Atypical waveform morphology in schizophrenia-visual evoked potential as a promising endophenotype

Sneh Babhulkar, Ruchi Kothari¹, Praveen Khairkar
Departments of Psychiatry and Physiology, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India

Address for correspondence:
Dr. Ruchi Kothari,
Department of Physiology,
Mahatma Gandhi Institute of Medical Sciences,
Sevagram, Wardha - 442 102,
Maharashtra, India.
E-mail: ruchi@mgims.ac.in

Background: Electrophysiological research has provided measures of dysfunction of visual pathway in schizophrenia through the use of visual evoked potential (VEP) as the neurophysiologic tool. Objective: The main objective of this study is to examine the morphology and topography of VEP responses in schizophrenic patients and to explore the potentiality of VEP as an endophenotype. Materials and Methods: The study included 20 patients of schizophrenia who were recruited from the outpatient and inpatient department of psychiatry of a tertiary care rural hospital. The patients were assessed by tools such as Positive and Negative Symptoms Assessment Scale and Clinical Global Impression Scale for Severity. Transient Pattern Reversal VEP recordings were taken using an Evoked Potential Recorder (RMS EMG EP MARK II), and it was a cross-sectional study. Results: The mean age of patients was 45.95 ± 10.14 years in the range of 35–60 years. Qualitative analysis of VEP waveforms in people with schizophrenia was performed. Abnormal waveform morphology was observed in 14/20 (70%) of the study population and all of them were the chronic and severe cases. Six out of 15 (40%) showed lack of differentiation of the evoked complex so that the three waves (negative-positive-negative [NPN] complex) could not be identified. In 5 of 15 (33.33%) VEP records, a distinct altered waveform with extinguished second negative component of NPN complex was obtained. Conclusion: Qualitative morphometric findings of this study in terms of pattern-reversal VEP waveform abnormalities emerged as a tool to provide evidence of relationship for emerging as first potential biomarker for diagnosing schizophrenia.

Keywords: Abnormal waveform, schizophrenia, topography, visual evoked potential

Schizophrenia is a clinical syndrome of variable, but profoundly disruptive psychopathology that involves cognition, emotion, perception, and other aspects of behavior. Despite marked advances in psychopharmacological management, there is no “quantum leap” in the etiopathogenetic processes of schizophrenia and as yet no pinpointed theory exist or substantiate the causal association to one specific reason. A central conceptual issue in the investigation of the etiology of schizophrenia is whether schizophrenia is a neurodevelopmental or a neurodegenerative disorder.

Access this article online
Quick Response Code:
Website: www.industrialpsychiatry.org
DOI: 10.4103/ipj.ipj_37_17

With the progression of neuroscience, the neurodevelopmental hypothesis of schizophrenia was formulated, which included educated guesses on the distinct roles of cortical and subcortical dopaminergic systems in the brain. The neurodevelopmental models posit that genetic and environmental risk factors act during prenatal, perinatal, and early adolescence periods, thus altering the developmental trajectory and leading to the onset during adolescence and young adulthood.¹ The idea that adult-onset disorder could have its origin in neurodevelopment was supported by the studies of

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Babhulkar S, Kothari R, Khairkar P. Atypical waveform morphology in schizophrenia-visual evoked potential as a promising endophenotype. Ind Psychiatry J 2017;26:155-61.
Endophenotypes are the measurable biological (physiological, biochemical, and anatomical features), behavioral (psychometric pattern), or cognitive markers that are found more often in individuals with a disease than in the general population.

Endophenotypes reflects disease liability-associated variants in structural and functional magnetic resonance images, neurophysiological sensory processing measures, and because many endophenotypes are present before the disease onset and in individuals with heritable risk for disease such as unaffected family members, they can be used to help diagnose and search for causal association in disorders like schizophrenia.

Visual sensory processing deficits have been consistently documented in schizophrenia using the visual evoked potential (VEP) technique.

VEP is an objective, noninvasive, simple, low-cost technique used to evaluate the functional integrity of the visual system and graphically illustrates cerebral electrical potentials produced by the occipital cortical areas evoked visually.

Quite a few studies have shown impairment of VEPs in patients of schizophrenia as compared to healthy controls in the past. The early marker of this impairment has been hypothesized in the variations of topographical form of P100 component of VEP. Based on this proposition, we designed a study for identifying the potential of this specific endophenotype provided with some degree of association, if any for schizophrenic patients. This may provide us the unique opportunity to endorse the support and strength of neurodevelopmental. Such a preliminary study has not been attempted so far as the literature could be traced in this part of the subcontinent.

**MATERIALS AND METHODS**

**Setting**

Recruitment of the sample was carried out at the inpatient and outpatient services unit in department of psychiatry affiliated to tertiary health-care multispecialty teaching hospital at a rural-based institute in the state of Maharashtra.

**Study design**

The study was an observational, noninterventional, hospital-based study.

**Study population**

Twenty patients of schizophrenia were investigated for VEP as soon they were cooperative and their psychomotor activity normalized. The average duration of disease in all cases was >10 years. Only those patients were selected who were adherent to medication and showed good compliance. The severity of schizophrenia was assessed by Positive and Negative Symptoms Assessment Scale (PANSS) as well as Clinical Global Impression Severity Assessment Scale (CGI–SS).

The study was approved by ethics committee of institution (IEC, MGIMS). We obtained a written informed consent from all the study participants before enrolling them in the study. Only those patients were selected who fulfilled inclusion and exclusion criteria.

Inclusion criteria were age 30–65 years, either gender (male or female), chronicity of the disease >10 years, presence of family history of schizophrenia in first- or second-degree relative, diagnosed cases of schizophrenia with predominant positive or negative symptoms (using International Classification of Disease-10 [ICD-10], Diagnostic and Clinical Research DCR criteria), those patients who are physically stable enough to undergo neurophysiological (VEP) evaluation.

Exclusion criteria were subnormal intelligence, any history of visual impairment beyond corrected-to-normal vision, organic brain disorder, mental retardation, or significant medical illness, history of comorbid diagnosed neurological disorder such as epilepsy or neurodegenerative disorders, history of head injury or having undergone recent neurosurgery, significant risk of suicidal or homicidal behavior, Whosoever refused to be a part of our study for any reason after due explanations for obtaining consent.

All participants reported normal or corrected-to-normal vision; where possible, this was corroborated by medical records.

Tools of assessment included semi-structured pro forma for sociodemographic and clinical profile, ICD criteria for diagnosing schizophrenia, PANSS scale, CGI scale, and pattern reversal VEP (PRVEP).

**Sociodemographic and clinical profile sheet**

This was modified from the sociodemographic and clinical profile sheet used routinely in the department of psychiatry. The pro forma elicited information on age, sex, mother
tongue, marital status, occupation, education status, family type, locality, source of referral, and clinical variables such as past medical illness, treatment history, substance use, and family history of psychiatric illness.

**International classification of disease 10th revision (diagnostic and clinical research criteria) for the diagnosis of schizophrenia**

The 10th revision of the International Classification of Diseases by the World Health Organization was used. Patients who were diagnosed with schizophrenia as per the criteria of this manual were recruited into the study.

**Positive and negative symptoms assessment scale**

It is a medical scale used for measuring symptom severity of patients with schizophrenia. Data gathered from this assessment procedure are applied to the PANSS ratings. Each of the 30 items is accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology as follows: 1 – absent, 2 – minimal, 3 – mild, 4 – moderate, 5 – moderate-severe, 6 – severe, and 7 – extreme. To assess a patient using PANSS, an approximately 45-min clinical interview is conducted. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers. Of the 30 items included in the PANSS, 7 constitute a positive scale, 7 a negative scale, and the remaining 16 a General Psychopathology Scale. The scores for these scales are arrived at by summation of ratings across component items.

**Clinical global impression-severity scale**

It is a 7-point scale that requires the clinician to rate the severity of the patient’s illness at the time of assessment, relative to the clinician’s past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

The CGI rating scales are commonly used measures of symptom severity, treatment response, and the efficacy of treatments in treatment studies of patients with mental disorders.

**Pattern reversal visual evoked potential recording**

PRVEPs were performed in adherence to the standardized methodology of International Federation of Clinical Neurophysiology Committee Recommendations and International Society for Clinical Electrophysiology of Vision Guidelines and montages were kept as per 10–20 International System of EEG Electrode placements.

The stimulus configuration consisted of the transient pattern reversal method, in which a black and white checkerboard is generated (full field) on a VEP monitor by an electronic pattern regenerator inbuilt in an evoked potential recorder (RMS EMG EP MARK II manufactured by Recorders and Medicare Systems, Chandigarh). The recording was done monoculary for the left and right eyes separately with the subject wearing corrective glasses if any during the test.

**Typical visual evoked potential waveform**

The starting point of VEP waveform is stimulus onset. The typical PRVEP waveform consists of the earliest negative peak (N1 or N70), succeeded by a large positive peak (P1 or P100) and followed by another negative peak (N2 or N155) (Figure 1). Positive wave P100 is shown with downward polarity and the negative waves are shown with upward polarity in the recording. P100, the prominent attribute of PRVEPs, is the most consistent and invariable peak.

**RESULTS**

A total of 20 patients of schizophrenia were recruited for the study. All of these patients were able to complete their study. The patients were not able to complete the study due to irregular follow-up, noncompliance, or refusal to participate were excluded.

The PRVEP investigation was performed on 20 (11 males and 9 females) patients with schizophrenia, aged 35–60 (mean 45.95 ± 10.14) years.

- The mean score on CGI for the patients was 6.82 ± 1.25
- The mean score on PANSS
  - For positive subset of patients was: 54.78 ± 9.52
  - For negative subset of patients was: 34.56 ± 11.12.

Qualitative analysis of VEP waveform in schizophrenic patients demonstrated abnormal waveform morphology in 14/20 (70%) of the study population and all of them were the chronic and severe cases. A few illustrations of atypical waveform in our study participants have been represented in Figures 2–6. Six of 20 cases (30%) had normal PRVEP waveform morphology.

**DISCUSSION**

Robust deviations in P100 component of the VEP including its topography have not been aptly and avidly reported in the literature.
A meager number of researchers have reported significant relationships between schizophrenic symptom patterns and EP parameters. Shagass\textsuperscript{[16]} showed that chronic, psychotic, and less depressed schizophrenic patients exhibited diminished shape variability of wave in the first 100 ms after visual stimulus compared with other schizophrenic patients. Topographical differences in the location of abnormalities, depending on the patient’s clinical symptoms have been observed when flash VEPs were recorded in normal and unmedicated schizophrenic patients using visual stimuli of differing intensities.\textsuperscript{[17]} Our results are in close agreement with earlier studies where P1 component deficit has been identified in chronic patients\textsuperscript{[7-9]}, and they have focused on the time course of these low-level visual processing deficits. In particular, it was revealed by topographic modulations in the VEP and demonstrated that P1 deficit follows from a change in the configuration of the underlying brain network.\textsuperscript{[9]}

![Figure 1: Normal pattern reversal visual evoked potential waveform](image1)

![Figure 2: Visual evoked potential record of a patient showing waveform with an atypical shape in the form of extinguished second negative component of negative–positive-negative complex (altered waveform)](image2)
PRVEP waveform abnormalities in schizophrenic patients have been previously ascribed\textsuperscript{[18–20]} to defects within dorsal visual stream structures on the basis of its topographic distribution, estimated sources, and relative sensitivity to luminance contrast. This notion is in solid agreement with studies\textsuperscript{[21–24]} demonstrating inadequacies in visuospatial functions in such patients.

Our study is bestowed with qualitative morphometric analyses of VEP waveform abnormalities with regard to clinical symptom ratings which we found in predominantly severe patients of schizophrenia. Distorted, altered waveform morphology was found in 14/20 (70%) of cases explicitly all of whom belonged to the group of severe and chronic cases.

Six of our VEP records out of 14 (42.85%) showed abnormal waveform morphology in the form of lack of differentiation of the evoked complex so that the three waves (negative–positive-negative complex) could not be identified and the parameters (namely, latencies and amplitude) could not be evaluated. In other 5 out of 14 (35.71%) VEP records, we noted a distinct waveform with an atypical shape in the form of extinguished second negative component of (NPN) complex (altered waveform).

The hallmark of VEP which is (NPN complex was found to be extinguished in 3 of 14 (21.42%) cases. These are very unique findings of VEP as none of the study previously conducted could specifically pinpoint for any of such distinct qualitative, morphometric abnormality in patients of schizophrenia. Such distinct morphometric qualitative finding may need another look from the vantage point of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Visual evoked potential record showing abnormal waveform morphology in the form of lack of differentiation of the evoked complex}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Visual evoked potential record showing improper waveform morphology such that the three waves (negative–positive-negative complex) could not be identified}
\end{figure}
speculation considering its potential role in diagnosis of schizophrenia.

There are at least two issues that still remain unsettled. First, the specificity of this deficit (and suitability as an endophenotype) is yet to be established, with evidence for altered P100 waveform in other clinical populations. Second, it remains unknown whether schizophrenia patients exhibit intact functional modulation of the P100 VEP component; an aspect that may assist in distinguishing effects specific to schizophrenia. On applying electrical neuroimaging analyses to VEPs from chronic schizophrenia patients and healthy controls in response to variation in the parafoveal spatial extent of stimuli, it was found that healthy controls demonstrated robust modulation of the VEP strength and topography as a function of the spatial extent of stimuli during the P1 component. By contrast, no such modulations were evident at early latencies in the responses from patients with schizophrenia. Source estimations have localized these insufficiencies to the left precuneus and medial inferior parietal cortex. These findings provide insights on potential underlying low-level impairments in schizophrenia.

The study of morphological characteristics of the waveform generated in pattern-reversal VEPs is probably capable of elucidating the abnormalities in brain network dynamics relevant to the visual information-processing deficits in schizophrenia patients. In contrast to P50 and P300 event-related potentials (ERPs), however, the results of VEP studies in schizophrenia patients are more consistent, promising, and reliable too.

**CONCLUSION**

To sum up, this study clearly offers the contribution of qualitative, morphometric analyses of VEP as potential
endophenotype which has been revealed as unique wave patterns in evoked responses obtained from the patients. Atypical P100 waveform morphological abnormalities unveiled in cases of schizophrenia was the conspicuous finding of this study that was undiscovered till date. Therefore, our results show that VEP waveform has a promising potential for emerging as a new diagnostic electrophysiological biomarker in doting the entity of schizophrenia.

Limitation of the study

No study is not devoid of limitations if it is analyzed critically. This endophenotypic study despite being having the proband(s) of a positive history of psychosis in the first-degree relative; we failed to get their chromosomal linkage analyses which would have otherwise raised our understanding (if any) in providing the clues for further missing threads for etiopathogenesis of enigmatic disorders like schizophrenia.

Suggestions for future

In future, using multicentric, longitudinal, multivariate, long-term, prospective cohort analysis in a large sample group from both hospital and community based on database should be planned to reaffirm if endophenotype cumulative factors can have direct relationship on predicting age, course, and outcome of schizophrenia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Waddington JL, Corvin AP, Donohoe G, O’Tuathaigh CM, Mitchell KJ, Gill M, et al. Functional genomics and schizophrenia: Endophenotypes and mutant models. Psychiatr Clin North Am 2007;30:365-99.
2. Allen AJ, Griss ME, Folley BS, Hawkins KA, Pearlson GD. Endophenotypes in schizophrenia: A selective review. Schizophr Res 2009;109:24-37.
3. Pearlson GD, Folley BS. Endophenotypes, dimensions, risks: Is psychosis analogous to common inherited medical illnesses? Clin EEG Neurosci 2008;39:73-7.
4. Butler PD, Schechtman Z, Zemon V, Schwartz SG, Groenestijn VC, Gordon J, et al. Dysfunctional early-stage visual processing in schizophrenia. Am J Psychiatry 2001;158:1126-33.
5. Foxe JJ, Doniger GM, Javitt DC. Early visual processing deficits in schizophrenia: Impaired P1 generation revealed by high-density electrical mapping. Neuroreport 2001;12:3815-20.
6. Misra UK, Kalita J, editors. Visual Evoked Potential, Clinical Neurophysiology. New Delhi: Churchill Livingstone; 2011.
7. Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch Gen Psychiatry 2002;59:1011-20.
8. Foxe JJ, Murray MM, Javitt DC. Filling-in in schizophrenia: A high-density electrical mapping and source-analysis investigation of illusory contour processing. Cereb Cortex 2005;15:1914-27.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. USA: American Psychiatric Association; 1994.
10. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry 1982;39:789-94.
11. Guy W. Clinical Global Impressions (CGI) Scale. Modified From: Rush J, et al.: Psychiatric Measures. Washington, DC: APA; 2000.
12. Celesia GG, Bodis-Wollner I, Chatrian GE, Harding GF, Sokol S, Spekreijse H. Recommended standards for electroretinograms and visual evoked potentials. Report of an International Federation of Clinical Neurophysiology (IFCN) Committee. Electroencephalogr Clin Neurophysiol 1993;87:421-36.
13. Odom JV, Bach M, Brigg M, Holder GE, McCulloch DL, Terrone AP, et al. ISCEV standard for clinical visual evoked potentials (2009 update). Doc Opthalmol 2010;120:111-9.
14. American Clinical Neurophysiology Society. Guideline 5: Guidelines for standard electrode position nomenclature. J Clin Neurophysiol 2006;23:107-10.
15. Shagass C. Brain potential studies of psychopathology. Compr Psychiatry 1980;21:483-91.
16. Connolly JF, Gruzelier JH, Manchanda R, Hirsch SR. Visual evoked potentials in schizophrenia. Intensity effects and hemispheric asymmetry. Br J Psychiatry 1983;142:152-5.
17. Martínez A, Hillyard SA, Dias EC, Hagler DJ Jr., Butler PD, Guilfoyle DN, et al. Magnocellular pathway impairment in schizophrenia: Evidence from functional magnetic resonance imaging. J Neurosci 2008;28:7492-500.
18. Coleman MJ, Cestnick L, Krastoshevsky O, Krause V, Huang Z, Mendell NR, et al. Schizophrenia patients show deficits in shifts of attention to different levels of global-local stimuli: Evidence for magnocellular dysfunction. Schizophr Bull 2009;35:1108-16.
19. Kiss I, Fábián A, Benedek G, Kéri S. When doors of perception open: Visual contrast sensitivity in never-medicated, first-episode schizophrenia. J Abnorm Psychol 2010;119:586-93.
20. Cadenhead KS, Serper Y, Braff DL. Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. Biol Psychiatry 1998;43:132.
21. Brenner CA, Lysaker PH, Wilt MA, O’Donnell BF. Visual processing and neuropsychological function in schizophrenia and schizoaffective disorder. Psychiatry Res 2002;111:125-36.
22. Butler PD, DeSanti LA, Maddox J, Harkavy-Friedman JM, Amador XF, Goetz RR, et al. Visual backward-masking deficits in schizophrenia: Relationship to visual pathway function and symptomatology. Schizophr Res 2003;59:199-209.
23. Schwartz BD, Maron BA, Evans WJ, Winstead DK. High velocity transient visual processing deficits diminish ability of patients with schizophrenia to recognize objects. Neuropsychiatry Neuropsychol Behav Neurol 1999;12:170-7.
24. Knebel JF, Javitt DC, Murray MM. Impaired early visual response modulations to spatial information in chronic schizophrenia. Psychiatry Res 2011;193:168-76.