz. P300 evoked potential was identified in the EEG tracing on the Pz electrode and defined as the largest positive-going peak occurring within 300-800ms.The P50 evoked potentials were identified on the Cz electrode and defined as the most prominent peak in the 40-80msec post-stimulus window.[7]

The amplitude of the evoked potentials was measured manually from the peak to trough (Peak-to peak amplitude) while the peak latency was measured from the time of stimulus onset.

The amplitude of the evoked potentials was measured manually from the peak to trough (peak to peak amplitude) while the peak latency was measured from the time of stimulus onset.

Data Analysis

Data was analyzed using the Statistical Package for Social Sciences version 20(SPSS v20)
Continuous variables were presented as means with standard deviation and the categorical variables as proportions.

Unpaired t-test or Mann Whitney U test was used to compare continuous variables while categorical variables were compared using Chi-square test. Logistic regression analysis was done to control for possible confounders and Receiver Operating Characteristic (ROC) Curve analyses was used for diagnostic accuracy determination. Significant P value was set at < 0.05.

RESULTS

1.The schizophrenia patients were significantly more associated with no formal education and being unmarried than the healthy controls as shown in Table 1.

2. Schizophrenia patients were significantly more associated with higher mean rank conditioning and test amplitudes compared to their conditioning P50 amplitude. Also, Schizophrenia patients were statistically more associated with higher mean rank P50 amplitude ratio compared to healthy controls. Schizophrenia patients were significantly associated with higher amplitude of P300 auditory event-related potential and delayed P300 Peak Latency compared to healthy controls. These are as shown in Table 2.

3. The P300 Event-related Amplitude Potential, P300 Peak Latency and P50 Amplitude ratio had an Area Under the Curve (AUC) of 0.78, 0.76 and 0.73 respectively. These are as shown in Table 3 and Figure 1-3.

4. The P300 Peak latency was the most specific (Specificity=0.93) while P50 Amplitude ratio was the most sensitive (Sensitivity=0.76). The determined Cutoff point for the P300 Event-related Amplitude Potential, P300 Peak Latency and P50 Amplitude ratio were 6.84μv, 445ms and 0.89 respectively. These are as shown in Table 4.

5. Among Schizophrenia patients, the Spearman's correlation coefficient was used to determine the socio-demographic and clinical variables correlation with each neurophysiological marker. There was no statistically significant correlation between Duration of illness, Total PANSS score, Positive PANSS score, Negative PASS score, General Psychopathology scale score, Age of onset of illness, Duration of treatment, Chlorpromazine equivalent dose and each neurophysiological marker. There was a significant positive correlation between age and

The P50 amplitude ratio measurements among patients with Schizophrenia. There was however, no significant correlation P300 event-related amplitude, P300 peak latency and age. These are as shown in Table 5

6. The P300 event-related potential amplitude, P300 peak latency and P50 amplitude ratio were also significant predictors of Schizophrenia after the regression analysis was carried out. These are as shown in Table 6.

Table 1: Comparison of Sociodemographic characteristics of schizophrenia patients and healthy controls

Variable	Schizophrenia	Healthy Control	X2/Fisher's exact/T/	p-value
Age (years) Distribution (n/%)				
18 – 28	23(32.9)	26(37.1)		
29 – 39	27(38.6)	17(24.3)		
40 – 50	15(21.4)	16(22.9)	5.23	0.25
51 – 61	4(5.7)	10(14.3)		
62 – 72	1(1.4)	1(1.4)		
Age (mean)	34.31(10.48)	35.46(12.49)	-0.59	0.56
Range in years	18 – 65	18 – 65		
Sex				
male (n/%)	52(74.3)	47(67.1)	0.86	0.35
Female (n/%)	18(25.7)	23(32.9)		
Employment Status				
Employed	39(55.7)	50(71.4)	3.73	0.05
Unemployed	31(44.3)	20(28.6)		
Education				
Formal	31(44.3)	57(81.4)	20.68	<0.001*
Informal	39(55.7)	13(18.6)		
Marital Status				
Married	31(44.3)	53(75.7)	14.41	<0.001*
Unmarried	39(55.7)	17(24.3)		
Tribe				
Hausa	68(97.1)	68(97.1)		
Non-Hausa	2(2.9)	2(2.9)	0.00	1.00

Table 2: Comparison of Neurophysiological Markers between Schizophrenia Patients and Healthy Controls

Variable	Schizophrenia (Mean Rank)	Healthy Control (Mean Rank)	Mann-Whitney U	Z	p-value
P50 amplitude (Conditioning) R1	80.59	60.41	1744.000	-2.95	<0.001*
(Test) R2	89.58	51.42	1114.500	-5.57	<0.001*
P50ratio ($R2/R1$)	86.32	54.68	1342.500	-4.62	<0.001*
P300 Amplitude	90.11	50.89	1077.000	-5.76	<0.001*
P300 Latency	88.49	52.51	1191.000	-5.26	<0.001*

Table 3: Receiver Operating Characteristic Curve Analysis of P300 Auditory event-related Potential Amplitude, P300 Peak Latency and P50 Amplitude ratio of Participants.

	Variable	Area Under Curve	Std Error	p-value	95% Confidence Interval	
					Lower band	Upper band
1.	**P300 auditory event-related potential amplitude**	0.78	0.039	<0.001*	0.70	0.86
2.	**P300 Peak Latency**	0.76	0.042	<0.001*	0.67	0.84
3	**P50 amplitude ratio ($R2/R1$)**	0.73	0.043	<0.001*	0.64	0.81

Table 4: Sensitivity, Specificity, Likelihood Ratios and Cut-off point of the Neurophysiological markers

Variable	Youden Index	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Cutoff point
P300 event-related potential amplitude	0.43	0.53	0.90	5.29	0.52	6.84μv
P300 Peak Latency	0.44	0.51	0.93	7.24	0.52	445ms
P50 amplitude ratio	0.39	0.76	0.63	2.04	0.39	0.89

Table 5: Sociodemographic and Clinical variables associated with P50 Amplitude ratio in Schizophrenia patients (continuous variables).

Variable	Spearman's(rho) correlation coefficient	p-value
Age (years)	0.29	0.02*
Duration of illness	0.17	0.17
Duration of Treatment	0.16	0.20
Chlorpromazine equivalent dose	-0.14	0.26
Positive PANSS Scale score	-0.02	0.90
Negative PANSS Scale Score	-0.11	0.37
General Psychopathology Scale Score	-0.03	0.82
Total PANSS Score	-0.05	0.7
P300 Amplitude	0.14	0.24
P300 Latency	-0.16	0.18
Age of Onset of illness	0.2	0.09

n=70

Table 6: Logistic regression analysis of independent variables associated with Schizophrenia

	Variable	B	Std Error	p-value	Exp(B)	95% CI Exp (B)	
						Lower band	Upper band
1.	**Education (1)**	1.36	0.50	0.01*	3.90	1.451	10.468
2.	**P300 amplitude**	0.17	0.07	0.01*	1.18	1.037	1.343
3	**P300Peak Latency**	0.01	0.00	0.00*	1.01	1.004	1.016
4.	**P50 amplitude ratio**	2.38	0.72	0.00*	10.81	2.661	43.895
5.	**Marital Status (I)**	1.42	0.49	0.00*	4.14	1.598	10.733
6.	**Constant**	-8.39	1.60	0.00	0.00		

Education (I) – Informal; Marital Status (I) – Not married; Occupation (1) – Unemployed
B-Unstandardized beta

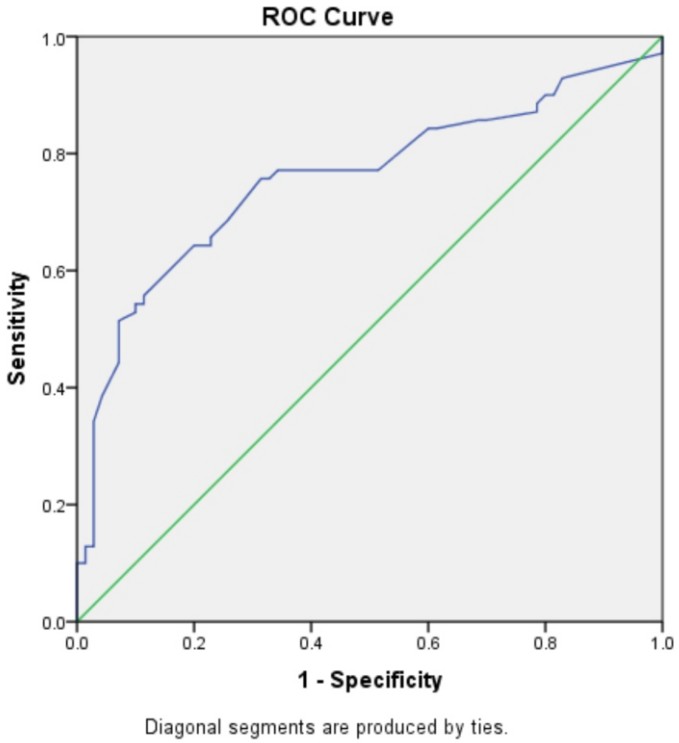


Figure 1: Receiver Operating Characteristic Curve of P300 Auditory Event-related Potential Amplitude of Participants

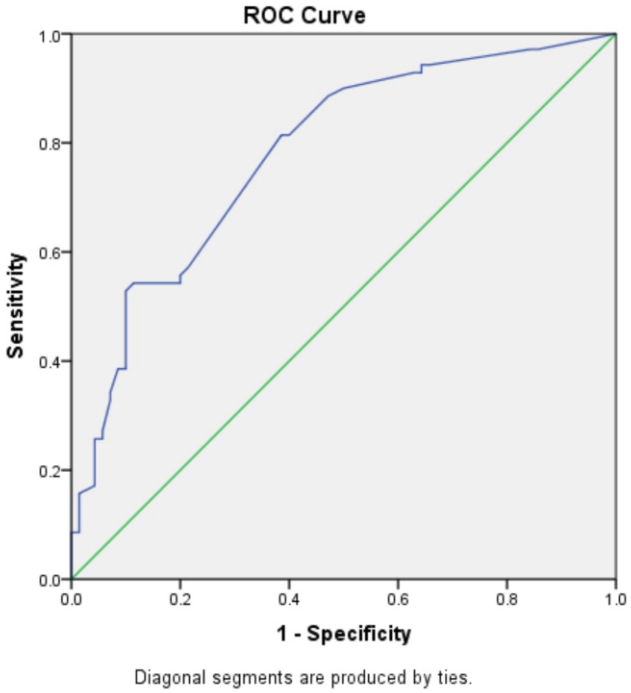


Figure 2: Receiver Operating Characteristic Curve for P300 Peak Latency of Participants

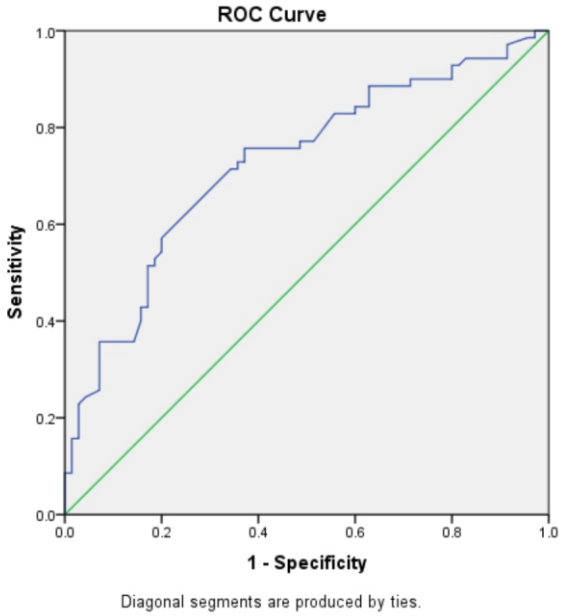


Figure 3. Receiver Operating Characteristic Curve for P50 Amplitude Ratio(R2/R1) of Participants

DISCUSSION

The socio-demographic pattern of participants showed that the healthy controls differ significantly in terms of educational status compared to schizophrenia patients in having higher proportion of participants with formal education in that group. This is supported by a previous study which reports that there is increased risk of no secondary or higher education among schizophrenia patients compared to healthy controls.[17] Cognitive deficits which are usually present before onset of psychiatric symptoms,[18] low socio-economic background and possible family history of mental disorder may contribute to higher risk of lack of formal education.

This study showed that schizophrenia patients were significantly more associated with being unmarried compared to healthy controls. Several studies have reported significant difference in terms of marital status between schizophrenia patients and healthy controls. Adewuya, [19] reported that patients with schizophrenia were more likely to be unmarried in Nigeria while Gupta *et al*.,[20] in Canada reported the same thing. This has been attributed to divorce or marital separation sequel to disability in marital relationship. Also, the earlier onset of the disorder may lead to socio-occupational decline that will make marriage impossible.

In P50 Auditory event-related potential, there were higher test amplitudes in schizophrenia patients that were significant compared to their conditioning P50 amplitude. This is consistent with previous studies among Caucasians.[21-22] where schizophrenia patients exhibited significant P50 non-suppression more than the controls and higher mean P50 ratio (That is, ratio of test amplitude to conditioning amplitude).

Abnormal sensory gating has been postulated to be the reason for some of the symptoms seen in schizophrenia and the P50 amplitude non-suppression. This is said to occur following sensory overload leading to impaired concentration in schizophrenia patients.[23] Furthermore, a link has been reported between abnormal Alpha-7 nicotinic receptors and abnormal P50 response.[24] The Alpha-7 nicotinic receptor is a type of nicotinic acetylcholine receptor (nAchRs) implicated in long term memory and positive effects on neurocognition in schizophrenia patients .[25]They are also widely distributed in different brain regions. These findings need further investigation to authenticate the validity of P50 non-suppression in schizophrenia diagnosis and to serve as a new pathophysiologic target for drug discovery.

Auditory P300 evoked potential has been used as an evaluation of cognitive processes, like attention allocation, activation of immediate memory, updating of task-relevant information in the working memory in many studies.[26-27] In this study, schizophrenia patients had significantly larger amplitude and increased (delayed) latency of P300 auditory evoked potential compared to healthy controls. Most of the previous studies reported lower amplitude among schizophrenia patients.[15, 28-29]while other studies have found no significant difference in the P300 amplitudes of schizophrenia patients compared to controls.[30] The finding on P300 amplitude in this study is unlike most of the previous studies that were carried out among Caucasians. A study however, reported a differential impact of race on the association between schizophrenia and P300.[31] It initially found amplitude reduction among African-American controls, rather than the patients. This difference was lost when use of psychoactive substances was controlled for, in the study. However, this finding was not observed among

Caucasians in the same study. Another study found schizophrenia patients having significant reduction in temporo-parietal P300 amplitude and higher frontal P300 amplitude than controls.[32] This may be due to increased eye movements among schizophrenia patients.[33] Another possible explanation could be that higher P300 amplitude among schizophrenia patients could reflect higher engagement of the temporoparietal cortex believed to have maximal P300 amplitude at the Pz location on the scalp.[34] This may be a way of compensating for a cortical defect either in that region or elsewhere like in the frontal lobe. Similarly, previous studies have reported greater cognitive demands among patients with schizophrenia when involved in tasking procedures.[35-36] Another study reported that schizophrenia patients are capable of producing larger P300 amplitude under certain conditions and that this may indicate increased effort to compensate for cognitive deficits.[37]Abnormalities in the brain neurotransmitters that differ among races may also explain this increased significant difference. The P300 event-related potential may be caused by a direct excitatory postsynaptic effect of glutamergic neurotransmission with cholinergic, noradrenergic and GABAergic neurotransmitters being neuromodulatory while dopaminergic and serotonergic influences are minor in its generation.[38-39] Acetylcholine specifically enhances P300 amplitude while GABA reduces P300 amplitude. A number of studies have reported better prognosis among Africans with Schizophrenia compared to Caucasians with Schizophrenia.[40-42]Although, this has been attributed to environmental factors, it is possible that this may be also due to differing neuropathological and biochemical influences on the brain of schizophrenia patients across races. Several studies, have reported delayed latency to P300 peak amplitude similar to the finding in this study.[15, 43] P300 latency is considered to be a measure of stimulus classification speed. It is unrelated to response selection processes and independent of behavioural response time as seen in P300 event-related potential. The P300 amplitude and latency have been hypothesized to follow a maturation path from childhood to adolescence, resulting in a period that marks a plateau, after which degenerative effects begin.[27] This point of deflection between maturation and degeneration stages are said to occur at different ages for P300 amplitude and latency. The findings from the study by Van Dinteren *et al*,[27] revealed that P300 latency possibly indicates neural speed or brain efficiency while P300 amplitude might indicate neural power or cognitive resources which increase with maturation. This suggests that latency and amplitude reflect different aspects of brain maturation. Precisely, P300 amplitude might be an index for the number of cognitive resources being used, increasing in the first year of life and decreasing with further aging beyond adolescence.[27] Higher amplitudes are related to higher proportion of allocated cognitive resources and intra-subject re-routing of neural pathways to improve cognitive performance in a background cognitive decline. P300 latency may be a more direct index of information-processing speed and indirectly cognitive performance.[27]

The Area Under the Curve (AUC) of P300 amplitude, P300 Peak latency and P50 Amplitude ratio as a test variable was acceptable in the ability to predict schizophrenia diagnosis based on the current diagnostic guidelines.[44] The P50 amplitude ratio was least in discriminating ability between schizophrenia and healthy controls.

The finding on the diagnostic accuracy of P300 auditory event-related potential and P50 amplitude ratio is partly similar to findings in other studies. A study that utilized a three-factor solution comprising P200 and P300 amplitudes,

P50 ratio and differences scores including P300 latency resulted in an AUC of 0.793 with sensitivity of 0.829 and specificity of 0.703.[45] A similar study on P50 and P300 event-related potential also classified schizophrenia and healthy controls with 71% accuracy with a combined sensitivity of 0.70 and specificity of 0.72.[46] Another study utilized visual event-related potential to demonstrate P300 amplitude and latency and reported that they were able to classify schizophrenia by 61% and healthy control by 80% accuracy.[47] Although the present study did not set out to develop a combined ROC analysis, the average AUC, sensitivity and specificity were close to these previous studies. However, the specificity of the markers in our study are higher than their sensitivity except for the P50 amplitude ratio. The inflection point of the sensitivity and specificity of each marker in this study was generally fairly acceptable based on the principles of high-quality testing.[48] These inflection points show that the P50 ratio may be more useful as a screening test while P300 auditory event-related potential may be more relevant as a diagnostic test. These markers may be useful as an adjunct to the syndromic diagnosis that currently exist for schizophrenia. The determined Youden Index and cut-off point in this study for P300 event-related amplitude, P300 Peak latency and P50 Amplitude ratio have not been done in all known previous study on these markers. This will ultimately serve as a template for future studies on the diagnostic accuracy of these markers.

Previous studies have reported weaker P50 gating with increased age.[49-50] It was however, also reported in these studies that age seem to account for only a minimal part of the changes in P50 gating. Increase in age has been reported to have a significant influence also on P300 latency prolongation among schizophrenia patients.[51-52] while younger people have been reported to demonstrate increased P300 amplitudes.[53] The fact that P300 is affected by age-related changes which may actually be related to changes in cognitive capacities, suggests that P300 is a sensitive metric for cognitive performance.[27] It was also reported that developmental trajectories of the P300 amplitude across the lifespan exist for frontal and parietal electrode sites. The parietal P300 increased in childhood to reach its peak in adolescence, then declined for the rest of the lifespan. In contrast, the frontal P300 reached its peak at a mid-older age. This is about 46years after which it remains constant for the rest of the lifespan. This has been said to reflect compensatory activity within the brain which has been highlighted earlier.[27] The preponderance of young adults among the participants and the lower mean age of schizophrenia patients may partly contribute to the differences observed in this study.

The total PANSS score has been reported to have a negative correlation with P300 amplitude and latency in medicated schizophrenia patients.[43] Another study among unmedicated schizophrenia patients found similar inverse relationship between total PANSS score and P300 amplitude.[54] This present study found no relationship between PANSS score and any of the neurophysiological markers investigated. Some studies have also reported no significant correlation between PANSS positive/negative symptoms and P50 amplitude ratio .[55-57] The schizophrenia patients in this study were on medication for the psychotic symptoms. Therefore, the PANSS scores were likely to be significantly lower than at the onset of the illness prior to the use of medication. This may influence the relationship between PANSS score and these neurophysiological measures that are believed to be independent of the clinical state of the patients.

CONCLUSION

The study has determined cut-off point for the neurophysiological measures that are absent in previous studies. This will serve as an additional useful criterion in improving the diagnostic accuracy of schizophrenia and this could also be useful in medico-legal purposes.

LIMITATIONS

The manual method of measurement of the evoked potential parameters rather than the computerized method may limit the level of preciseness in measurements.

The inability to achieve a fully noise-proof setting for the neurophysiological procedures might have distracted some of the participants and affected their performance during the procedures.

It was a cross-sectional study and may not be sensitive to some changes that may occur over time.

RECOMMENDATIONS

(a) This study is paving a way for further studies on investigating neurophysiological makers among patients with schizophrenia in Nigeria. It will therefore be necessary to explore further, the diagnostic possibilities in P300 auditory event-related potential in future studies in this region.

(b) Neuropathological studies involving neuroimaging and genetic studies should be encouraged to validate the likely aetiology of the findings in this study.

(c) The investigation of these neurophysiological markers should be conducted among relatives of schizophrenia patients in order to assess the possible heritability of these measures and their genetic underpinnings.

ACKNOWLEDGEMENT

The research was self-funded. No external funds was received for any stage of this study.

AUTHOURS CONTRIBUTION

Adebayo Sunday Adebisi, Chinedu Onwuchekwa, Umar Zayyanu Usman and Bello Sirajo Shiitu-Study Design

Adebayo Sunday Adebisi -Data collection and Literature review

Chinedu Onwuchekwa, Umar Zayyanu Usman and Bello Sirajo Shiitu-Literature review proofreading and corrections.

Adebayo Sunday Adebisi, Chinedu Onwuchekwa, Umar Zayyanu Usman and Bello Sirajo Shiitu--Data analyses.

CONFLICT OF INTEREST

There is no conflict of interest to disclose.

REFERENCES

1. Smith T, Horwath E, Cournos F. Schizophrenia and other psychotic disorders. New York, NY: Oxford University Press; 2010 Apr 28.
2. Greenwood TA, Shutes-David A, Tsuang DW. Endophenotypes in schizophrenia: digging deeper to identify genetic mechanisms. Journal of psychiatry and brain science. 2019;4(2).
3. Owens E, Bachman P, Glahn DC, Bearden CE. Electrophysiological endophenotypes for schizophrenia. Harvard review of psychiatry. 2016 Mar;24(2):129.
4. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Molecular psychiatry. 2010 Aug;15(8):789-97.
5. Cohen MX. Where does EEG come from and what does it mean?. Trends in

neurosciences. 2017 Apr 1;40(4):208-18.
6. Del Re EC, Bergen SE, Mesholam-Gately RI, Niznikiewicz MA, Goldstein JM, Woo TU, Shenton ME, Seidman LJ, McCarley RW, Petryshen TL. Analysis of schizophrenia-related genes and electrophysiological measures reveals ZNF804A association with amplitude of P300b elicited by novel sounds. Translational psychiatry. 2014 Jan;4(1):e346.
7. Earls HA, Curran T, Mittal V. A meta-analytic review of auditory event-related potential components as endophenotypes for schizophrenia: perspectives from first-degree relatives. Schizophrenia bulletin. 2016 Nov 1;42(6):1504-16.
8. Banea OC, Pegolo E, Marcu S, Friðriksdóttir R, Ívarsson E, Jónasson AD, Jónasson VD, Magnusdóttir BB, Haraldsson M, Wassermann E, Gargiulo P. P50 and P300 Event Related Potentials in Patients with Schizophrenia Recorded from High-Density EEG. In Mediterranean Conference on Medical and Biological Engineering and Computing 2019 Sep 26 (pp. 1071-1077). Springer, Cham.
9. Sasidharan A, Nair AK, Marigowda V, Lukose A, John JP, Kutty BM. Simultaneous assessment of P50, MMN, ERN and P300 event-related potentials among patients with Schizophrenia–an exploratory study. BioRxiv. 2019 Jan 1:837815.
10. Hedges D, Janis R, Mickelson S, Keith C, Bennett D, Brown BL. P300 amplitude in Alzheimer's disease: a meta-analysis and meta-regression. Clinical EEG and neuroscience. 2016 Jan;47(1):48-55.
11. Lijffijt M, Moeller FG, Boutros NN, Steinberg JL, Meier SL, Lane SD, Swann AC. Diminished P50, N100 and P200 auditory sensory gating in bipolar I disorder. Psychiatry research. 2009 May 30;167(3):191-201.
12. Thoma L, Rentzsch J, Gaudlitz K, Tänzer N, Gallinat J, Kathmann N, Ströhle A, Plag J. P50, N100, and P200 sensory gating in panic disorder. Clinical EEG and Neuroscience. 2020 Sep;51(5):317-24.
13. Sinha SR, Sullivan LR, Sabau D, Orta DS, Dombrowski KE, Halford JJ, Hani AJ, Drislane FW, Stecker MM. American clinical neurophysiology society guideline 1: minimum technical requirements for performing clinical electroencephalography. The Neurodiagnostic Journal. 2016 Oct 1;56(4):235-44.
14. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. 1987 Jan 1;13(2):261-76.
15. Qiu YQ, Tang YX, Chan RC, Sun XY, He J. P300 aberration in first-episode schizophrenia patients: a meta-analysis. PLoS One. 2014 Jun 16;9(6):e97794.
16. Sullivan LM. Essentials of biostatistics in public health. Jones & Bartlett Learning; 2017 Feb 14.
17. Hakulinen C, McGrath JJ, Timmerman A, Skipper N, Mortensen PB, Pedersen CB, Agerbo E. The association between early-onset schizophrenia with employment, income, education, and cohabitation status: nationwide study with 35 years of follow-up. Social Psychiatry and Psychiatric Epidemiology. 2019 Nov;54(11):1343-51.
18. Dickson H, Laurens KR, Cullen AE, Hodgins S. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. Psychological medicine. 2012 Apr;42(4):743-55.
19. Adewuya AO, Makanjuola RO. Subjective quality of life of Nigerian schizophrenia patients: sociodemographic and clinical correlates. Acta Psychiatrica Scandinavica. 2009 Aug;120(2):160-4.

20. Gupta M, Bassett E, Iftene F, Bowie CR. Functional outcomes in schizophrenia: understanding the competence-performance discrepancy. Journal of psychiatric research. 2012 Feb 1;46(2):205-11.
21. Wang H, Zhang M, Chen X, Lou F, Liang J, Chen C, Shi T, Lu Q. P50 auditory sensory gating in first onset schizophrenics and normal healthy adults. Frontiers of medicine in China. 2007 Oct;1(4):429-32.
22. Shen CL, Chou TL, Lai WS, Hsieh MH, Liu CC, Liu CM, Hwu HG. P50, N100, and P200 auditory sensory gating deficits in schizophrenia patients. Frontiers in Psychiatry. 2020 Aug 27;11:868.
23. Vlcek P, Bob P, Raboch J. Sensory disturbances, inhibitory deficits, and the P50 wave in schizophrenia. Neuropsychiatric disease and treatment. 2014;10:1309.
24. Bencherif M, Stachowiak MK, Kucinski AJ, Lippiello PM. Alpha7 nicotinic cholinergic neuromodulation may reconcile multiple neurotransmitter hypotheses of schizophrenia. Medical Hypotheses. 2012 May 1;78(5):594-600.
25. Freedman R. α7-nicotinic acetylcholine receptor agonists for cognitive enhancement in schizophrenia. Annual review of medicine. 2014 Jan 14;65:245-61.
26. Polich J. Updating P300: an integrative theory of P3a and P3b. Clinical neurophysiology. 2007 Oct 1;118(10):2128-48.
27. van Dinteren R, Arns M, Jongsma ML, Kessels RP. P300 development across the lifespan: a systematic review and meta-analysis. PloS one. 2014 Feb 13;9(2):e87347.
28. Jeon YW, Polich J. Meta analysis of P300 and schizophrenia: Patients, paradigms, and practical implications. Psychophysiology. 2003 Sep;40(5):684-701.
29. Sahoo S, Malhotra S, Basu D, Modi M. Auditory P300 event related potentials in acute and transient psychosis—Comparison with schizophrenia. Asian Journal of Psychiatry. 2016 Oct 1;23:8-16.
30. Park EJ, Jin YT, Kang CY, Nam JH, Lee YH, Yum MK, Han SI, Jeon YW. Auditory and visual P300 in patients with schizophrenia and controls: Stimulus modality effect size differences. Clinical Psychopharmacology and Neuroscience. 2005 Feb 1;3(1):22-32.
31. Turetsky BI, Dress EM, Braff DL, Calkins ME, Green MF, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Nuechterlein KH, Radant AD. The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. Schizophrenia research. 2015 Apr 1;163(1-3):53-62.
32. Winterer G, Egan MF, Raedler T, Sanchez C, Jones DW, Coppola R, Weinberger DR. P300 and genetic risk for schizophrenia. Archives of general psychiatry. 2003 Nov 1;60(11):1158-67.
33. Benson PJ, Beedie SA, Shephard E, Giegling I, Rujescu D, Clair DS. Simple viewing tests can detect eye movement abnormalities that distinguish schizophrenia cases from controls with exceptional accuracy. Biological psychiatry. 2012 Nov 1;72(9):716-24.
34. Schröder E, Kajosch H, Verbanck P, Kornreich C, Campanella S. Methodological considerations about the use of bimodal oddball P300 in psychiatry: topography and reference effect. Frontiers in Psychology. 2016 Sep 21;7:1387.
35. Gold JM, Kool W, Botvinick MM, Hubzin L, August S, Waltz JA. Cognitive effort avoidance and detection in people with schizophrenia. Cognitive, affective, & behavioral neuroscience. 2015 Mar;15(1):145-54.

36. Fuentes-Claramonte P, López-Araquistain L, Sarró S, Sans-Sansa B, Ortiz-Gil J, Maristany T, Salvador R, McKenna PJ, Pomarol-Clotet E. Brain functional correlates of formal thought disorder in schizophrenia: examining the frontal/dysexecutive hypothesis. Psychological Medicine. 2021 Oct;51(14):2446-53.
37. Baving L, Rockstroh B, Rößner P, Cohen R, Elbert T, Roth WT. Event-related potential correlates of acquisition and retrieval of verbal associations in schizophrenics and controls. Journal of Psychophysiology. 2000;14(2):87.
38. Frodl-Bauch T, Bottlender R, Hegerl U. Neurochemical substrates and neuroanatomical generators of the event-related P300. Neuropsychobiology. 1999;40(2):86-94.
39. Schutte I, Deschamps PK, van Harten PN, Kenemans JL. Dopaminergic and noradrenergic manipulation of anticipatory reward and probability event-related potentials. Psychopharmacology. 2020 Jul;237(7):2019-30.
40. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures A World Health Organization Ten-Country Study. Psychological Medicine monograph supplement. 1992;20:1-97.
41. Kulhara P. Outcome of schizophrenia: some transcultural observations with particular reference to developing countries. European Archives of Psychiatry and Clinical Neuroscience. 1994 Dec;244(5):227-35.
42. Harrison G, Hopper KI, Craig T, Laska E, Siegel C, Wanderling JO, Dube KC, Ganev K, Giel R, Der Heiden WA, Holmberg SK. Recovery from psychotic illness: a 15-and 25-year international follow-up study. The British journal of psychiatry. 2001 Jun;178(6):506-17.
43. Hassan WA, Darweesh AE, Abdel-Rahman AA, Ahmad HE, Hassaan SH, Noaman MM, Fahmy IF. P300 cognitive assessment in patients with first-episode psychosis: a prospective case-control study. Middle East Current Psychiatry. 2020 Dec;27(1):1-8.
44. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. Journal of Thoracic Oncology. 2010 Sep 1;5(9):1315-6.
45. Peters RM, Gjini K, Templin TN, Boutros NN. A statistical methodology to improve accuracy in differentiating schizophrenia patients from healthy controls. Psychiatry research. 2014 May 30;216(3):333-9.
46. Johannesen JK, O'Donnell BF, Shekhar A, McGrew JH, Hetrick WP. Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder. Schizophrenia bulletin. 2013 Nov 1;39(6):1219-29.
47. Chun J, Karam ZN, Marzinzik F, Kamali M, O'Donnell L, Tso IF, Manschreck TC, McInnis M, Deldin PJ. Can P300 distinguish among schizophrenia, schizoaffective and bipolar I disorders? An ERP study of response inhibition. Schizophrenia research. 2013 Dec 1;151(1-3):175-84.
48. Power M, Fell G, Wright M. Principles for high-quality, high-value testing. BMJ Evidence-Based Medicine. 2013 Feb 1;18(1):5-10.
49. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophrenia bulletin. 2007 Jan 1;33(1):69-94.
50. Petersen L, Sørensen TI. Studies based on the Danish Adoption Register: schizophrenia,

BMI, smoking, and mortality in perspective. Scandinavian journal of public health. 2011 Jul;39(7_suppl):191-5.
51. Yu YW, Chen TJ, Chen MC, Tsai SJ, Lee TW. Effect of age and global function score on schizophrenic p300 characteristics. Neuropsychobiology. 2005;51(1):45-52.
52. Bourisly AK. Effects of aging on P300 between late young-age and early middle-age adulthood: an electroencephalogram event-related potential study. NeuroReport. 2016 Sep 28;27(14):999-1003.
53. Juckel G, Karch S, Kawohl W, Kirsch V, Jäger L, Leicht G, Lutz J, Stammel A, Pogarell O, Ertl M, Reiser M. Age effects on the P300 potential and the corresponding fMRI BOLD-signal. Neuroimage. 2012 May 1;60(4):2027-34.
54. Chang WH, Chen KC, Yang YK, Chen PS, Lu RB, Yeh TL, Wang CS, Lee IH. Association between auditory P300, psychopathology, and memory function in drug-naïve schizophrenia. The Kaohsiung Journal of Medical Sciences. 2014 Mar 1;30(3):133-8.
55. Ringel TM, Heidrich A, Jacob CP, Fallgatter AJ. Sensory gating deficit in a subtype of chronic schizophrenic patients. Psychiatry research. 2004 Mar 15;125(3):237-45.
56. Louchart-de la Chapelle S, Levillain D, Ménard JF, Van der Elst A, Allio G, Haouzir S, Dollfus S, Campion D, Thibaut F. P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. Psychiatry Research. 2005 Jul 15;136(1):27-34.
57. Thoma RJ, Hanlon FM, Moses SN, Ricker D, Huang M, Edgar C, Irwin J, Torres F, Weisend MP, Adler LE, Miller GA. M50 sensory gating predicts negative symptoms in schizophrenia. Schizophrenia research. 2005 Mar 1;73(2-3):311-8.

Adebisi SA, Onwuchekwa C, Usman UZ, Shiitu BS. Determination of Neurophysiological P300 and P50 in Patients with Schizophrenia at a Tertiary Hospital in Sokoto, Nigeria. Afr. J. Trop. Med. & Biomed. Res. 2024; 7(2) 77-93
https://dx.doi.org/10.4314/ajtmbr.v7i2.8