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Neuronal Degeneration in the visual system: analysis, diagnosis, prognosis.

Department of Neuroscience
Submitted in partial fulfillment of the requirements for the degree of Master of Medicine, M.D.

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SUMMARY

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Research Title: Neuronal degeneration in the visual system: analysis, diagnosis, and prognosis.

Aim: To analyze theoretically neuronal degeneration process in the visual system and to study VEPs in diseases caused by optic nerve degeneration.

Objectives of the study: 1. To analyze demyelination process in an optic nerve. 2. To review the literature about related diseases in the visual system. 3. To review the literature about related medical diagnostics techniques. 4. To simulate neuronal degeneration principal in an optic nerve. 5. To study visual evoked potentials (VEPs) due to different visual system disorders.

Methodology: Neuron software was used to create simulations that represent a simple optic nerve model. Apart from computational modeling, VEPs were obtained from previously known subjects with optic neuritis and multiple sclerosis and the data was compared with cases of normal VEPs.

Results: A simple structure of the optic nerve with a soma, axon with myelinated node and multiple nodes of Ranvier was built using the cell builder of the neuron software. Biophysical properties were chosen similar from literature to construct an action potential of a normal myelinated optic nerve; subsequently, different stimulation types were tested to demonstrate the effect of changes in biophysical properties. The second part of the result demonstrates tables of visually evoked potentials gathered from 27 normal cases, 26 optic neuritis cases and 7 multiple sclerosis cases. The data demonstrates the differences in latencies and amplitudes between normal VEPs and VEPs from optic neuritis and multiple sclerosis cases.

Conclusion: Simple optic nerve model was build using NEURON software and using different simulation types biophysical properties changes of the cell membrane and the effect on the cell propagation is demonstrated. This leaves room for further computational studies like building a more realistic and complex Optic nerve model. VEPs waveforms and their mean values of latencies and amplitudes in optic neuritis and multiple sclerosis show optic nerve demyelination and disturbances in conductance compared to normal VEP waveforms. This shows the vital use of VEPs in research of diseases caused by optic nerve degeneration such as multiple sclerosis. Hypothetically it is possible to relate the computational demyelination of the optic nerve used in NEURON to more realistic experimental VEPs waveforms.

Recommendations: Further skills are needed in operating and programming the NEURON software.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to Dr. Asta Kybartaite-Ziliene for her patience, guidance, and encouragement throughout my final year project. Her efforts and excellent teaching methods enabled me to develop an understanding and interest in the subject of Neuroscience.

CONFLICT OF INTEREST

I Namrata Udani the author report no conflicts of interest.

BIOETHICS CLEARANCE

No real patient data were involved in this study.

ABBREVIATIONS

CNS – Central Nervous System

LGB – Lateral Geniculate Body

SAS – Subarachnoid Space

MS – Multiple Sclerosis

OCT – Optical Coherence Tomography

VEP – Visually Evoked Potentials

ERG – Electroretinogram

INTRODUCTION

The Practical significance of the work is to demonstrate mathematically the impact of optic nerve degeneration using computational methods and the theoretical significance of the work is to review literature related to diseases caused by optic nerve degeneration and their diagnostic methods. The optic nerve transmits sensory information from the retina of the eye to the primary visual cortex of the brain. The retinal ganglion cells receive impulses from the photoreceptors (rods and cones) of the eye, and the convergence of the axons from the retinal ganglion forms the optic nerve. The optic nerve from each eye meets within the medial cranial fossa to form the optic chiasm. At the chiasm, the medial fibers from each retina cross over to form the optic tracts. The left optic tract contains fibers from the left lateral retinal fibers and right medial retinal fibers and the right optic tract contains fibers from the right lateral retinal fibers and left medial retinal fibers. Each optic tract travels to its cerebral hemispheres and reaches lateral geniculate body (LGB) where the fibers synapse. Axons from the LGB carry visual information to the visual cortex via a pathway known as the optic radiation [1]. In summary origination from the retinal ganglion cells, the optic nerve carries approximately 1.2 million afferent nerve fibers to the LGB where most of them synapse and others are destined for the midbrain and other centers [2]. These nerve fibers are axons, and any disorders affecting the integrity of the axons influences vision.

An axon is a long neuronal process that conducts information from the cell body to the cell terminal. There are two types of axons in the peripheral and the central nervous systems: myelinated and unmyelinated. The optic nerve contains myelinated axons. The fibers of the optic nerve are myelinated by the oligodendrocytes. The presence of myelin sheath changes the physiology of the axon; the effective membrane resistance of the axon is locally increased by several orders of magnitude thereby increasing conduction velocity [3]. According to *Debanne et al* "myelinated axons can be considered as a three compartment: The initial segment where the action potential is initiated and propagated throughout the variable length of the axon to the final segment the axon terminal" [3]. An action potential is a function in neuronal cell bodies and axons. In neuronal cell bodies, theyencode information in their frequency and pattern whereas in axons they serve primarily to rapidly propagate signals over distance [4]. An action potential is mediated by voltage-gated ion channels that open and close when subjected to thermodynamic fluctuations which introduce a source of electrical noise in the neurons known as channel noise[5].

An evoked potential is an electrical potential recorded from the nervous system in response to a stimulus and detected by electrophysiological recording method. Visually evoked potential (VEP) is a neurophysiologic technique used to assess the visual function and to assist in the diagnosis of the

specific disorders associated with degeneration in the sensory visual pathways [6]. Conditions such as optic neuritis caused by demyelination of the nerve affect the vision and therefore can give an abnormal wave recording of the VEPs [7]. In this study, multiple VEPs were studied to note the different waveforms caused by different pathologies of the optic nerve.

The purpose of this research is to explore the possibility of using computational methods in understanding the degenerative processes of the optic nerve and its consequence which affects the nerve conduction. The idea of using VEPs as a diagnostic method and an important research tool for optic nerve degeneration diseases such as multiple sclerosis and optic neuritis is also explored.

AIM

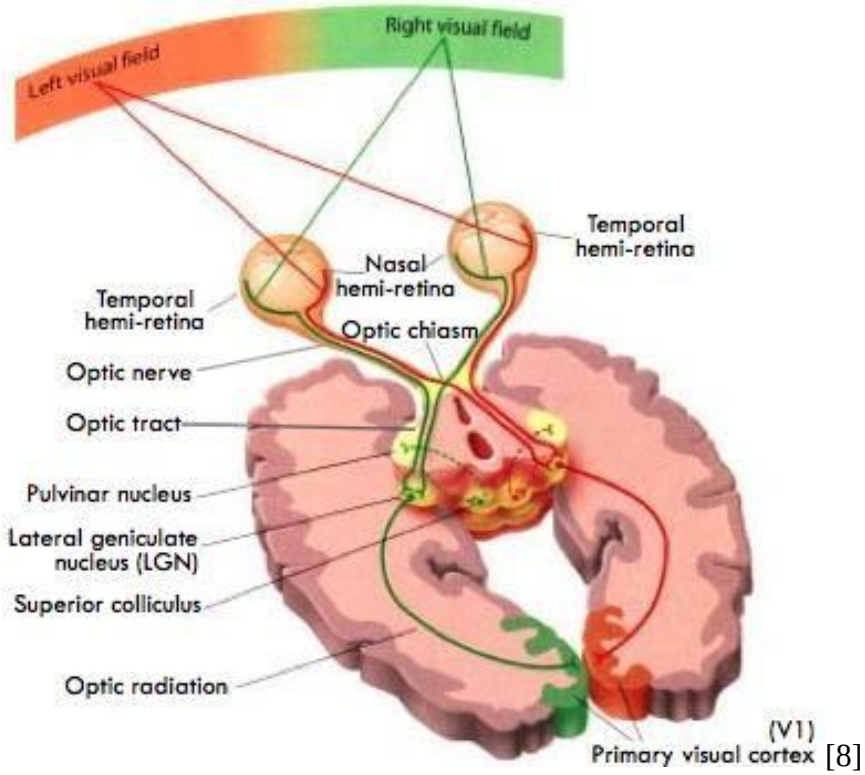
To analyze theoretically neuronal degeneration process in visual systems and to study VEPs in diseases caused by optic nerve degeneration.

OBJECTIVES OF THE STUDY

1. To analyze demyelination process in an optic nerve.
2. To review the literature about related diseases in the visual system.
3. To review the literature about related medical diagnostics techniques.
4. To simulate neuronal degeneration principal in an optic nerve.
5. To study visual evoked potentials (VEPs) due to different visual system disorders.

LITERATURE REVIEW

The visual system is part of the central nervous system, which gives the organisms the ability to process the visual detail. It includes the eye (especially the retina) and the connecting pathway through to the visual cortex (the optic nerve, the optic chiasm, the optic tract, the lateral geniculate body (LGB), the optic radiation, the visual cortex, the visual association cortex). The task of the visual system is the reception of light and the formation of monocular representations, the build-up of a nuclear binocular perception from a pair of 2-dimensional projections, the identification, and categorization of visual objects, accessing distances to and between objects and guiding body movements in relation to the objects seen [8,9].



[8]

Fig. 1. ***Diagram of the eye and its connecting visual pathway through the brain***

Eye: Light entering the eye is refracted as it passes through the clear cornea. It then passes through the pupil (which is controlled by the iris) and is further refracted by the lens. The cornea and lens act together to project an inverted image onto the retina.

Retina: The retina translates light into nerve signals. It contains photoreceptors and its function is phototransduction, adaption, receptive fields (concentric organization, “on” and “off” ganglion cells), and colour vision [10]. The retina consists of three layers of nerve cell bodies separated by two layers of synapses made by the axons and dendrites of these cells. The layers of cells at the back of the retina contains the photoreceptors called rods and cones. Rods and Cons are responsible for carrying light energy

into electrochemical changes which eventually generate an action potential in the visual pathway. The numbers of rods and cones vary on the surface of the retina, in the very center where there are only cones is called the fovea. The middle layer between the photoreceptors and the ganglion cell layer is a layer containing bipolar cells, horizontal cells, and amacrine cells. They all link the retina to the ganglion cells. Ganglion cell layer only ganglionic cells produce action potentials. Depolarization "on" excite ganglionic cells and generate action potential while hyperpolarization "off" means no action potential. The ganglion cells whose axons pass across the surface of the retina collect in a bundle at the optic disc and the eye to form the optic nerve [10].

The optic nerve: the optic nerve is myelinated by oligodendroglia (myelination in the CNS). Optic nerve does not regenerate. It is a central nerve (cranial nerve II) surrounded by dura matter + arachnoid space + SAS + pia throughout its length. The optic nerve is called the special somatic afferent. Different populations of ganglion cells in the retina send information to the brain through the optic nerve.

The ganglion cell's processes, these fibers will move towards the optic disc, then these fibers will move as the optic nerve to the optic chiasm there they decussate. The fibers diverge again backward and laterally as the optic tract. Optic tract diverge backward and 10% of them enter the midbrain and 90% of the tract enter the LGB. From the LGB optic radiations or the lateral genicular radiations move to the upper tracts to parietal → occipital (upper bank calcarine fissure) and lower tracts to the temporal lobe → occipital (lower calcarine fissure) [8,11].

Related diseases/ clinical significance

Damage to the optic nerve causes permanent and potentially severe loss of vision, as well as an abnormal pupillary reflex. The type of visual field loss will depend on which portions of the optic nerve were damaged. Injury to the optic nerve can be the result of congenital or inheritable problems like Leber's Hereditary Optic Neuropathy, glaucoma, trauma, toxicity, inflammation, ischemia, infection (very rare) or compression from tumors or aneurysms. The most common are glaucoma, optic neuritis and anterior ischemic optic neuropathy [12]. As the most common diseases due to injury to the optic nerve are glaucoma, optic neuritis and ischemic neuropathy I will elaborate further on each of these diseases below.

Glaucoma is a group of diseases with multifactorial etiology characterized clinically by intraocular pressure associated optic neuropathy. It is associated with increased intraocular pressure that damages the optic nerve evidence suggesting the primary site of damage being the optic nerve head (neuronal degeneration of the retinal ganglion cell axons). All forms are progressive and can lead to blindness [13]. The neuronal structural changes lead to functional changes which are fundamental to clinical findings and diagnosis. Functional changes include peripheral visual field defects, reduction in contrast sensitivity and deterioration of visual acuity late in the disease progression.

Diagnosis is by tonometry which examines inner eye pressure, Ophthalmoscopy which examines the shape and colour of the optic nerve, perimetry which examines the complete visual field, gonioscopy which examines angle in the eye where the iris meets the cornea, pachymetry which examines the thickness of the cornea, nerve fiber analysis examines the thickness of the nerve fiber layer [12,14].
Optic neuritis is a demyelinating inflammation of the optic nerve, it is most often caused by multiple sclerosis (MS) and it may lead to complete or partial loss of vision in one or both eyes. When the head of the nerve is involved it's called optic papillitis and when the posterior of the optic nerve is involved it's called retrobulbar neuritis. Other causes of optic neuritis include infection, autoimmune disorders, B12 deficiency, and diabetes. Diagnosis is usually by the signs and symptoms presented by the patient like blurry vision, loss of vision and examination of the optic nerve head by direct ophthalmoscopy. *In MS, there is episodic partial vision loss or blurry vision [12].
Anterior ischemic optic neuropathy is the loss of vision due to damage to the optic nerve from insufficient blood supply. It can be due to temporal arteritis and non-arteritis related diseases such as diabetes, hypertension and increased cholesterol. Diagnosis is made by ophthalmoscopy [12].

Diagnostic methods of diseases of optic nerve pathology

Optical coherence tomography (OCT) is a non-invasive imaging test that uses light waves to take cross-section pictures of the retina, the light-sensitive tissue lining the back of the eye. With OCT, each of the retina's distinctive layers can be seen, allowing the ophthalmologist to map and measure their thickness. These measurements help with diagnosis and treatment guidance of glaucoma and retinal diseases (age-related macular degeneration and diabetic eye disease). OCT is also used to evaluate disorders of the optic nerve, it's helpful in determining changes to the fibers of the optic nerve such as those caused by glaucoma. OCT's advantages are that it provides tissue morphology imagery at much higher resolution than any other imaging modalities such as MRI or ultrasound. Other benefits are instant, direct imaging of tissue morphology, no preparation of the sample or the subject is needed, no ionizing radiation and it provides live sub-surface images at near-microscopic resolution. Disadvantages of OCT are that it has low tissue penetration. It cannot be used successfully with any condition that interferes with light passing through the eye such as dense cataracts or significant bleeding in the vitreous [15].
Ophthalmologic ultrasound is most prevalently used. It is used to obtain globe length to calculate corrective lens power requirements, the measurements of the tumor including choroidal melanomas, visualization of lens dislocation and detection of retinal detachment. The benefits of US include improved visualization of structures obscured by opaque substances such as dense cataracts or vitreous hemorrhage. The ability to define the relationship of iris, posterior chamber, ciliary body and the lens is helpful in clarifying mechanisms of glaucoma [16].

Ophthalmoscopy examines fundus the posterior segment of the eye to get a sense of the patient's overall vasculature. The fundoscopic exam can help diagnose pathological process such as infection and help to stage diabetes and hypertension. In normal fundoscopy, arteries are narrower than veins. The cup-to-disc ratio at the physiologic limit is of 0.5. In a case of pathology such as increased intracranial pressure (papilledema), infarction, inflammation, and infiltration show the optic disc is elevated and its surface is covered by cotton wool spots (damaged axons) and flame hemorrhages (damaged vessels). Chronic hypertension stiffens and thickens arteries; at AV crossing points, arteries indent and displace veins this is called Arterio-Venous nicking. Fundoscopy also shows emboli and infracts [17, 18, and 19].

Electroretinography (ERG) is an eye test used to detect abnormal function of the retina. In this test, the light-sensitive cells of the eye, the rods and cones, and their connecting ganglion cells in the retina are examined. The full-field electroretinogram (ffERG) is a widely used electrophysiological test of retinal function. "In 1989, ISCEV standardized basic clinical ERG protocols so that comparable ERGs could be recorded throughout the world" [20] the defined ISCEV standard ERG series includes six protocols. Four dark-adapted ERGs for 20mins, two light adapted ERGs for 10 mins. Standard ERG tests can be selected as indicated for specific patients, the four dark-adapted standard ERGs are 1. Dark-adapted 0.01 ERG (response of bipolar cells). 2. Dark-adapted 3 ERG (a wave comes from the photoreceptors and b-wave comes from bipolar cells). 3. Dark-adapted 10 ERG (combined response with enhanced a-waves reflecting photoreceptor function). 4. Dark-adapted oscillatory potentials (responses primarily from amacrine cells) [20].

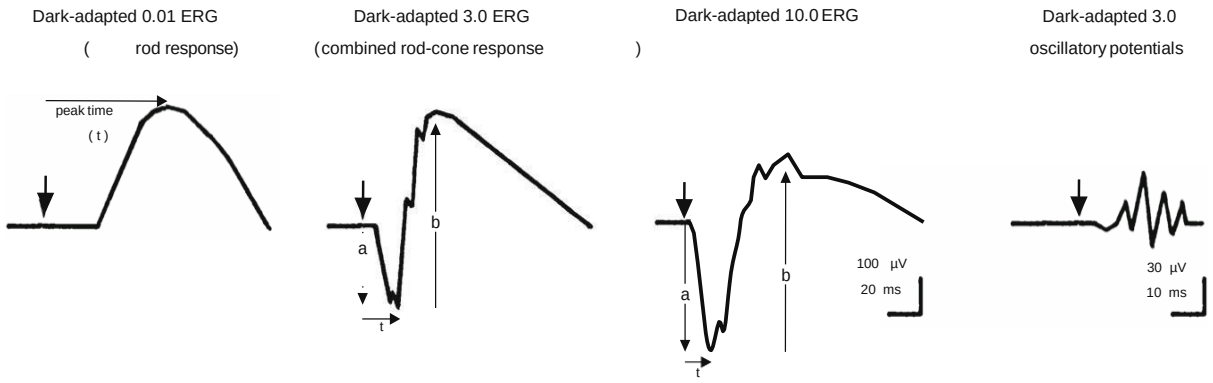


Fig. 2. ***4 Dark-adapted ERGs*** [20]

The two standard light-adapted ERGs are 1. Light-adapted 3 ERG (cone response, a-waves arise from cone photoreceptors and cone Off-bipolar cells, b-wave comes from On- and Off-cone bipolar cells). 2. Light-adapted 30 Hz flicker ERG (a sensitive cone response) [20].

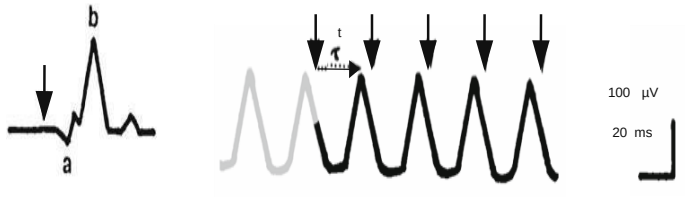


Fig. 3. ***2 Light-adapted ERGs*** [20]

Applications: Electroretinogram is used to distinguish between diffuse and focal retinal damage, useful in evaluating chronic ischemic damage from vascular damage, may aid detection of certain hereditary disorders and to estimate the extent of damage from trauma or drug toxicity.

Visually evoked potential (VEP) is used to assess change in visual function. This examination is an objective measure of the function of the entire visual system (retina to cortex). VEPs record an electrical signal registered at the occipital cortex in response to a visual stimulus. Therefore, in theory, the full integrity of the visual system is assessed in detail {photoreceptor → bipolar → ganglion cell axon → relay neuron → visual cortex neuron} [21].

Generally, how VEP works: 1. the patient observes a visual stimulus 2. The retina generates electrical energy. 3 Potential = sensors measure electrical activity at the visual cortex. 4. Graphical results recorded allow quantification of the therapeutic results and monitoring of disease [21].

The International Society of Clinical Electrophysiology of Vision (ISCEV) standard VEP protocols is defined for a single recording channel which is intended for assessment of pre-chiasmal function (eye, optic nerve anterior to the optic chiasm). And extended multichannel protocols are required to evaluate the post chiasmal lesions. ISCEV has selected a subset of stimulus and recording conditions and there are:

1. Pattern-reversal VEPs
2. Pattern onset/offset VEPs
3. Flash VEPs = Elicited by a flash

Elicited by checkerboard stimuli

The standard does not require that all 3 protocols should be used for investigation of every patient; pattern-reversal is a preferred stimulus for most of the clinical purposes. Specific circumstances in patients with nystagmus the pattern onset/offset stimulus is more effective. The flash VEPs is useful when the use of pattern stimulation is inappropriate in poor optical quality, poor cooperation or poor vision. Recording parameters: Amplification systems: DC amplifiers or AC-coupled amplifiers with a minimum input impedance of 10 MΩ in the 50 – 60 Hz range may be used.

Analysis time: the minimum analysis time for all adult transient flash and pattern-reversal VEPs is 250ms post-stimulus. For onset/offset and VEP in infants, the analysis time may be extended to 500ms.

ISCEV standard waveforms: the time from stimulus to the maximum positive or negative deflection or excursion of the VEP is referred to as the peak time [22].

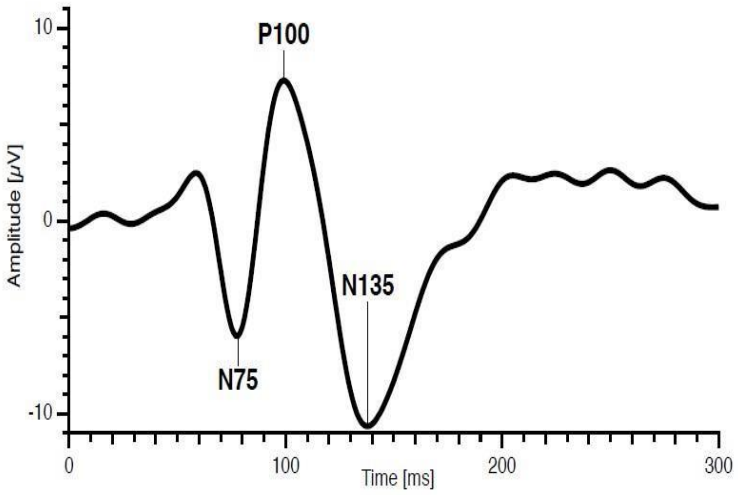


Fig. 4. ***A typical pattern-reversal VEP*** [22]

A typical pattern-reversal VEP waveform consists of N75, P100, and N135 peaks. These peaks are designated as negative (N75 & N135) and positive followed by the typical mean peak time [22].

Amplitude: measured in microvolts (μV), anatomy = usually translates to the number of axons conducting along the visual pathway.

Latency: measured in milliseconds (ms), physiology = usually translates to the function of axons conducting along the visual pathways [22].

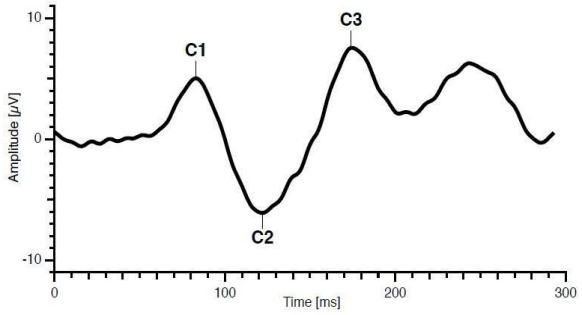


Fig. 5. ***A typical pattern onset/offset VEP*** [22]

Standard pattern onset/offset stimulation typically consists of 3 main peaks in adults; a positive peak of approximately 75ms, a negative peak at approximately125 ms and a positive peak at approximately 150ms termed C1, C2, and C3 respectively [22].

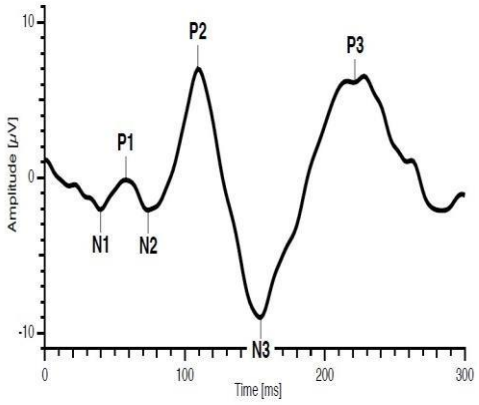


Fig. 6. ***A typical flash VEP*** [22]

Standard flash stimulation consists of a series of negative and positive waves. The most consistent peaks in a typical adult are N2 a negative peak at around 90ms and P2 a positive peak at around 120ms [22].

Computational Neuroscience

Computational neuroscience is the study of how the brain computes information using computational approaches to investigate the properties of the nervous system at a different level of details, which implies simulation of numerical models on computers [29]. The origination of computational neuroscience dates back to the Hodgkin-Huxley model a mathematical model of a giant squid axon action potential [25]. Next, Wilfrid Rall used mathematical approaches based on cable theory to show the dendritic effect of synaptic input [30]. He initiated the use of digital computers in neuroscience and developed the discretized version of cable theory, compartmental modeling which forms the basis for the software packages used in neuroscience such as NEURON [31, 32]. The cable equation by Rall combined was combined with the Hodgkin-Huxley type models of voltage-gated channels to model the effect of neural excitability on synaptic integration which now extends from molecules to large neuronal networks which are a major strength of computational modeling [32].

Information is transmitted rapidly along the axons using action potentials (AP), therefore the reliability of the action potential is essential for computing neural information. The AP signaling mechanism involves voltage-gated ion channels which are subject to thermodynamic changes. In a myelinated axon, the conduction is impacted due to the myelin sheath. The membrane capacitance is reduced and membrane resistance is increased by several magnitudes. The myelin sheath is interrupted by nodes of Ranvier which mean that patches of the axons are exposed to the external medium. The region at the node is involved in the propagation of impulses and ions cannot flow in and out of the high-resistance internodal regions. The impulse, therefore, jumps from node to node increasing the conduction velocity this is known as the saltatory conduction [33]. According to Huxley and Stampfli, they measured currents in a single axon; they noticed that in a compartment containing a node of Ranvier, stimulation of

the nerve resulted in a large inward current whereas a nerve containing an internode no inward current was recorded thus indicating that there is no regenerative activity [34].

In diseases such as MS where there are periods of remission where the patient's recovery is due to recovery and proliferation of the sodium channels in the demyelinated regions. The main consequence is the partial or complete loss myelin of the optic nerve [35]. The changes in ionic conductance influence the action potential shape and firing, this makes it ideal for mathematical modeling. Computational modeling of the optic nerve is advantageous in a way of building simple models in understanding the alterations in conductance properties and building more detailed nerve models, which will be a powerful link between modeling and experimenting in wetlabs.

RESEARCH METHODS AND METHODOLOGY

For practical work software called Neuron was used. *NEURON* is an extensible nerve modeling and simulation program. It's used to create complex nerve models by connecting multiple one-dimensional sections together to form arbitrary cell morphologies and allows you to insert multiple membrane properties into these sections (including channels, synapses, ionic concentrations, and counters) [9]. The neuron simulation environment has been used in the field of computational neuroscience. The Hodgkin-Huxley model of the nerve axon describes excitation and propagation of the nerve impulse by means of a nonlinear partial differential equation. The equation relates to conservation of electric current passing through the axon representing transport of ions through the nerve membrane. A neuron has highly quantifiable elements like action potential shape, firing rates and patterns and membrane voltage that can be measured very accurately, because of these features the system is suited for mathematical modeling. Such modeling has given us an insight into asking how tolerant is the system to alterations in the magnitude or properties of the system elements? [24, 25, 26]. of the tools that are provided by NEURON's GUI were used. A graphical tool for constructing and managing models of individual neuron *CellBuilder* was employed (tested). The initial focus was on creating a representation of very simplified single axon model, but not on considering synapses, stimulating electrodes, or simulation control.The *CellBuilder* made it easier to create a model of the axon by allowing to specify it's simple architecture and biophysical properties through a graphical interface.

Signals of visually evoked potentials were analyzed. Signals were collected in advance in accordance with the Declaration of Helsinki. A single channel EEG was registered using an active electrode placed on the scalp over the visual cortex at Oz with a reference electrode at Fz and grounding electrode on a forehead according to the International 10/20 system [22]. This is a common electrode configuration in clinical ophthalmology studies. A stimulus and recording conditions were selected so that they could provide core clinical information; pattern-reversal monocular recording with one eye closed. VEPs were elicited by checkerboard stimuli with large checks (i.e., 60 min of arc/ min) and small checks (15 min) [7] on CRT (cathode ray tube monitors) display and subtended 17 degrees in diameter at a viewing distance of 1 meter. The stimulus alternated at 1 Hz rate (2 reversals per second). At first, signals were registered for the right eye (OD), then for the left one (OS). Signals were registered as 300 ms intervals after each visual stimulus. Single sweep contained 512 samples at 12-bit resolution. Inter-sample interval was 0.5871ms. Signals were filtered by 0.5-50 Hz band-pass filter and stored on a computer disk for offline analysis. The amplitude and latency of the major positive peak (P100) were measured according to the ISCEV standard [22]. The VEPs analysis was

performed using software made in MatLab^{TM} environment. Further statistical analysis was done using Excel environment. P100 peak amplitudes and latencies were evaluated for normal conditions of the optic nerve and in pathological conditions such as optic neuritis and multiple sclerosis.

RESULTS

A very primitive structure of the optic nerve axon was created using Neuron software [23]. It consisted of soma, axon hillock, myelinated internodes [n=5]: d=5; l =10, nodes of Ranvier [5]: d=2, l=5 (here n – number, d – diameter, l – length).

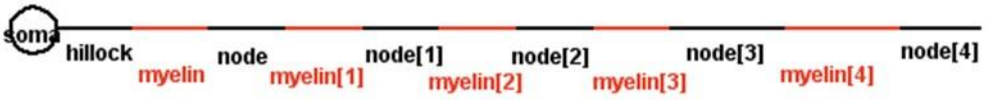


Fig. 7. ***Primitive structure of optic nerve axon***

Initial biophysical properties were selected as shown in the following figure. Biophysical properties were reviewed in the literature [26].

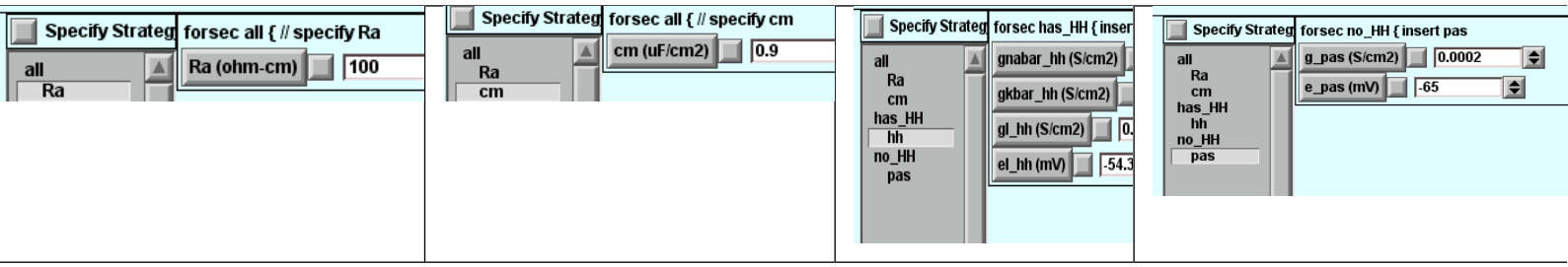
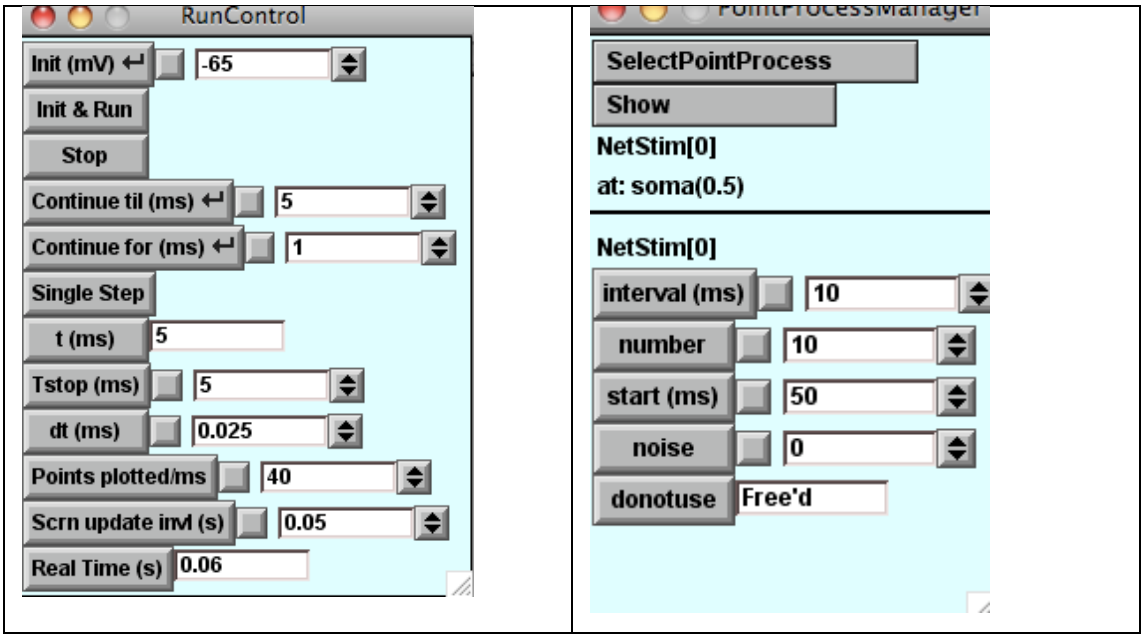


Fig. 8. ***Selected biophysical properties***

It was important to find the effect of different stimulation type. NetStim stimulation type was tested.



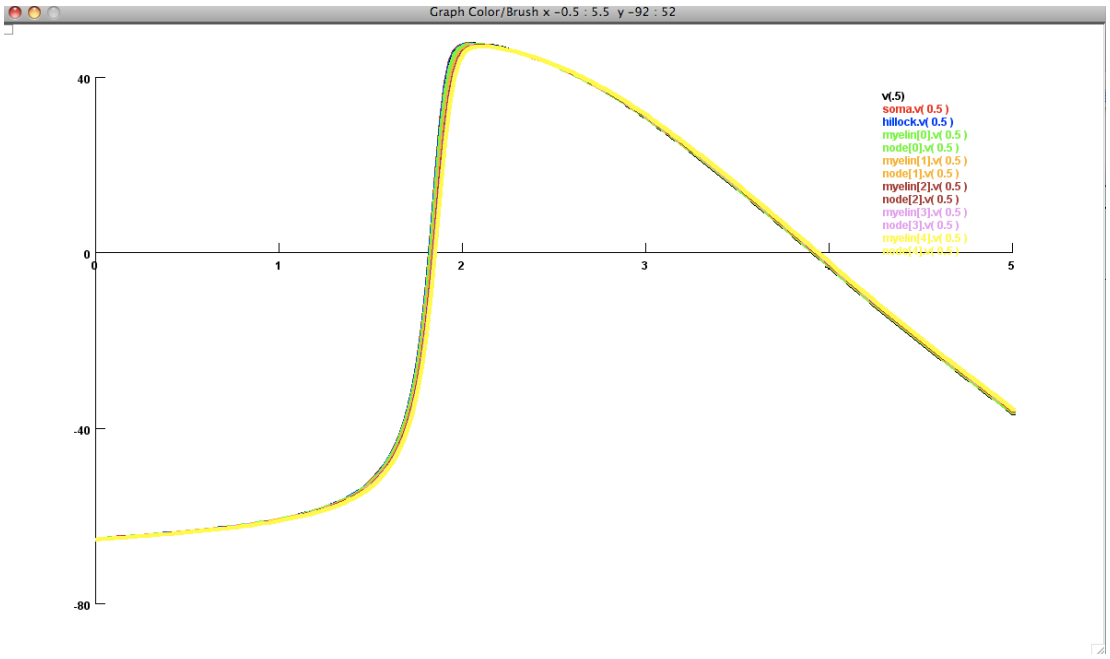
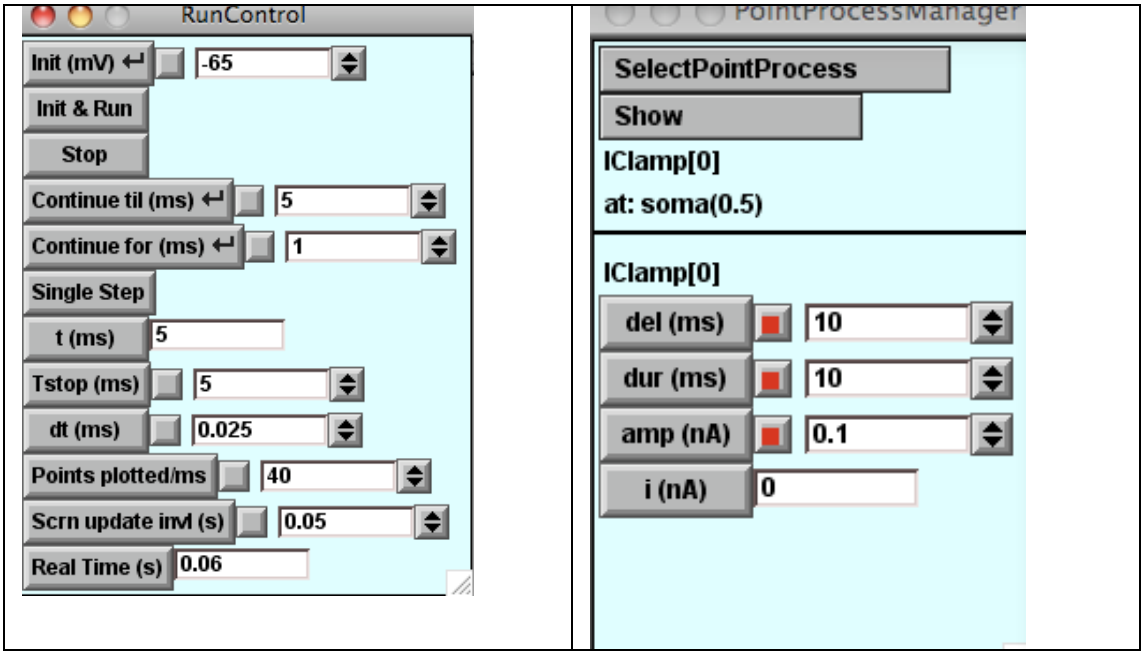


Fig. 9. ***Netstim stimulation type***

Netstim stimulation generates presynaptic stimuli with intervals of 10 ms and noise at 0.

Another stimulation type IClamp at Soma was tested.



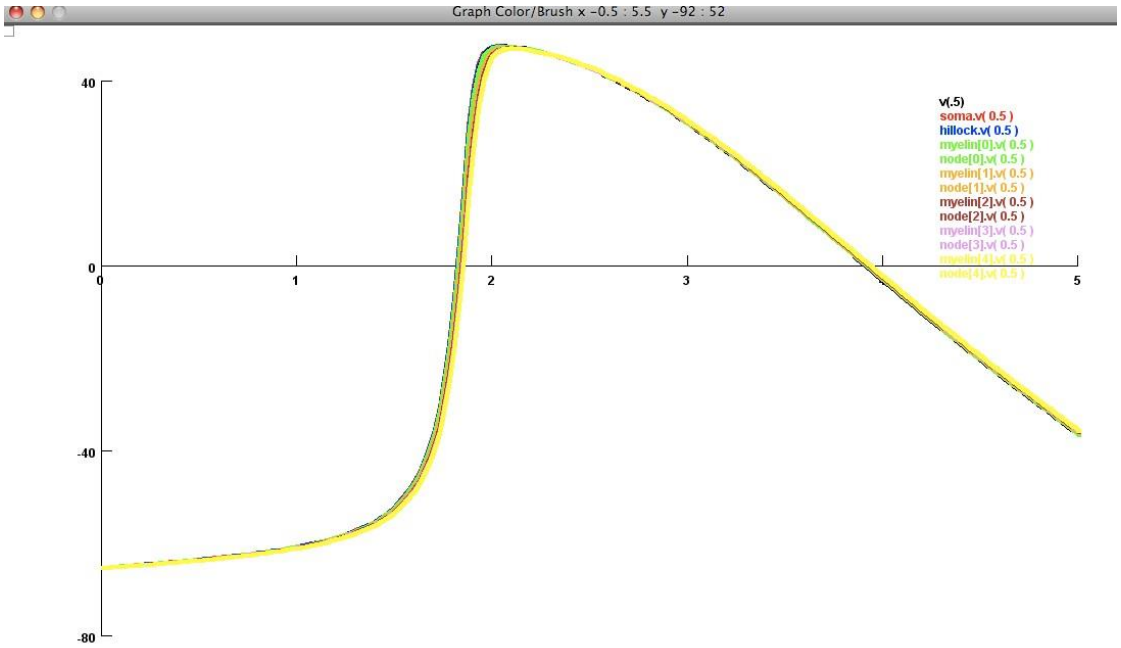
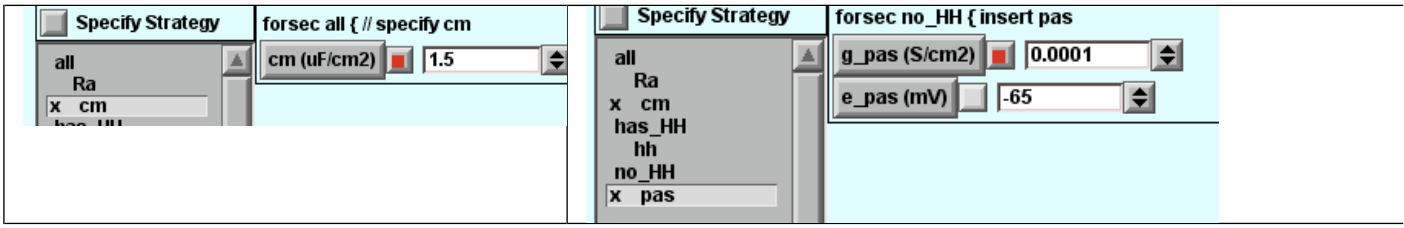
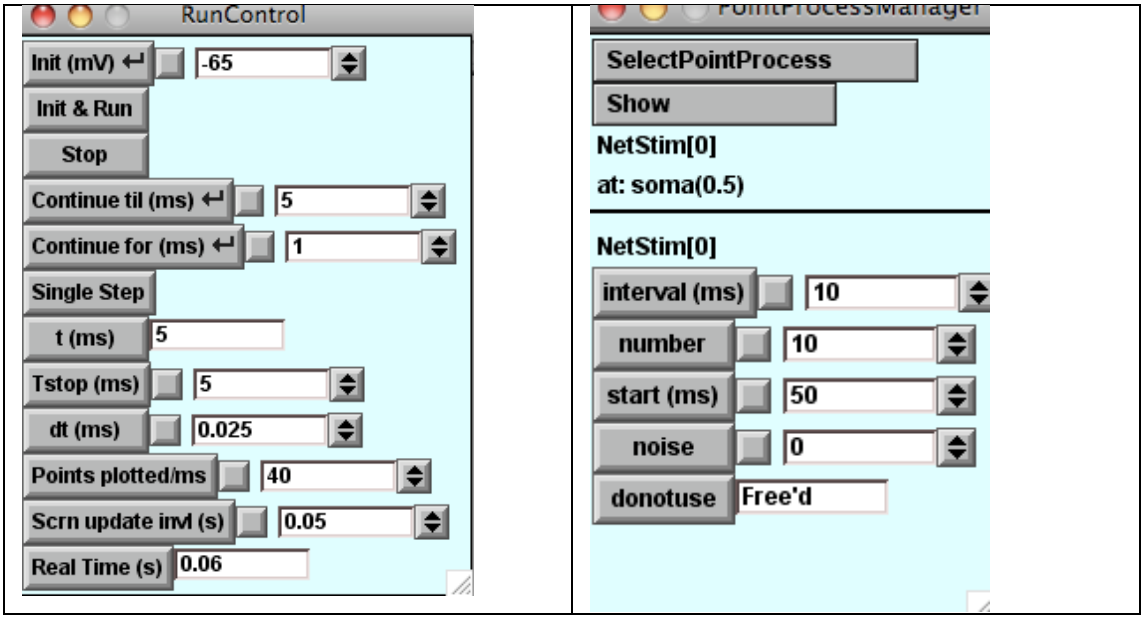


Fig. 10. ***IClamp Stimulation type***

IClamp stimulation type demonstrating depolarisation of the cell.

Loss of myelin simulation was performed (capacitance=cm: increase, resistance=g_pas: decrease).





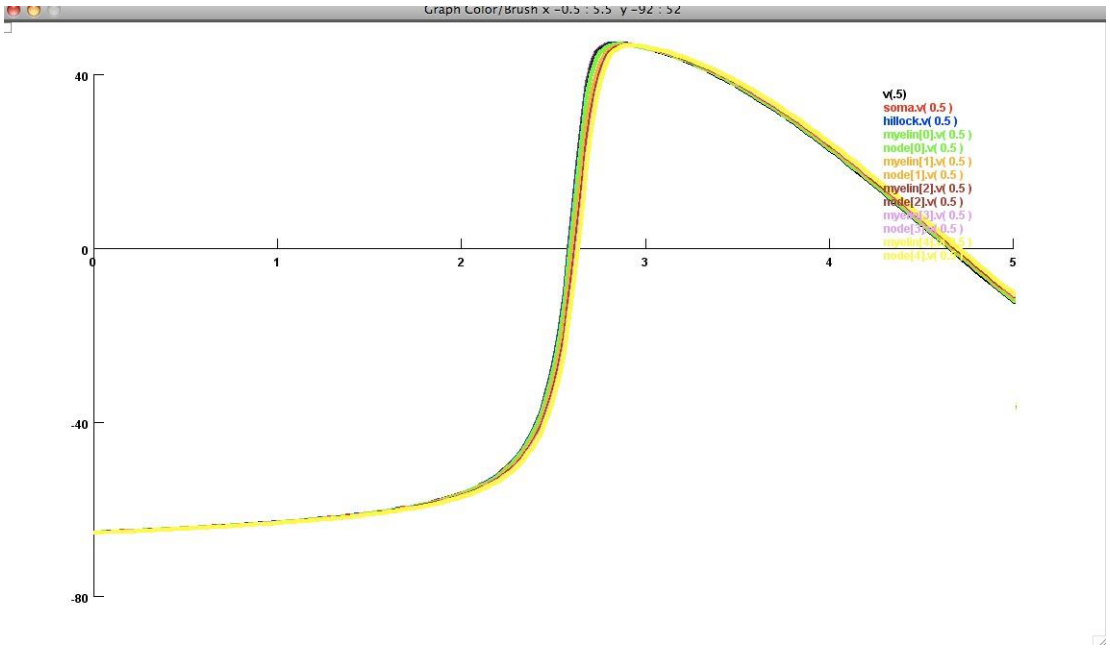


Fig. 11. ***capitance and g_pas stimulation type***

The graph above shows a delay in conductance using capitance and g_pas stimulation type demonstrating demyelination of the axon.

Membrane properties of active channels were changed (gnabar_hh; changing from 0.5 to 0.25).

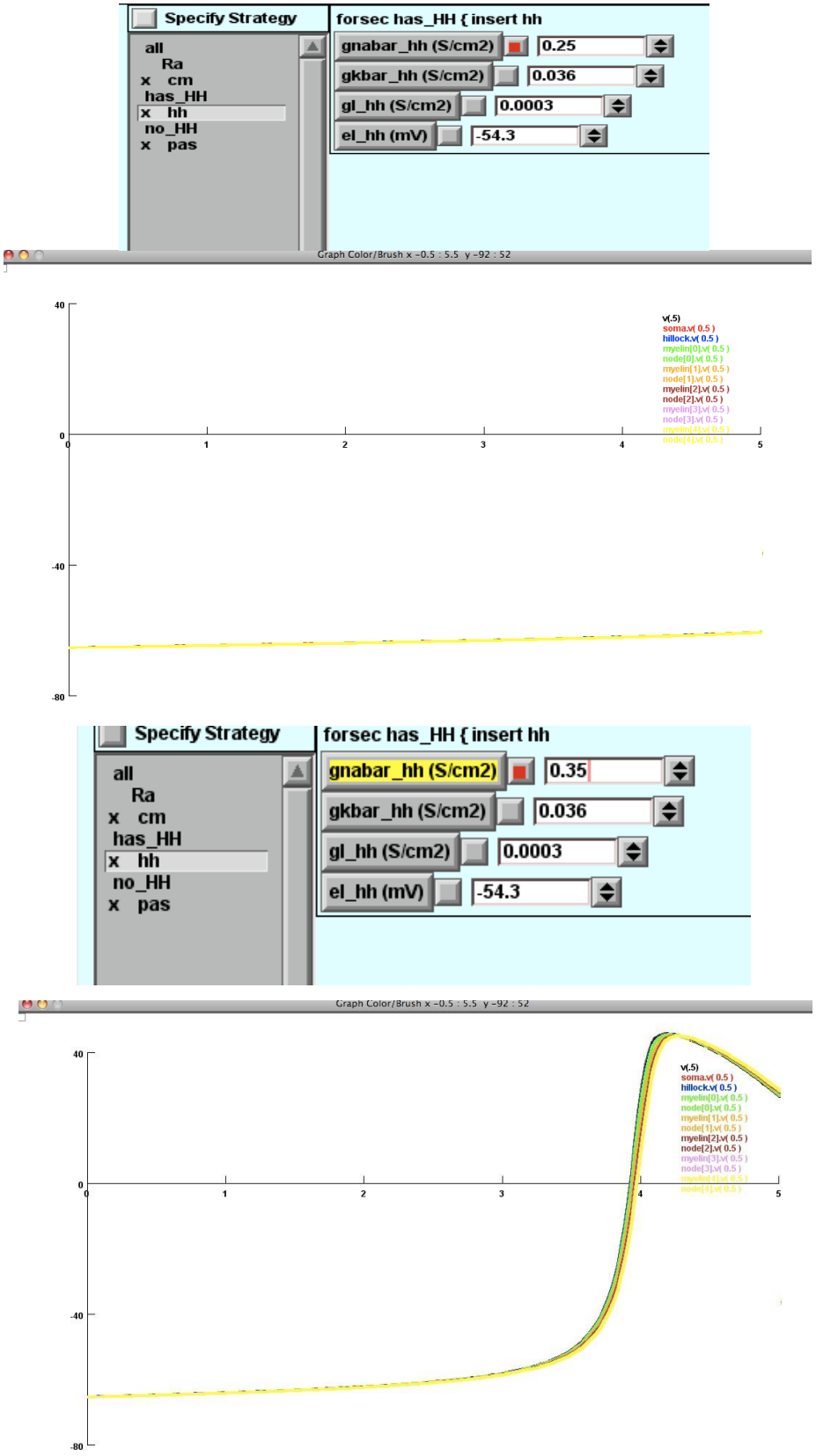


Fig. 12. ***gnabar_hh simulations***

This stimulation where membrane properties were changes in particular density of the sodium channels on the soma the graph demonstrating the effect of the ion channels on the initiation of the AP.

Another part of the work was related to an analysis of realistic visually evoked potentials. Preliminary identified 27 normal cases, 26 cases diagnosed with optic neuritis, and 7 cases with multiple sclerosis were analyzed.

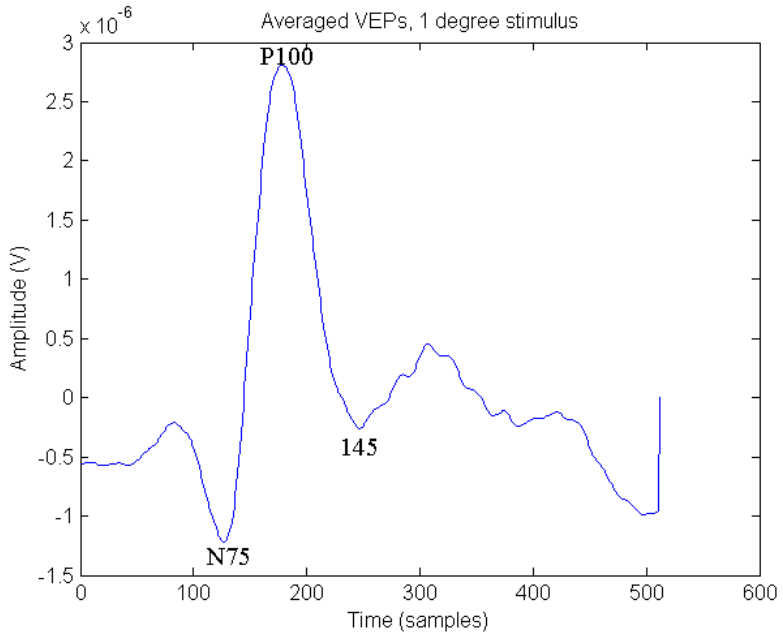
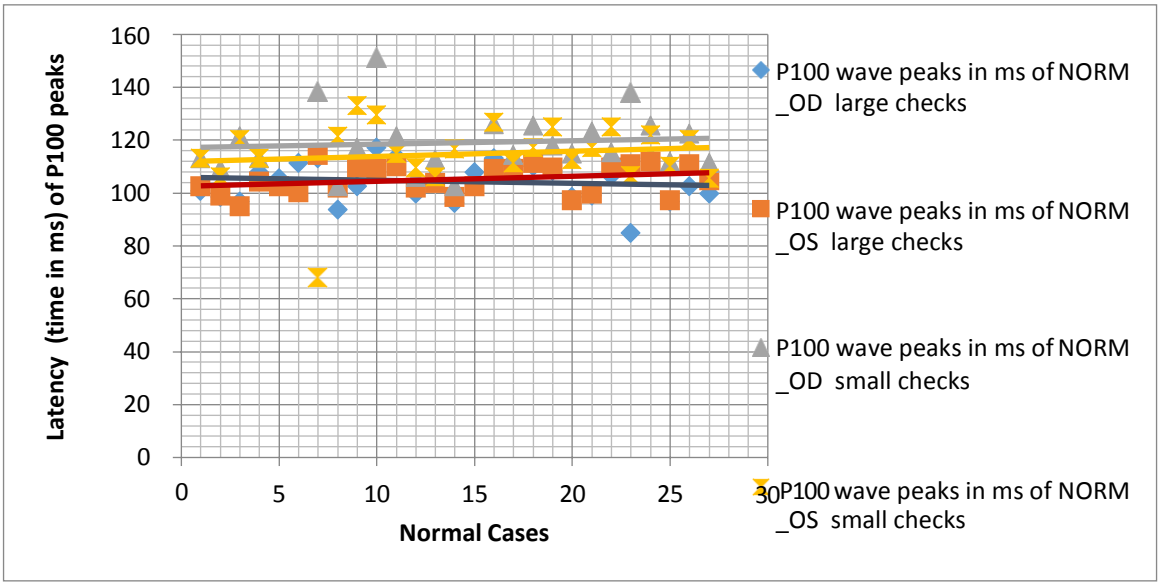


Fig.13. ***P100 in normal cases***

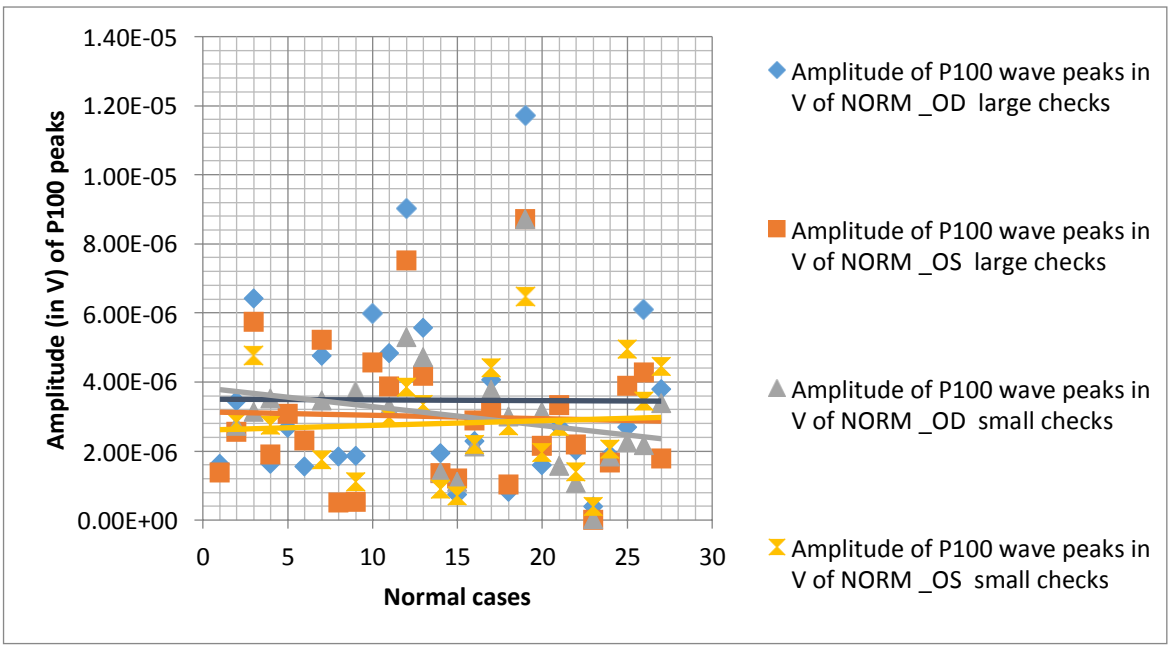
Normal cases (n=27): Latencies of P100 averaged waves (peaks, ms)



Average time ± SD of P100 peaks of NORM_OD large checks (ms)	Average time ± SD of P100 peaks of NORM_OS large checks (ms)	Average time ± SD of P100 peaks of NORM_OD small checks (ms)	Average time ± SD of P100 peaks of NORM_OS small checks (ms)
104±7	**105±5**	**119±11**	**115±12**

Fig.14. ***Latencies in normal cases***

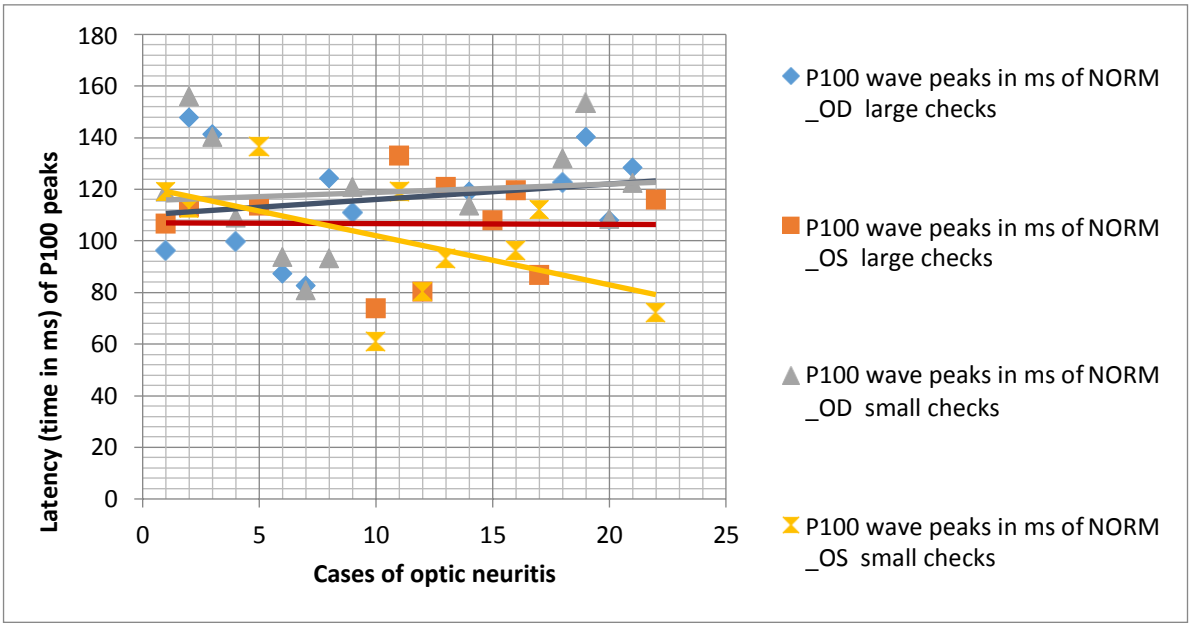
Normal cases (n=27): Amplitudes of P100 averaged waves (peaks, V)



Average amplitude ± SD of P100 peaks of NORM_OD large checks (V)	Average amplitude± SD of P100 peaks of NORM_OS large checks (V)	Average amplitude ± SD of P100 peaks of NORM_OD small checks (V)	Average amplitude ± SD of P100 peaks of NORM_OS small checks (V)
$3,47*10^{-6}±2,59*10^{-6}$	**$3,00*10^{-6}±2,04*10^{-6}$**	**$2,97*10^{-6}±1,74*10^{-6}$**	**$2,82*10^{-6}±1,51*10^{-6}$**

Fig.15. ***Amplitudes in normal cases***

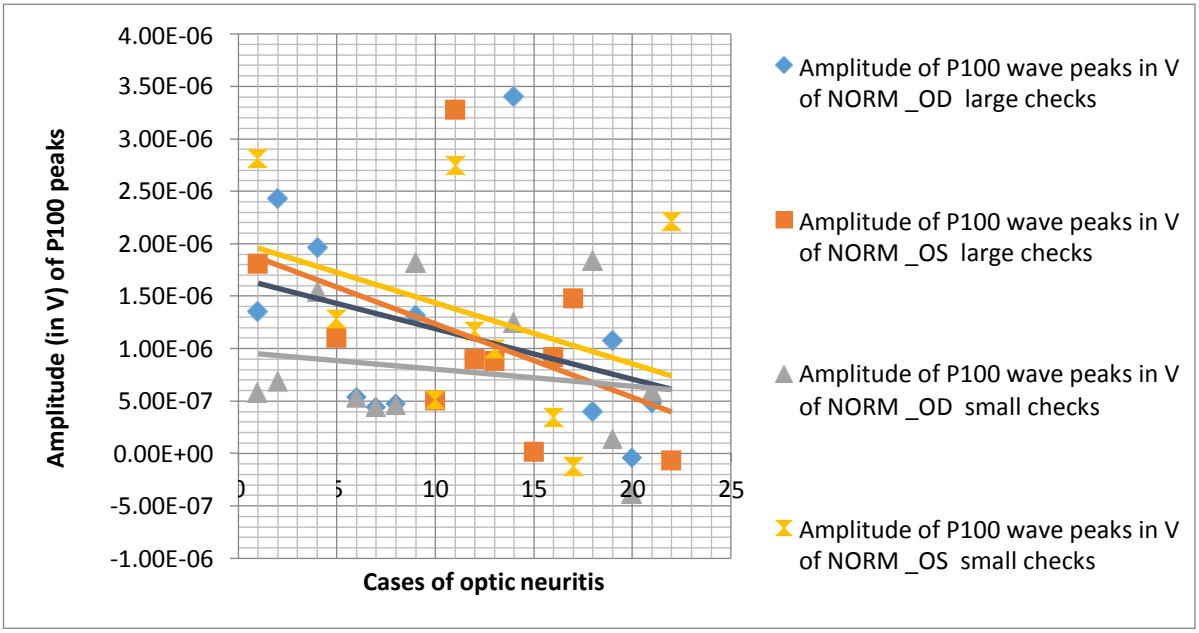
Cases of optic neuritis (22): Latencies of P100 averaged waves (peaks, ms)



Average time ± SD of P100 peaks of NORM_OD large checks (ms)	Average time ± SD of P100 peaks of NORM_OS large checks (ms)	Average time ± SD of P100 peaks of NORM_OD small checks (ms)	Average time ± SD of P100 peaks of NORM_OS small checks (ms)
116±20	**107±18**	**119±22**	**100±23**

Fig. 16. ***Latencies in Optic neuritis cases***

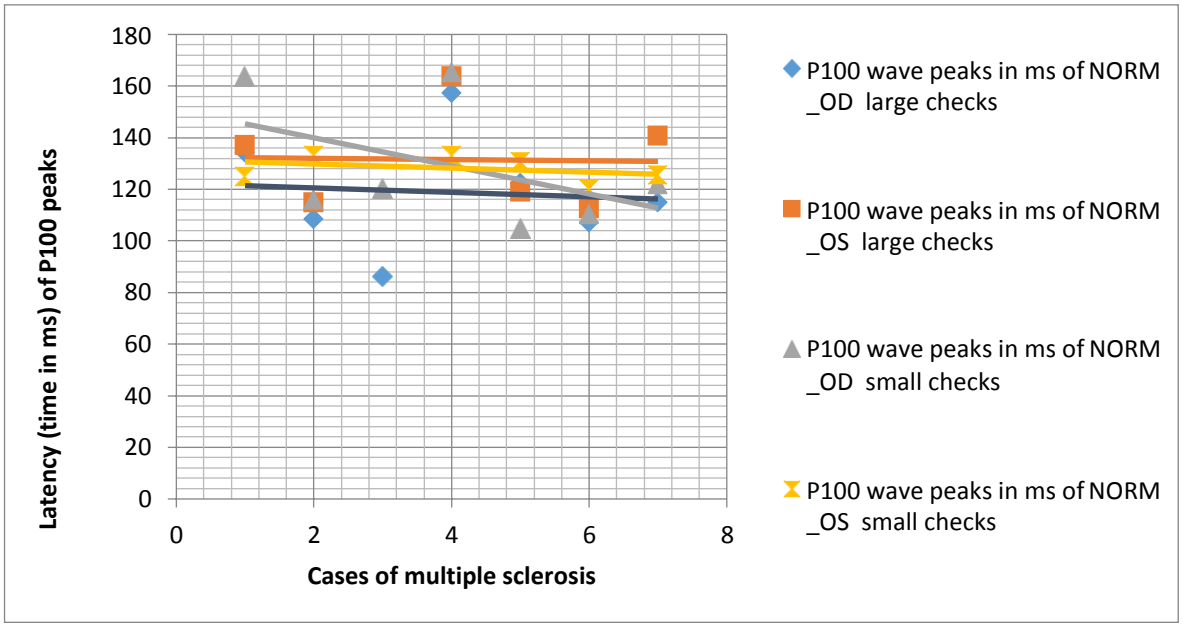
Cases of optic neuritis (22): Amplitudes of P100 averaged waves (peaks, V)



Average amplitude ± SD of P100 peaks of NORM_OD large checks (V)	Average amplitude± SD of P100 peaks of NORM_OS large checks (V)	Average amplitude± SD of P100 peaks of NORM_OD small checks (V)	Average amplitude± SD of P100 peaks of NORM_OS small checks (V)
$1{,}15*10^{-6}±9{,}66*10^{-7}$	**$1{,}08*10^{-6}±9{,}17*10^{-7}$**	**$0{,}79*10^{-6}±6{,}54*10^{-7}$**	**$1{,}33*10^{-6}±9{,}92*10^{-7}$**

Fig.17. ***Amplitudes in optic neuritis cases***

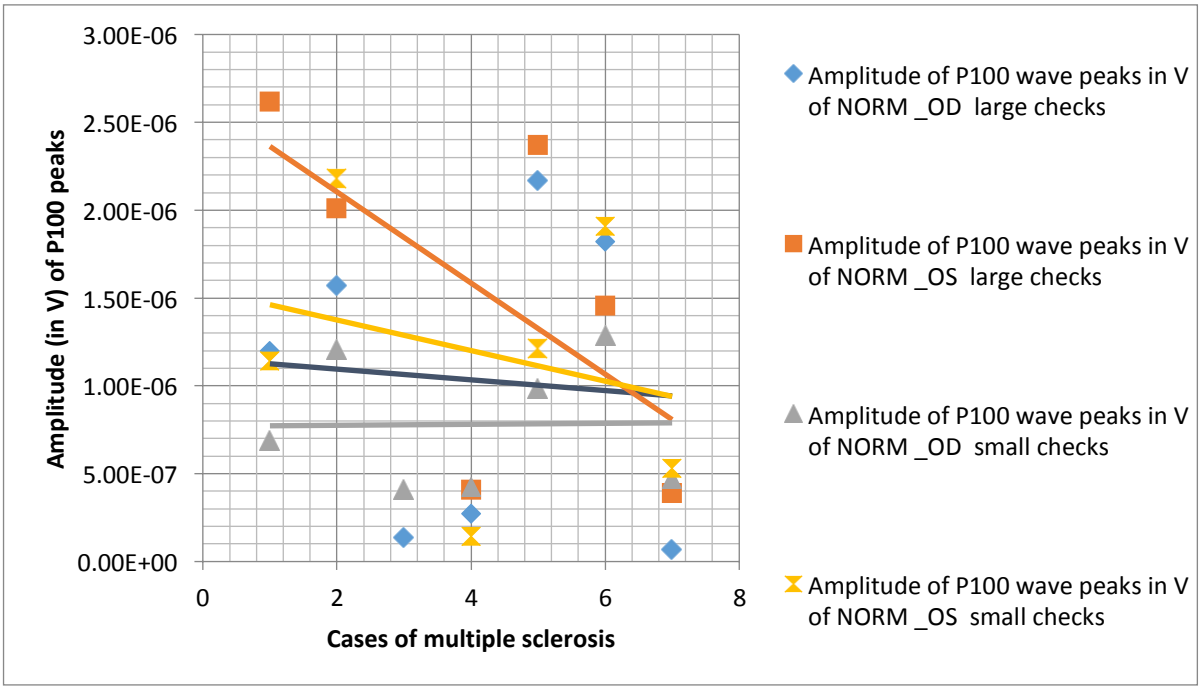
Cases of multiple sclerosis (7): Latencies of P100 averaged waves (peaks, ms)



Average time ± SD of P100 peaks of NORM_OD large checks (ms)	Average time ± SD of P100 peaks of NORM_OS large checks (ms)	Average time ± SD of P100 peaks of NORM_OD small checks (ms)	Average time ± SD of P100 peaks of NORM_OS small checks (ms)
119±21	**132±18**	**129±23**	**128±5**

Fig. 18. ***Latencies in multiple sclerosis cases***

Cases of multiple sclerosis (7): Amplitudes of P100 averaged waves (peaks, V)



Average amplitude ± SD of P100 peaks of NORM_OD large checks (V)	Average amplitude± SD of P100 peaks of NORM_OS large checks (V)	Average amplitude± SD of P100 peaks of NORM_OD small checks (V)	Average amplitude± SD of P100 peaks of NORM_OS small checks (V)
$1{,}03*10^{-6}±8{,}05*10^{-7}$	**$1{,}54*10^{-6}±8{,}83*10^{-7}$**	**$0{,}78*10^{-6}±3{,}47*10^{-7}$**	**$1{,}19*10^{-6}±7{,}10*10^{-7}$**

Fig. 19. ***Amplitudes in multiple sclerosis cases***

DISCUSSION

The optic nerve axon may be considered as a cable connecting retinal ganglion cells and neurons in the brain cortex (particularly neurons in the visual lobe, occipital area). A cable equation may be applied to describe voltage conductance in the axon and compartmental modeling approach may be implemented by considering electrical circuit approach. The preliminary axon model has been developed with different segments and their electrical properties (a soma, an axon hillock, myelinated internodes and nodes of Ranvier) using Neuron software (Fig.7 & Fig.8). Parameters such as temperature, loss of myelin (increase in capacitance, decrease in resistance) Fig.11, change of membrane properties (sodium and potassium channels) Fig. 9, Fig.10 & Fig.12, and effect of stimulation type, location, and time duration have been analyzed. Comparing to other studies stochastic models have shown that channel noise accounts for variability in action potential threshold at nodes of Ranvier and action potential initiation in membrane patches. The channel noise can affect the timing of the action potentials. Stochastic simulation show in this study that it's a few amount of ion channels that are open rather than the number of ion channels present that affect the AP. The effect of channel noise increases dramatically as neurons become smaller. The opening of the ion channels affects the membrane potential proportionally to the membrane resistance which increases with decreasing diameter [36]. A study done by Maarten HP et al showed that generation of action potential required high densities of sodium channels at the Axon initial segment (AIS). Their computer models required a sodium channel densities of 2,500ps um2 at the AIS [37].

This type of computational modeling is important in order to predict and investigate the properties of the optic nerve in more details. Another advantage of computational modeling is the possibility to stimulate morphologically reconstructed neurons in more detail, in this case, to implement more accurate and realistic structures of the optic nerve axon, to include layers/ wraps with different resistivity values representing pia matter, arachnoid layer and dura matter on the myelinated internodes of the axon. The main questions remain open for further studies: how to develop a more accurate model, an axon bundle (not just a single axon), in order to make it similar as the real optic nerve and how to run relevant simulations implementing extracellular modeling approach? The results of such a computational electrophysiological simulation could be useful in analyzing and may be helpful in explaining the results of real measurements, i.e., visual evoked potentials, and even relating them to the processes that are happening within the optic nerve during certain disease, e.g., multiple sclerosis.

It was also important to relate theoretical modeling with practical therefore realistic VEPS and

their processed signals were analyzed. These signals are very different and it is complicated to identify normal and abnormal cases. The signal of VEPs normally contains a prominent positive component P100, which occurs approximately 100 ms after the pattern reversal stimuli [7, 22]. Usually, there are a smaller negative component N75 with a latency of about 75 ms. the latency of P100 is affected by a number of factors including the brightness and contrast of the stimulus and the angle subtended by the squares in the checkboard. The two periods of life where VEP physiology varies a lot are the first few years during early maturation and after 60 years of age. The components of VEP like amplitude and latency of P100 appears to vary little with age from childhood through adult life, but after the age of 55 years, there is a slowing in P1 component and attenuation in amplitude [7].

Abnormalities such as retrobulbar optic neuritis restricted to one eye indicate a problem affecting that eye or its optic nerve and are particularly common in optic neuritis. The abnormality may take the form of a delayed P100 component, as demyelination increases over the years the VEPs in patients with MS become progressively slower eventually attenuating in amplitude [7]. MS is the most common cause of neurological dysfunction in young adults in the developed world. It is characterized by progressive physical and cognitive disability which can have a profound effect on patient's personal life. The etiology of MS is still unknown therefore it is crucial to diagnose MS early as possible to start the treatment which might reduce the progression of MS [28]. Altered VEPs with its typically delayed latency are a characteristic sign of damage of the visual pathway in MS and early onset of MS in some with optic neuritis. Analysis of optic nerve atrophy cases indicates that amplitudes of all waves were reduced in 74 % of patients using pattern stimulation. The latency of P100 varies due to the different degree of disturbances of nerve conduction [27]. In a study done to assess the correlation between morphological and functional retinal impairment in MS patients VEPs were performed on MS patients. VEP (15-min arc and 60- min arc checks) showed a significant delay in latency and reduction in amplitude which was concluded as patients with MS/ON displaying impairment of neural conductance in the visual pathway [29]. In our study of selected number of normal (27), ON (26) and MS (7) VEPs there was a significant difference in latency and amplitude between each VEPs. There was a delay in latency in ON cases and even more of a delay in MS cases compared to normal cases this can be due to decreased function of axon conductance along the visual pathway. Differences in mean latency values between and MS and ON is seen due to optic neuritis being an initial disease in many cases of progressive MS. The numbers also show a decrease in amplitude between normal cases and ON/MS cases this is because of loss in a number of axons along the visual pathway in optic nerve diseases. The difference in amplitude between ON and MS cases was noted to not be as significant as latency this points to the demyelination of the axons as the disease progresses and not a significant loss in number of axons.

CONCLUSION

Preliminary computational model of an optic nerve axon was created using the software NEURON. Parameters such as temperature, loss of myelin (increase in capacitance, decrease in resistance), change of membrane properties (sodium and potassium channels), location and time duration have an effect on cell's activity. The effect of any changes in the above parameters on cell's activity was demonstrated graphically as an action potential curve. It is important to note in this computational modeling changes in parameters such as sodium/potassium ion concentration and the diameter of the axon had consequences on the conduction of the axon. Relating back to the optic nerve diseases like Optic neuritis and MS, where the optic nerve demyelination causes conductance disturbances is proven digitally shown in Fig 11 and 12. In conclusion, this simple axon model shows the possibility of data-driven modeling and programming to understand and build a realistic optic nerve bundle using computational methods.

Visually evoked potentials were analyzed of cases with optic neuritis, MS, and normal cases. Normal cases of VEPs showed near normal values of latencies and amplitude as ISCEV standard VEP. In cases of optic neuritis there was a mild delay in the median value of latency compared to the normal cases of VEPs, and in MS the median value of latency showed significant delay. The amplitude is reduced for MS and optic neuritis cases but is somewhat equally reduced implying the number of axon loss was equal in both cases. The use of VEP was valuable in this study to demonstrate the demyelination in the visual pathways in diseases such as MS and ON as seen in many previous studies.

PRACTICAL RECOMMENDATIONS

Further programming skills are needed to use the NEURON software to build complex and realistic optic nerve models.

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