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Neuroplasticity pathophysoiological mechanisms underlaying neuro-optometric rehabilitation in ischemic stroke – a brief review

BULBOACA Adriana Elena [1], STANESCU Ioana [2], NICULA Cristina[3], BULBOACA Angelo [2]

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Corresponding author: **Ioana Stanescu,** E-mail: ioanastane@yahoo.com

[1] Functional Biosciences Department, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania
[2] Neurosciences Department, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania
[3] Ophthalmology Department, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, County Clinical Emergency Hospital, Cluj-Napoca, Romania

Abstract
Neuroplasticity is an essential phenomenon underlying on neurorehabilitation process, by which the brain can remodel the dysfunction consequent to a lesion. Ischemic brain lesions are the most frequent brain lesions often associated with visual function disability. Experimental and clinical studies established that visual function disability can impede the neurorehabilitation therapy efficiency. Neuro-optometric therapy has been proved to significantly improve the patient outcome after brain lesions. The pathophysiological mechanisms underlying this process are yet to be deciphered. Current knowledge regarding the pathophysiological mechanisms involved in ischemic lesions and neuroplasticity as a reparation process offers real support to a more efficient neurorehabilitation therapy that can contribute to the improvement of life quality in stroke patients.

Keywords: *neuroplasticity, neuro-optometric rehabilitation, ischemic stroke,*

Introduction
The human brain has a large area designed for visual function consisting of two visual systems: one stream (ventral stream in the occipital cortex) vision for perception and one stream (dorsal stream in the parietal cortex) vision for action. The brain areas that control the visual information are at least 10 different specialized brain regions that are involved in controlling separate types of behavior regarding the guiding eyes and head movements towards an environmental object and adapt the body movement to the walking direction or even for a standing position (1). An important role in these actions is also played by subcortical structures such as pretectum and superior colliculus (2). There is another important factor that has to be taken into consideration represented by aging. Aging processes add ophthalmologic disorders such as lens opacities, age-related macular degeneration, or microangiopathic retinal vessel changes that can distort the image perception (3). Still, there is a specific individual variation of visual function pathophysiology that are orientated the practitioners to carefully assess each patient to indicate the most suitable individual treatment, according to individual clinical and paraclinical examination (4). This is specifically indicated in the neurorehabilitation process since the brain lesions can be complex and with various functional consequences and disabilities. Together with exercise interventions balneological procedures and other neurorehabilitation therapy, neuro-optometric methods can contribute to more efficient neurorehabilitation in ischemic stroke patients (5-7).
Neuro-optometric treatment comprises all the methods addressed to visual disabilities (perception, processing, motor disabilities) resulting from visual system disorders. Since the brain activity is highly orientated on visual information processing starting with the cortical perception of visual information and transmitting process to the specialized networks, the brain neuroplasticity offers various opportunities to set a new point of functionality by therapeutic methods to improve the visual system disabilities after brain damage (8). Various visual disabilities resulting from brain lesions can be alleviated by neuro-optometric rehabilitation (9,10). These are represented by cranial nerve lesions that can lead to disabilities such as oculomotor imbalances resulting in acquired strabismus and diplopia, convergence/accommodation, paresis/paralysis,

visuospatial dysfunctions, visual perceptual, and intracranial optic pathways lesions (11). The tree systems (visual, somatosensory, and vestibular systems) contribute to inputs that assure postural control and motor functions. None of these systems can provide alone the information needed for a precise motion and body position into the spatial environment. Consequently, the contribution of each system is essential and has a considerable effect on the outcome of the neurorehabilitation process. The visual system contributes to the orientation of the body in the space, assesses the position of the body and the spatiality of the objects around to transmit adequate information to the brain. The visual system function, after the ischemic stroke, is contributing essentially to prevent the patient to fall and, further, contribute to the motor coordination and movements into space (12). There is a degree of redundancy in the contribution of each system to postural balance. For a healthy subject, the visual system has more influence on the standing position for posture maintenance than the vestibular system (13). The vestibular system has more influence in moving, and stabilization of the body in the standing position (especially the head and the trunk) (14). In a healthy subject, visual system inputs can be balanced by vestibular function but the balance of the posture is more difficult (14). This evidence can be an important contributor to neurorehabilitation success. Opposite, the visual system can only partially compensate for the dysfunction of the vestibular system, the rehabilitation process being even slower in this instance (15).

Neuroplasticity applied to neuro-optometric rehabilitation in ischemic stroke

Perception is an essential process in vision function. The Eye-brain unit is unreplaceable for a perfect motor function commended by the cortex. Brain diseases that interfere with visual pathways can alter the optical perfect imagine. Neuroplasticity is the phenomenon of the brain's ability to reorganize the structure and molecular function to get new neural networks to ensure the response to environmental changes (16). Since visual function pathways are completely developed at the same time as the nervous system, the neuroplasticity phenomenon has to be addressed, in adult time, to a developed neural network. Despite the fact the classic concept of neuronal regeneration theorized the low capacity of neurons to regenerate, the new researches bring evidence of neural repair possibilities and a new generation of neuronal cell formation in adult life (17). The human brain possesses high capacities of neuroplasticity which has as a consequence the efficiency of the neuro-rehabilitation process. Since visual pathways are connected with a complex network with multiple cortical areas and are essential for various functions, brain plasticity can contribute to restoration at least partially of impaired functions. Cerebral reorganization after stroke consists of the overactivation of healthy neurons, synapses, and neuronal networks that can substitute the functions of affected brain tissue. These activations are often bilateral, involving sensory-motor, premotor, parietal, prefrontal areas, brainstem, and cerebellum. The initial overactivation was demonstrated to be more intense in those patients with the greatest clinical deficit (18). Various non-invasive techniques to assess brain functions (functional magnetic resonance imaging, positron emission tomography, and brain stimulation with transcranial magnetic stimulation) bring new inside in the neurorehabiltation process and demonstrated the rehabilitation therapies efficiency (18).

The impact of the revolution of science in neurorehabilitation as a basis for the neuroplasticity phenomenon and neural regeneration. Neurorehabilitation term was increased in scientific literature started with 1980, gradually accelerated in the last years. Application of basic science and evidence-based medicine on neurorehabilitation methods research improved their efficiency with significant benefit for the patients (19). Even the clear borders are yet not established, two types of neuroplasticity were studied: structural neuroplasticity and functional synaptic plasticity. The therapeutic manipulation of the neuroplasticity phenomenon relies on scientific studies starting from molecular levels of neuronal networks repair processes due to neurotransmitters and growth factors contribution and continued with clinical trials. Therefore, the achievements in the neurorehabilitation area are based on experimental studies designed to explore the anatomical and physiological pathophysiological substrate of the lesions induced by neuronal ischemia, with complex consequences on neuronal networks (20).

The neurorehabilitation process has to be addressed to repair methods due to the neuroplasticity process and to complete the best functional outcome. From the structural point of view, the brain has a lot of connections through synapses, building new connectivities even in normal conditions, to adapt to the environment and the daily tasks of the patient. Therefore, the brain is the proper organ where the plasticity phenomenon can exert and develop according to the new living condition or with the occurred lesions (21). Skill learning has previously demonstrated to imply the increase of synapses number and the synaptic activity, by the synthesis of a higher amount of neurotransmitters (22). To this synaptic plasticity, an increasment of dendrites number is also added (22). According to the intensity of stimulation, the synaptic activity can be modulated and synapsis efficiency can change, according to the new conditions (23,24). This extraordinary power of brain structure and function modulation can be very useful in the rehabilitation process for building new connectivities and empowering synaptic functions to replace the disability induced by brain lesions. Pharmacological manipulation of synaptic activity can be also a method to reshape the functional brain map by synaptic plasticity (25). Both γ-aminobutyric acid (GABA) and glutamate (through NMDA and AMPA receptors) can contribute to the efficiency of synapsis, facilitation or inhibiting the synaptic activity to build new neural networks for a diminished or lost function (25,26). The precise correlation between synaptogenesis and neurotransmitters synthesis and the neuroplasticity phenomenon linked to the neurorahabilitation process has to be further established.

Neurorehabilitation is a complex process that involves a specialized team, working interdisciplinary and having as a target the best possible treatment addressed to recuperate the lost or diminished functions. Even the rehabilitation process is slow and the achievements are not the desired ones, the socio-economic impact of any grade of re functional recovery can be considerable. A complex condition related to the patient's disability has to be approached by different medical specialists to get the most efficient rehabilitation program. This paper aimed to facilitate a brief review of the main technics addressed to the contribution of neuro-optometric rehabilitation to the entire neurorehabilitation process, and, finally to the quality of life improving in stroke patients.

Perceptual disorders and their rehabilitation

Perceptual disorders are represented mainly by unilateral spatial neglect (USN), reported in about 25 % are commonly associated with right parietal lesions (7). Patients with USN have a slow progression of rehabilitation results and usually need assistance after discharge. The current knowledge from the literature review shows that the presence of USN is an independent predictor of the functional outcome being associated with poor rehabilitation results (27). There is no consensus about the efficiency or benefits of different rehabilitation techniques, nor about the mechanisms that can constitute the substrate for the neuronal network of USN onset. Therefore, due to imprecise theories that explain the USN presence, the rehabilitation therapies' efficiency is only related to different experiences and clinical studies of several researchers focused on this field. The understanding of the pathophysiology of USN will be strongly related to the development of more efficient neuro-rehabilitation therapies. Patients with USN demonstrated that hemi-intention is implied in daily living activities, their performances being lower than ischemic stroke patients without USN (28).

The performances of daily living activities are strongly correlated with somotosensorial, motor, and visual function status. Daily living activities such as dressing or walking are less affected than hygiene maneuvers, eating, or using the telephone (28). Visual disability rehabilitation associated with USN can improve stroke patients' evolution and contribute to a better neurorehabilitation outcome (29). Small sample sizes are the main limitations in many published trials. Most of the published studies used stimulation of the direction of gaze towards the left, using top-down techniques where the patient has to follow the therapist's indications (30). According to Azouvi et al, there are four methods of USN rehabilitation, based on theoretical concepts that tried to explain the USN underlying mechanisms: enhance the attention of neglect behavior by top-down mechanisms; sensory stimulation by bottom-up methods; inhibitory processes modulation methods; arousal enhancement (29). All of the technics have no concerns of efficiency, but reported results are encouraging and since there is no optical rehabilitation therapy stated as a basis of visual recovery function, each study deserves attention and should be developed for new data collection. The interventions consisting of strategies addressed to the enhancement of the attention towards the neglected side stimulus, correcting the body position to better visualization of the stimulus, spatial representation of the patients to improve visual field and a to increase awareness to the visual stimulus, optometric corrections with prisms, eyepathcing, hemispatial glasses, caloric stimulation could be valuable methods to improve the patient attention and finally neurologic rehabilitation. The efforts made in this direction are focused on better neurological rehabilitation after ischemic stroke, and improvement of USN condition by visual function recovery could be a valuable helpful step.

One of the most used optometric technics consists in the modulation of spatial cognition by prism correction therapy. Most of the programs include one or two daily prisms optometric treatment, during the day – usually during the functional activities (over 2 weeks period) (31,32). The technique consists of three steps (31,32):

- assessing the patient's visual abilities without prisms (basal assessment); this step offers the reference values that need to be compared with after therapy visual outcome.
- prism prescription (the prisms has to deviate the environment with 10º to the right); the patients will gradually improve his error, after the prisms treatment
- assessment of the visual abilities to follow the visual target after the prisms treatment.

This simple non-invasive period has the advantages to improve spatial neglect by manipulating the plasticity of sensory-motor cortical networks through activation of associative cortical regions (during the prism treatment). There are no demonstrated effects following exposure to the prism treatment towards the left, therefore there is a specificity of this treatment that is direction-dependent

(33). Therefore, prims treatment is a promising treatment in neurorehabilitation therapy via the improvement of the visuomotor system. Adaptive neuroplasticity changes produced by prisms exposure, balancing the ischemic damages produced by brain hypoperfusion and ischemia. Frontal and parietal structures involved in these dysfunctions and consequently hemispatial neglect will undergo plasticity phenomenon and the molecular mechanism based on this phenomenon has to be still investigated (34). Improving the spatial neglect after prisms therapy proves the neuroplasticity ability to contribute to new neuronal network formation that is responsible to recuperate the lost functions after brain injury (35,36).

Sensory disabilities due to cerebral blindness

The pathophysiology of sensory disabilities is depending on permanency or temporarily visual disabilities. If light deprivation or cerebral blindness is permanent, is followed by the inability to avoid obstacles, tracking moving objects, optokinetic nystagmus, visuomotor behavior changes. Cerebral blindness is defined as bilateral vision loss, secondary to interruption on visual pathways, posterior to lateral geniculate nuclei (37). Cortical blindness (as a part of cerebral blindness) refers to the loss of vision without any ophthalmological diseases and with normal pupillary light reflexes due to bilateral lesions of the occipital cortex (38). Stroke and other causes can cause cerebral blindness. The most common causes that can produce cerebral blindness, besides stroke are represented by occipital lobe epilepsy, hyponatremia, severe hypoglycemia, vasculitis, hypertensive encephalopathy, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). Some of these etiologies can be reversible (39). The ophthalmoscopic examination reveals no abnormalities. The pupillary light reflex can be impaired, depending on the etiology of sensory disability (40). All visual sensorial parameters such as visual acuity, visual field, contrast sensitivity can be altered according to the topography of the lesions. Still, the human brain of patients with cerebral blindness possesses remarkable behavioral and neuroanatomical, and functional compensatory mechanisms for visual disabilities improvement, based on brain plasticity (41).

Conclusions

The effectiveness of neurorehabilitation methods could be improved by adding an important contributing element such as visual rehabilitation. Visual rehabilitation in stroke patients has as an important underlying process represented by brain plasticity. Functional augmentation can be achieved either by specific visual therapies or pharmacological methods addressed to improve synaptic activity and new neuronal network building and consolidation. New clinical studies that can describe the pathological mechanisms associated with visual disabilities after cerebral ischemia could be specifically useful to improve the life quality for stroke patients.

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