Review Article

"EVOKED POTENTIAL STUDIES: A DIAGNOSTIC TOOL FOR NEUROLOGICAL DISORDERS"

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Abstract: Clinical neurophysiology has come a long way in the last 50 years and is being used increasingly in the diagnosis of various neurological disorders. Evoked potentials are the electrical signals generated by the nervous system in response to sensory stimuli. Evoked potentials studies measure electrical activity in the brain in response to stimulation of sight, sound, or touch. Stimuli delivered to the brain through each of these senses evoke minute electrical signals. These signals travel along the nerves and through the spinal cord to specific regions of the brain and are picked up by electrodes, amplified, and displayed for a doctor to interpret. There are three kinds of evoked potentials in widespread clinical use: Auditory evoked potentials, usually recorded from the scalp but originating at brainstem level; Visual evoked potentials and Sensory evoked potentials which are elicited by electrical stimulation of peripheral nerves. Although evoked potential studies have been extensively used for diagnosis of various neurological diseases, these studies have some limitations and are not highly standardized which requires attention from the researchers.

Key words: Auditory evoked potentials, evoked potential, neurophysiology, sensory evoked potentials, visual evoked potentials

Introduction: Clinical neurophysiology has come a long way in the last 50 years and is being used increasingly in the diagnosis of various neurological disorders. The electro diagnostic techniques involve recording, displaying, measurement and interpretation of action potentials arising from CNS [Evoked potential], peripheral nerves [Nerve conduction studies] and muscles [Electromyography].

Evoked potentials are electrical activities that occur in the neural pathways and structures as a response to various external stimulations induced by light, sound, electric, smell, or taste. An evoked potential or evoked response is an electrical potential recorded from the nervous system of a human or other animal following presentation of a stimulus, as distinct from spontaneous potentials as detected by electroencephalography (EEG), electromyography (EMG), or other electrophysiological recording method[1]. Signals can be recorded from cerebral cortex, brain stem, spinal cord and

peripheral nerves. Usually the term "evoked potential" is reserved for responses involving either recording from, or stimulation of, central nervous system structures. Thus evoked compound motor action potentials (CMAP) or sensory nerve action potentials (SNAP) as used in nerve conduction studies (NCS) are generally not thought of as evoked potentials, though they do meet the above definition. Evoked potentials are polyphasic waves that oftenly present with an amplitude between 0.1- 20 μA which are formed within 2-500 ms. The source of these activities is probably the summation of the action potentials generated by the afferent tracts and the electrical fields or activities of the synaptic discharges or post-synaptic potentials on those tracts[2]. Understanding evoked potentials bears importance in terms of controlling the entire pathway from stimulation point to the cortical areas, in other words, to the primary cortex. Evoked potential amplitudes tend to be low, ranging from less than a microvolt to several microvolts, compared to tens of microvolts for EEG, millivolts for EMG, and often close to a volt for ECG[3].

Evoked potentials studies measure electrical activity in the brain in response to stimulation of sight, sound, or touch. Stimuli delivered to the brain through each of these senses evoke minute electrical signals. These signals travel along the nerves and through the spinal cord to specific regions of the brain and are picked up by electrodes, amplified, and displayed for a doctor to interpret. By examining evoked potentials, we can find answers to many questions such as: Does the response against the stimulus reach intended destinations on time? Does the response show any loss of intensity? If there is a problem in the neural pathways, what is its exact location? Most of the responses elicited due to external stimulation are not observed very clearly because the tiny little responses that we call “evoked potentials” can not be seen in EEG signals which may have amplitudes reaching 100 μV. Moreover, there are non-neural activities that suppress those signals such as EEG: ECG (electrocardiogram), EMG (electromyogram), and other biologic signals. In addition, when the noises of the electronic devices and the environment are also considered, the difficulty of isolating evoked potentials can be figured out more easily. Currently, there are two methods used for eliminating those external interferences and both of them should be used in combination: “filtration” and “averaging”.

Today, novelties in the electronics and computerized devices give capability of recording evoked potential studies in any kind of environment and have made routine use of evoked potential recording systems in clinics.

Different types of Evoked Potential Studies

There are three kinds of evoked potential studies in widespread clinical use[4,5].

- **Somatosensory evoked response (SSER) test.** This test can detect problems with the spinal cord as well as numbness and weakness of the extremities. For this test,

electrodes are attached to the wrist, the back of the knee, or other locations. A mild electrical stimulus is applied through the electrodes. Electrodes on the scalp then determine the amount of time it takes for the current to travel along the nerve to the brain.

- **Auditory evoked response (AER) test.** This test can diagnose hearing ability and can indicate the presence of brain stem tumors and multiple sclerosis. Electrodes are placed on the scalp and earlobes. Auditory stimuli, such as clicking noises and tones, are delivered to one ear.

- **Visual evoked response (VER) test.** This test can diagnose problems with the optic nerves that affect sight. Electrodes are placed along the scalp. The patient is asked to watch a checkerboard pattern flash for several minutes on a screen and the electrical responses in the brain are recorded.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) consist of a series of waves that reflect sequential activation of neural structures along the somatosensory pathways. While SSEPs can be elicited by mechanical stimulation, clinical studies use electrical stimulation of peripheral nerves, which gives larger and more robust responses. They are used for evaluating the synaptic terminals extending towards cortex, by stimulating the peripheral sensory pathways via delivery of an electric current. Sensory evoked potentials (SEP), are recorded from the central nervous system following stimulation of sense organs (for example, visual evoked potentials elicited by a flashing light or changing pattern on a monitor; auditory evoked potentials by a click or tone stimulus presented through earphones) or by tactile or somatosensory evoked potential (SSEP) elicited by tactile or electrical stimulation of a sensory or mixed nerve in the periphery. They have been widely used in clinical diagnostic medicine since the 1970s, and also in intra operative neurophysiology monitoring (IONM), also known as surgical neurophysiology[6,7]. The stimulation sites typically used for clinical diagnostic SEP studies are the median nerve at the wrist, the common peroneal nerve at the knee, and the posterior tibial nerve at the ankle. Recordings of SEPs to stimulation of the ulnar nerves at the wrists are useful for intra operative monitoring. We place the active electrode over the contralateral parietal region and reference electrode over the back of the hand in order to stimulate the median nerve via wrist, and acquire an evoked potential signal. SSEPs are used for evaluating the synaptic terminals extending towards cortex, by stimulating the peripheral sensory pathways via delivery of an electric current. In short, it is aimed to acquire a response that can be recorded electrically in the central nervous system against a stimulation applied on vibration, position, or epicritic tactile senses.

The SEP components generated in the brainstem and in the cerebral cortex are mediated entirely by the dorsal columns (posterior columns) of the spinal cord, the fasciculus cuneatus for upper limb SEPs and the fasciculus gracilis for lower limb SEPs. Lesion of the dorsal columns of the spinal cord rostral to the root levels where the afferent somatosensory activity enters the spinal cord abolishes the SEPs generated in the brain. SEPs can persist following lesions of the anterolateral spinal cord, however. SEPs are abnormal in diseases of the dorsal columns in which joint position sense and proprioception are impaired[8].

SEPs are used for clinical diagnosis in patients with neurologic diseases, to evaluate patients with sensory symptoms that might be psychogenic, for prognostication in comatose patients, and for intra operative monitoring during surgeries that place parts of the somatosensory pathways at risk. Abnormal SEPs can result from dysfunction at the level of the peripheral nerve, plexus, spinal root, spinal cord, brain stem, thalamocortical projections, or primary somatosensory cortex. SEPs are valuable as a diagnostic and as a prognostic tool in patients who are comatose as a result of anoxic brain injury. Sensory evoked potentials may also be used during surgeries. This technique is known as transcranial electrical motor potential (TcMEP) monitoring. Their role in the operating room has expanded and interest remains high in SEPs as research tools for unraveling of fundamental aspects of sensory physiology[9,10,11].

Possible sources of the waves

Median nerve stimulation

Brachial plexus activity (action potential).

- Spinal medulla dorsal root activity (or dorsal root + cuneate fascicle activity).
- Dorsal funiculus activity (post-synaptic lemniscal medial tract activity).
- Thalamus posterolateral nucleus activity?
- Parietal cortex activity.

Tibialis posterior stimulation

Grey matter activity.

- Lemniscal tract and nucleus activity (lemniscal nucleus and prethalamic
- Spinal roots and spinal column activity.
- Nucleus gracilis activity.
- Parietal cortex activity.

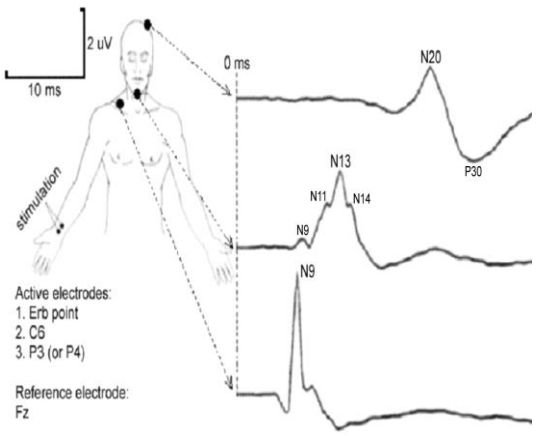

Fig 1: Peripheral, subcortical and cortical somatosensory evoked potentials (SSEP) obtained from three different recording sites.

In clinical practice, active electrodes are P3–P4 or C3–C4 in the upper extremity test and C1-C2 or only Cz in the lower extremity test; whereas reference electrode is Fz or A1–A2. Again in clinical practice, the most commonly used upper extremity nerves are median and ulnar (at wrist level) nerves, whereas most commonly employed lower extremity nerves are tibial (at ankle level) and peroneal nerves (at knee level). Spike potential observed in the record obtained from Erb point is named as N9 due to the fact that it is a negative wave occurring nearly 9 ms after the stimulus. Spike potential observed in the record obtained from cervical region is named as N13 due to the fact that it is a negative wave occurring nearly 13 ms after the stimulus. The spur on the ascending arm of the N13 is N11 and the spur on the descending arm of the N13 is N14. Moreover, N9 wave can be observed here, as a negative potential just before N11 (far-field record). The first wave observed in the record obtained from the parietal region is N20, which is a negative wave that occurs 20 ms after the stimulus. Approximately 10 ms after this, a positive wave is seen which is named as P30. Moreover, N9 and N13 waves can also be observed as low-amplitude waves (far-field records), but as having a positive character this time (due to the location relative to the reference electrode).

Indications

SSEP test is applied for checking the peripheral (thick ones) sensory fibers, spinal cord, and somesthetic cortex. It is useful in evaluating and supporting the already established diagnosis concerning the below mentioned cases.

1. Plexus injuries
2. Thoracic outlet syndrome
3. Carpal tunnel syndrome
4. Tarsal tunnel syndrome
5. Evaluation of the peripheral nervous system
6. Cervical and back pain
7. Musculoskeletal injuries
8. Brachial neuritis
9. Spinal cord injuries
10. Nerve root irritations and traumas
11. Neuromuscular diseases
12. Neuritis
13. Radiculitis
14. Motor/sensory deficits
15. Vertebral subluxation complex
16. Systemic neuropathies
17. Lower back pain
18. Plexus injuries and irritations

Other indications

1. Evoked potential tests are indispensable tools for diagnosis and following of multiple sclerosis, a demyelinating disease.
2. It is applied for monitoring purposes in operations involving spinal cord and vertebra
3. Can be used in the early diagnosis of sensory problems in newborns.
4. Myelinization can be monitored.

Auditory Evoked Potential

Auditory evoked potentials, usually recorded from the scalp but originating at brainstem level. Auditory evoked potential

can be used to trace the signal generated by a sound through the ascending auditory pathway. The evoked potential is generated in the cochlea, goes through the cochlear nerve, through the cochlear nucleus, superior olivary complex, lateral lemniscus, to the inferior colliculus in the midbrain, on to the medial geniculate body, and finally to the cortex. Auditory evoked potentials (AEPs) are a subclass of event-related potentials (ERP)s. ERPs are brain responses that are time-locked to some "event", such as a sensory stimulus, a mental event (such as recognition of a target stimulus), or the omission of a stimulus. For AEPs, the "event" is a sound. AEPs (and ERPs) are very small electrical voltage potentials originating from the brain recorded from the scalp in response to an auditory stimulus, such as different tones, speech sounds, etc. AEP test is used for checking the auditory canals up to the primary cortex ie; Heschl gyrus neighboring the temporal lobe; by applying auditory stimulus above hearing threshold to the external auditory canal. The auditory stimulus is applied through a classic audiometric earphone by delivering a square wave of 100 - 200μs duration for 10 times a second. This is a "click" sound. Until finishing one ear, the other ear is subjected to white noise which is a "hissing" sound containing all frequencies at equal intensity. The intensity of the sound applied for stimulus is generally above hearing threshold and range between 65-70 dB; in patients with a hearing loss, this value should be increased. Long and Allen reported the abnormal brainstem auditory evoked potentials (BAEP) in an alcoholic woman who recovered from Ondine's curse. These investigators hypothesized that their patient's brainstem was poisoned, but not destroyed, by her chronic alcoholism[12].

Indications

1. Hearing loss, hearing imbalance
2. Balance disorders
3. Tinnitus
4. Assessment of type and level of hearing loss in children below 5 years of age
5. Metabolic, demyelinating, degenerative diseases and tumors of the brainstem
6. Ear canal lesions outside the brainstem
7. Monitorization during operations concerning brainstem
8. Control and follow-up after operations concerning brainstem
9. Headaches
10. Head traumas
11. Hyperflexion/hyperextension
12. Comas (with EEG).

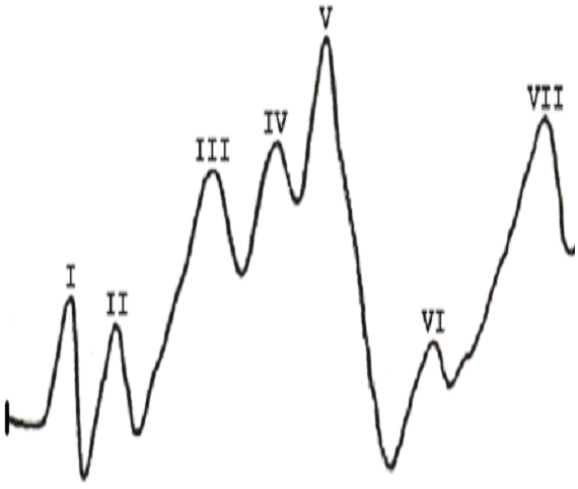

Fig 2: Waveforms seen in AEP recording.

Visual Evoked Potential

In 1934, Adrian and Matthew noticed potential changes of the occipital EEG can be observed under stimulation of light. Ciganek developed the first nomenclature for occipital EEG components in 1961. During that same year, Hirsch and colleagues recorded a visual evoked potential (VEP) on the occipital lobe (externally and internally), and they discovered amplitudes recorded along the calcarine fissure were the largest. Broadly speaking visual evoked potentials are obtained from the optic tract by recording the evoked potentials generated by retinal stimulation[13]. The sources of the stimulus are as follows:

1. Stroboscopic flash light with regular flashing intervals: Applied on babies and uncooperative patients.

2. Flashing LED: Applied as an intraoperative stimulus source. However, it requires use of specially designed lenses.

3. Alternating checkerboard pattern stimulation: This is the stimulation method used most commonly and it is a more sensitive and stable technique. VEP test performed by applying this stimulation is also called as PSVEP (Pattern-Shift Visual Evoked Potential).

The diffuse light flash stimulus is rarely used due to the high variability within and across subjects. However, it is beneficial to use this type of stimulus when testing infants or individuals with poor visual acuity[14]. The checkerboard and grating patterns use light and dark squares and stripes, respectively. These squares and stripes are equal in size and are presented to one at a time via a television or computer screen[15,16,17]. In 1965, Spehlmann used a checkerboard stimulation to describe human VEPs. An attempt to localize structures in the primary visual pathway was completed by Szikla and colleagues. Halliday AM and colleagues completed the first clinical investigations using VEP by recording delayed VEPs in a patient with retro bulbar neuritis[18]. A wide variety of extensive research to improve procedures and theories has been conducted from the 1970s to today.

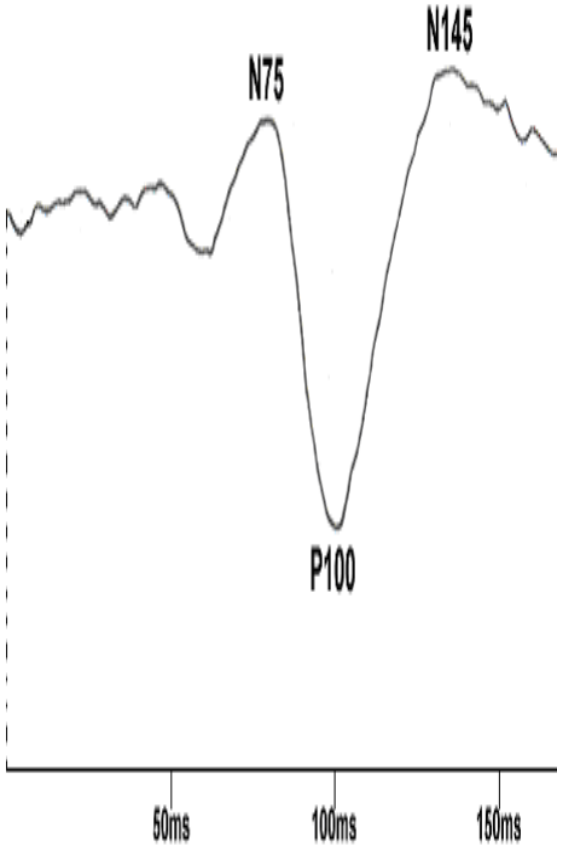

Fig. 3: Components of the VEP recording.

As seen in Figure 22, since N75 and N145 show high variability during 3-component VEP recording, only P100 wave, which is

the essential component, is evaluated (VEP test is also called as “P100 test”). Bilateral comparison bears great importance in the evaluation. However, first, latency and amplitude values of the P100 wave should be identified.

Indications

1. Optic nerve damage
2. Optic neuritis
3. Headache
4. Head trauma
5. Brain aneurysm
6. Brain tumors
7. Blurred vision
8 Intra operative monitoring

Procedure Overview of Evoked Potential Studies

Risks of Evoked Potential Studies

The evoked potential studies are considered safe procedures. The tests cause little discomfort. The electrodes only record activity and do not produce any sensation.
There may be risks depending on your specific medical condition. Be sure to discuss any concerns with your doctor prior to the procedure.
Certain factors or conditions may interfere with the results of the test. These include, but are not limited to, the following:

- Severe nearsightedness
- Presence of earwax or inflammation of the middle ear
- Severe hearing impairment
- Muscle spasms in the head or neck

The test will generally proceed as follows:

Somatosensory evoked response (SSER)

- Electrodes will be placed on the scalp and at one or more locations on your body, such as the wrist, back of the knee, or the lower back.
- Minute, painless electrical shocks will be delivered through the electrodes placed on the body.
- For each of the tests, the electrical activity detected by the electrodes on the scalp will be fed into a recorder, which amplifies the signal and charts it so that your doctor can interpret the results.

Auditory evoked response (AER)

- You will sit in a soundproof room and be asked to wear earphones.
- Electrodes will be placed on top of your head and on one earlobe and then the other.
- A clicking sound or another auditory stimulus will be delivered through the earphones to the ear being tested while a "masking" noise will be delivered to the other ear to shield it from the stimulus.

Visual evoked response (VER)

- You will be seated about three feet away from a screen.
- Electrodes will be placed on your scalp over the areas of the brain

responsible for interpreting visual stimuli.

- You will be asked to focus your gaze on the center of the screen.
- You will then be asked to close one eye at a time while the screen displays a checkerboard pattern. The squares of the checkerboard reverse color once or twice a second.

Conclusion

Which conditions indicate Evoked Potential Tests?

1. Persistence of symptoms despite decided and ongoing treatment
2. Presence of subjective complaints without supportive objective findings
3. Negative X-ray, CT, MRI, or EMG results despite existing complaints
4. Presence of radicular complaints
5. Existing nerve irritation or damage requiring definition
6. Need for advanced diagnosis/treatment
7. Cases requiring confirmation of presence of pain

Significance of Evoked Potential Studies

Evoked potential studies may be used to assess hearing or sight, especially in infants and children, to diagnose disorders of the optic nerve, and to detect tumors or other problems affecting the brain and spinal cord. The tests may also be performed to assess brain function during coma. Although modern imaging methods other than PET can depict pathological localizations in detail, they cannot provide data on functional/physiological structures (ie. metabolic cerebral diseases). Thus, evoked potential tests compensate for this shortcoming. Subcortical components of auditory and somatosensory evoked potentials are not influenced by general anesthesia, sleep, and states of consciousness. These tests are non-invasive in character and give objective measurements. They are also significantly of low cost compared with the modern imaging modalities.

Disadvantages of Evoked Potential Studies

A disadvantage of these tests is that they detect abnormalities in sensory function, but usually do not produce a specific diagnosis about what is causing the abnormality. However, the evoked potentials test can confirm sometimes a diagnosis of multiple sclerosis. There may be other reasons for your doctor to recommend an evoked potentials test. There is still no standard in technical regard. Even the fundamental terminological standards have not been completed yet, let alone being a “gold standard”. However, currently; SSEP, AEP, and VEP techniques have been almost standardized. Tests are long and tedious for patients and the risk of technical error, therefore the likelihood of repeating the test, is high. While the characteristics of the acquired recordings are mostly known, their sources and mechanisms have not yet been completely or clearly understood; due to the complexity of the brain anatomy and nonlinear nature of the brain physiology. Although evoked potential studies have been extensively used for diagnosis of various

neurological diseases, these studies have some limitations and are not highly standardized which requires attention from the researchers.

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