Visual evoked potentials – current concepts and future perspectives
Vizuelni evocirani potencijali – sadašnji koncepti i buduće perspektive

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Introduction

Sensory evoked potentials (EPs) represent changes in electrical activity of the nervous system, triggered by stimulating sensory receptors or peripheral nerves or either an external or internal impulse. Although every sensory modality can be investigated, sensory EPs mostly used in clinical practice are the following three types: visual evoked potentials (VEP), short latency brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) 1. The above EPs modalities are commonly used in combination, as complementary methods in clinical neurophysiology, so they are called multimodal EPs 2. EPs can also represent brain response as a result of cognitive activity (event related response – ERP) 1.

EPs are recorded in different clinical contexts. They may be used to assess peripheral sensory function, to evaluate the functional integrity of sensory projection pathways in the central nervous system (CNS), and cerebral cortical sensory areas 3.

EPs are recorded by using scalp electrodes for standard electroencephalography (EEG) 1. Due to low amplitudes of EPs, computer summation or averaging is necessary to isolate them from the background “noise” consisting of spontaneous electrical brain activity on which EPs are superimposed 1, 3, 4.

EPs were introduced in the early years of clinical EEG within 1930s. The first device for signal processing in the field of EPs using signal averaging method was introduced by Dawson in 1951, while widespread use was enabled in 1970s 4.

Non-invasiveness and harmlessness both represent the clear advantages of EPs, as well as their repeatability, objectivity and resistance to drugs and anaesthetics. On the other hand, the disadvantage of EPs is their low disease specificity 2, 5.

Visual evoked potentials – background

Visual evoked potentials (VEPs) are electrophysiological responses to stimulation by either patterned or un-patterned visual stimuli. Low rate stimulation, referring to pattern checks shifts (reversal of black and white) up to 4 Hz (mostly 1–2 Hz), produces “transient” VEPS. Stimulation at higher rates (≥ 10 Hz) produces responses occurring at the same frequency, lasting during the stimulation as “steady-state” VEPS. Responses evoked by patterned stimuli are “pattern” VEPS or PVEPs whereas those evoked by unpatterned stimuli are “flash” VEPS or FVEPs 6.

In healthy individuals, low rate stimulations PVEP have a tendency to produce typical “V” shaped wave (Figure 1). This wave consists of 3 components (often named “picks”), marked as N1 or N75 (referring to mean latency in ms, at which the response will occur after stimulation), P1 or P100 (representing the most important and stable component of the response) and N2 or N145. N and P represent negative and positive deflections in the response wave 1, 2.
Fig. 1 – Normal full-field pattern visual evoked potentials (PVEP) finding in a female subject aged 51.
Recording montages the Queen Square System of electrode placement (MO: midoccipital, in midline 5 cm above inion; LO₁, RO₁, LO₂ and RO₂, lateral occipital, 2.5 and 5 cm to left and right of MO, respectively). Each trace represents different electrode placement with the same stimulation pattern (monocular stimulation). Two responses were recorded to ensure reproducibility of major response components.

The clinical interpretation of PVEP is mostly based upon the latency of P100 and to a much lesser extent to its P100 amplitude. In clinical analysis of multifocal visual evoked potentials (mfVEP), the magnitude (amplitude) of responses and inter-ocular differences are often more relevant finding than latency delay.

FVEPs are less sensitive than PVEPs. Therefore, their use in clinical testing is limited to subjects who cannot visually resolve a pattern stimulus due to severe refractive errors or the opacity of ocular media and to those who are too young or not cooperative enough to be able to fixate reliably on a pattern stimulus. After flash stimulation, FVEPs typically consist of up to six peaks in the first 250 ms, labelled sequentially from I to VI. The latency of the individual peaks may show considerable variations among the patients. For this reason, their clinical relevance is reduced with the absence of a demonstrable response being the only definite significant abnormality. This test tends to offer more qualitative than quantitative information.

Neuronal generators of VEP are located in the peristriate and striate occipital cortex.

Recording techniques and technical aspects

Standard EEG electrodes are commonly used for VEP recording. Electrode placement can be performed by using two internationally approved systems: Queen Square System of placement (occipital leads are labelled LO, MO, and RO) and the International 10–20 System of placement (leads O₁, O₂, and O2). Type of the stimulus, stimulation characteristics and testing protocols depend on the type of VEP being tested.

Pattern VEP

Depending on the part of visual field tested, full visual field pattern VEP, partial visual field pattern VEP and multifocal VEP can be defined.

Full visual field pattern VEP can be used for testing lesions of visual system anterior to optic chiasm. This technique is more sensitive for the lesions affecting the central 8–10 degrees of visual field.

Lesions affecting half or a part of visual field but sparing the central part are better assessed with partial visual field pattern VEP. This method can detect partial prechiasmal, postchiasmal or chiasmal lesions at the cost of being more time consuming.

Computer screen is most commonly used for the presentation of patterns. There are different pattern types, checkerboard patterns being the most extensively studied and used in clinical testing; bar and sinusoidal grating stimuli also produce clinically useful response. Check size is measured using the visual angle (distance from subject eyes to screen should not be less than 70 cm). A fixation point is used as an object to focus the subject’s attention. Pattern check reversal rate is less than 4 Hz, usually 1–2 Hz.
Multifocal VEP

The multifocal VEP (mfVEP) was introduced in 1994 by Baseler et al. 11. It is a mathematically improved technique for the extraction of hundreds of VEPs, with the help of only 4 occipital scalp electrodes 4. This technique uses a multifocal circular dartboard array that usually has two binary sequences, each mathematically independent, determining two stimulus states, e.g. two contrast polarities of the pattern 12. The response is evoked by the change between the two states of the pattern and the stimulation procedure requires 7 to 8 minutes duration for one monocular recording 11–13. The mfVEP enables separate stimulation of 60 different sectors of full visual field, involving both central and peripheral locations 4, 11. In this way, standard mfVEP provides a cleaner separation of focal response contributions and is distinct from full-field pattern VEP, which is mostly dominated by responses from macular area 14. Thus, the main advantage of mfVEP is to demonstrate the topography of visual fields damage with a greater precision than other VEP methods and thus detect localized damage in the form of small scotomata or peripheral visual fields defects 15. The main indications for mfVEP in ophthalmology include: ruling out functional causes, evaluating patients with unreliable or questionable subjective perimetry tests, and following disease progression 15.

Flash VEP

Unpatterned visual stimuli consist of brief flashes of light with no observable pattern or contour. Stimulation may be presented by a photostimulation lamp (stroboscope), a matrix of light emitting diodes (LEDs, within board or goggles), or a Ganzfeld stimulator. The rate should be approximately 1/s or slower 6.

Influence of subject/patient factors

Age

By the age of 6 to 12 months FVEPs show significant maturational changes; after this period latencies decrease, waveforms merge and FVEPs reach adult morphology 7. Defining the physiological age in infants is rather difficult, since the nervous system neither matures at the constant rate nor follows the precise defined time frame. For this reason it is rather hard to define the precise normative data for early infancy. During the first 4 to 5 years of life, morphology rather hard to define the precise normative data for an early development. By the age of 5, PVEP resembles that of the adults 7. Studies have revealed that PVEP P100 latencies tend to increase after the 6th decade, but this increment depends on the check size used in the study. Data for P100 amplitude changes after the 6th decade are scarce 7.

Gender

Females usually have shorter P100 latencies than males 7.

Visual acuity

Generally, visual acuity should be determined before testing VEP 1, 6. PVEP P100 amplitude is more sensitive to visual acuity changes than P100 latency 7.

Reproducibility

Unlike FVEP, PVEP is very sensitive to the state of the subject’s arousal, concentration and attention 1, 6, 7.

Clinical application

Multiple sclerosis and optic neuritis

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the CNS, affecting myelinated axons 17. Optic neuritis (retrobulbar neuritis) is one of the common disease manifestations 18. PVEP shows great sensitivity in patients with optic neuritis, having prolonged latencies of P100 wave component in almost all affected subjects (Figure 2). Prolonged P100 latencies were also discovered in more than half subjects having only clinical spinal cord involvement 19, 20. Compared to SSEP and BAEP, VEPs are the most efficient in detecting the silent lesions in MS 21. Earlier diagnostic criteria for MS included VEP tests, but due to magnetic resonance imaging (MR) superiority VEPs were later excluded, but are still frequently used 22, 23. However, new MS diagnostic criteria revision (for 2016) proposes to reintroduce optic nerve lesions as a part of criteria for dissemination in space, suggesting VEP as a useful diagnostic method 24.

Prolonged latencies and reduced amplitudes of VEP can also be found in optic neuritis of different etiology, such as in neuromyelitis optica (NMO). Delayed P100 latencies in the eyes without prior optic neuritis suggest subclinical affection 25. The mfVEP has the advantage over both the PVEP and perimetry in the follow-up of patients with optic neuritis. Patients converting to clinically definite MS during one year follow-up demonstrate the largest amplitude reduction and the longest latency delay of the optic neuritis eye 26.

Two studies comparing the sensitivity of PVEP and mfVEP in the assessment of patients with optic neuritis caused by multiple sclerosis in 26 14 and 19 patients 27, respectively. Both studies suggested that the mfVEP have superior performance but in the study that tested the reproducibility, PVEP had also very good sensitivity 27. Therefore, it was recommended that PVEP, as a more readily available and currently a shorter test, should be used to screen patients for optic neuritis/MS while mfVEP testing has to be added when the PVEP test is negative and the damage is local 27.

Effects of treatment on optic neuritis have been tested with PVEP in many studies 28–32. Corticosteroids as common medication used for optic neuritis of different etiology can influence VEP latencies.
Fig. 2 – Pattern visual evoked potentials (PVEP) finding in male patient aged 27, with optic neuritis as the initial manifestation of multiple sclerosis. Otherwise, the conventions and arrangements were the same as those shown in Figure 1.

The oral methylprednisolone can influence faster improvement of VEP latencies in initial period after optic neuritis onset (up to 4 weeks). In later follow-up (12 weeks and 1 year after onset) there were no benefits of steroid therapy 28.

VEPs, combined with other EPs, proved useful in evaluating the efficacy of drugs designed to impede the course of MS, such as interferon 1b 29, natalizumab 30, and fingolimod 31. Compared to the pre-treatment delays, latency of PVEPs in these studies improved after the treatment with natalizumab, and VEP sum score was stable in 95% of patients and 5% worsened 1 year after the start of fingolimod treatment 31. The improvement is most likely explained by the occurrence of remyelination in treated patients (Figure 2) 32.

Migraine

Migraine is considered to be a neurovascular disorder 33. It is also listed as the sixth highest specific cause of disability in adults 34. Worldwide prevalence of migraine in children and adolescents was estimated to be between 7% and 11% 35. Earlier studies have revealed central stimulus processing defects in people with migraine (with and without aura), manifesting as an interictal lack of habituation for acoustic, somatosensory, nociceptive and visual stimuli 36. However, the latest research casts a doubt on this finding concerning the lack of habituation measured by PVEP in migraine, considering it as a researcher’s bias 37. Diagnosis of migraine remains predominantly the clinical one, but VEP could be useful as a secondary diagnostic tool. PVEP amplitudes between N1 - P1 and P1 - N2 are significantly larger in children with migraine headaches (Figure 3) 38. Migraine subtypes in teenage population may also be differentiated on the basis of N2 wave latency prolongation 39.

Neuropathy of optic nerve

Retinal and optic nerve neuropathies of different origin can also influence VEP testing results, affecting both wave latencies and amplitudes 7, 16.

Leber’s hereditary optic neuropathy

Leber’s hereditary optic neuropathy (LHON) is the most common mitochondrial disorder. It is characterized by acute or subacute painless loss of central vision, usually in young adult males 40–42. PVEP findings are distorted to a great extent, with increased P100 latencies as well as decreased amplitudes. As the disease progresses and the vision fades, only FVEP can be applied showing further prolongation of latencies and the decline of response wave amplitudes (Figure 4) 2, 7, 40. Multifocal VEP identifies abnormal neural conduction along the visual pathways in LHON, pointing out the involvement of axons driving responses from the central retina 41.
Fig. 3 – Pattern visual evoked potentials (PVEP) finding in a female subject aged 11, with migraine headache showing normal latencies and larger amplitudes of evoked response. Recording montage is the International 10-20 System placement (Oz-Fz). Note that each trace represents the same electrode placement, but different mode of stimulation (mono- vs. binocular stimulation).

Glaucoma

Glaucomas are a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells, leading to a characteristic appearance of the optic disc as well as the visual loss 44. Multifocal VEP is an effective method for detecting visual field loss in glaucoma and represent additional test to subjective automated static perimetry 45. A comparative study of 50 patients with glaucoma proved that misses and false-positive results occurred with both the automated static perimetry and mfVEP 46. Therefore, combined use of the two tests may increase the yield of true-positive results indicating glaucomatous damage of ganglion cells.

Ischemic optic neuropathy

Apart from optic neuritis, the most common optic nerve pathology is ischemic optic neuropathy. VEP amplitude decreases significantly in ischemic optic neuropathies, whereas latency delay is more significant in the patients with optic neuritis 47.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri) is a disorder followed by an increased intracranial pressure with no clinical, laboratory or radiological evidence of an intracranial space-occupying lesion.

Prolongation of VEP latencies is observed prior to clinical visual impairment 48. Repeated VEP showing prolonged latencies in patients with relatively rapid progression of substantial visual field defects may have some prognostic value indicating a need for decompressive neurosurgical treatment to prevent optic atrophy and vision loss 49.

Compressive lesions of the anterior visual pathways

Papilledema arising from the lesions which don’t involve optic nerve will not produce P100 alterations unless they are severe. On the other hand, extrinsic and intrinsic tumours compressing anterior visual pathways tend to decrease amplitude and to increase latency of PVEP waveforms 7. During surgical removal of the tumours which compress anterior visual pathways (e.g. pituitary region tumours), VEP monitoring can be useful. Changes in the latency of P100 and/or changes in the amplitudes of N1-P1 can indicate iatrogenic injury of the visual pathways during an operative procedure 16.

Epilepsy and anti-epileptic drugs (AED)

Epilepsy is very common in childhood. It is estimated that 0.5%–1.0% of all children suffer from epilepsy. The abnormalities of VEPs in epilepsy may be related to the disease itself (seizure types and aetiology) or to the effects of AEDs on the GABA-ergic neurotransmitter system and/or other
CNS functions. Children treated with sodium valproate and carbamazepine have prolonged latencies and reduced amplitudes of P100 wave component of PVEP 16, 50. The use of VEP and electroretinography (ERG) in children taking vigabatrin may detect visual field constrictions in the early treatment phase and its persistence long time after the drug withdrawal 10, 51.

Conversion disorder

VEPs are commonly used in both adult and paediatric population in order to objectively predict visual acuity in the patients with functional visual loss 45.

VEP in paediatrics

In addition to the aforesaid entities which are also encountered in the paediatric population, VEPs are used in assessment of many disorders specific for childhood: neonatal asphyxia, neurofibromatosis type I (NF1), leukodystrophies, neuronal ceroid lipofuscinosis, coma, hydrocephalus, developmental defects and delay, detection of amblyopia, numerous metabolic and toxic disorders 2, 7, 16, 52.

Combination of VEPs and other neurophysiological methods proved useful in the prognostic assessment of comatose patients and in neurometabolic disorders affecting various levels of CNS. Simultaneous assessment of ERG, VEPs and EEG is useful in the early detection of visual dysfunctions in neuronal ceroid lipofuscinosis (NCL) – the most common neurodegenerative disorder occurring in children. The main use of ERG is in the early diagnosis of juvenile form of NCL 53.

EPs vs. MRI

In comparison with MRI, VEP was far more useful in detecting optic nerve lesions in MS 54 or equally sensitive in detecting subclinical lesions 55. Nowadays, combined use of gadolinium enhanced MRI and PVEP is very suitable to detect whole brain demyelination and axonal degeneration in MS 56. SSEP was less sensitive than MRI in detecting spinal cord lesions. BAEP was able to localize lesions along the auditory pathways at a rate which was almost similar to that of MRI. EPs can be used when MRI is negative or cannot be performed. They can also be performed in treatment response evaluation, long-term prognosis and nonspecific changes on MRI 57.

New tendencies in the VEP application

Combined use of MRI 3Tesla scanner and mfVEP technique in the follow-up of 30 patients with acute optic neuritis demonstrated that lesion length and mfVEP latency and were strongly correlated 58. Future studies of this type may give new insight into the structure-function relationships during optic nerve demyelination and remyelination processes, and axonal degeneration.

Some new technical systems apply VEP in Brain–computer interface (BCI) paradigms to help people with motion disability. For example, steady-state visual evoked potentials (SSVEPs) are frequently used as a control signals as they can offer the user to select among several commands, suitable to drive a BCI based menus. Each option/command in such menu is associated with one of the stimuli presented to the user, differing from each other only by their repetition frequency. All stimuli are simultaneously presented and the user can choose one by focusing the visual attention to it, eliciting the corresponding SSVEP response in the EEG measured over the primary visual cortex. The SSVEP amplitude is greater for the attended stimuli than for the unattended ones, even when the stimuli are presented in the same region of visual field. These SSVEP based BCIs are developed for communication and/or control of electrical devices for different purposes (for example, a wheelchair) 59, 60. Recent findings show the potential of BCI technology to be used either for long term substitution or further enhancement of the impaired motor function, defining two approaches in BCI applications for neurorehabilitation: assistive and restorative, respectively (for example, SSVEP-based selection of the appropriate electrical stimulation pattern for intended type of trained grasp) 61.

Late wave component of VEP, named P300 (P300 event related potential) is regarded as a neurophysiological indicator of cognitive processing of a stimulus. This response can also be induced by using the auditory or somatosensory stimulus, and it is usually detected between 300 and 600 ms after stimulus presentation. It is widely used in the field of cognitive neuroscience 16, 62.

Conclusion

Visual evoked potentials are very important additional clinical method in diagnosing of many diseases in neurology, as well as their follow-up. Owing to their non-invasiveness, simplicity of implementation, repeatability, low cost and reliability. VEPs are widely used in many research areas of neuroscience. A special advantage of VEPs is their application in low compliance subjects, especially young children and comatose patients. With the advancement of computed technology and neurophysiology, the possibilities of VEP applications have become reality.

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