Early Intervention in Special Education and Rehabilitation

Beograd 2016.

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THEMATIC COLLECTION OF INTERNATIONAL IMPORTANCE

Belgrade, 2016

Early Intervention in Special Education and Rehabilitation
Thematic Collection of International Importance

Publisher
University of Belgrade – Faculty of Special Education and Rehabilitation
Publishing Center of the Faculty

For publisher
PhD Snežana Nikolić, Dean

Processing and printing
Planeta print, Belgrade

Cover design
Boris Petrović, MA

Technical Editor
Biljana Krasić

Circulation 150

ISBN 978-86-6203-086-3

By decision no. 3/9 from March, 8th 2008. The Teaching and Research Council of the University of Belgrade – Faculty of Special Education and Rehabilitation initiated Edition: Monographs and papers.

By decision no. 3/122 from August, 30th 2016. The Teaching and Research Council of the University of Belgrade – Faculty of Special Education and Rehabilitation has given approval for the printing of Thematic Collection "Early Intervention in Special Education and Rehabilitation".

BRAIN PLASTICITY: DEVELOPMENTAL AND CLINICAL ASPECTS OF IMPORTANCE FOR EARLY INTERVENTION

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SUMMARY

Brain plasticity is not only accommodation of young brain tissue that can change own characteristics, but process that occurs during whole life period, even during old age. Mechanisms of plasticity incorporate: formation of new axon terminals and new synapses, change in neuronal membrane excitability, change in the balance of excitation and inhibition, a long-term potentiation (LTP) or long-term depression (LTD). Molecular mechanisms of brain plasticity encompass neurotrophins, NMDA receptors, the role of calcium ions and calcium channels, free radicals and lipid peroxides. Neuroplasticity also may lead to destabilization of neuronal connections therefore without control of this process plasticity becomes excessive and as a result pathological destabilization and disease may occur. Compensation, which is reorganisation of behavior aimed at minimizing or circumventing a particular disability, is also possible due to process of neuroplasticity. Although, without any doubt, younger and growing brain has greater potential for compensation of damage and higher ability for correction of dysfunctions.

Here we discussed biological potential of brain plasticity and importance of this process for early intervention is special education and rehabilitation. Early intervention will have full effect only if it is applied well-timed, otherwise the effects will be reduced. Accurate early intervention should consider: definition of optimal time period for beginning of early intervention; composition of proper protocols for methods of stimulation and systemic exercise; and application of these measures in connection with prospective biological potentials.

Key words: neural plasticity, brain, rehabilitation, early intervention, motor impairment, cognition

INTRODUCTION

Theory and practice of special education and rehabilitation was under dynamic influence of social changes for last few decades. Therefore, it was mainly focused on solving acute problems of children with impairments and their families. Model of education (special and inclusive education) and content of rehabilitation, as well as systemic measurements, are determined by the state policy. Transitions from one

model of education to another model of education bring children with impairments and their families in situations that are often dramatic. Solutions for their problems determined by professionals were therefore often forced.

We believe that changing focus from these measurements towards inner scientific aspects would be much more appropriate. Reflection of biological foundations, as key determinants for early determination, represents reconsideration of connections between methods of special education and rehabilitation and their influence on children with impairments. Validity in acceptation and application of certain methods should be dependent on their influence, not only on magnification of functional capabilities of children with impairments, but also on whole biological development.

Terminological considerations

Brain plasticity is, according to the theory of special education and rehabilitation, state of biological readiness and susceptibility to influences from environment that affects brain. Development in children with impairments is affected and interrupted with some biological factors. They develop on "qualitatively different way" (Vygotsky, 1996). Starting from these facts, from centuries ago, methods of education and rehabilitation were created and oriented towards certain specific impairment in development. As a consequence, methods of education and rehabilitation were developed for children with intellectual impairment; children with motor impairment; children with visual impairment; and children with hearing impairment. Later it became obvious that inclusion of these children in education and rehabilitation as early as possible gives the best results. From this observation term "early intervention" developed in special education and rehabilitation. Early intervention imply: methods, techniques and procedures of stimulation and systematic training whose main goal is to achieve and/or recover specific functions.

Neuroplasticity is defined as capability of neural system that enables functions and structure to be modified according to the requirements of surroundings and inner organism stimuli. Neuroplasticity encompasses changes in structure, especially strengthening of synapses, which further leads to final modifications in function (Porto et al., 2015; Zheng et al., 2014). Brain plasticity is not only accommodation of young brain tissue that can change own characteristics (Krstić, 2008), but process that occurs during whole life period, even during old ages (Porto et al., 2015).

Four major types of plasticity could be observed: adaptive plasticity, impaired plasticity, excessive plasticity, and the 'Achilles heel' of the developing brain (Eriksson et al., 1998). Mechanisms of plasticity incorporate: formation of new axon terminals and new synapses, change in neuronal membrane excitability, change in the balance of excitation and inhibition, a long-term potentiation (LTP) or long-term depression (LTD) (Kulak & Sobaniec, 2004). Neuroplasticity might have positive, but also some negative effects on an individual. Plasticity in axon growth could be observed in prenatal but also in postnatal period as a consequence of brain trauma (Huttenlocher, 2002). Failure in establishment of connection from one neuron to other neuron doesn't have always as a consequence resorption of that neuron. Outcome of this process could be also strengthening of connections to other different neurons. This phenomenon

mainly occurs in cells of motor cortex where apoptosis is less expressed comparing to subcortical areas and especially comparing to spinal cord.

Synaptogenesis also occurs according to hierarchical principle. Development of secondary sensor and associative areas depends on development of primary sensor areas, and they depend on sensor input. This way surroundings may affects on brain development as on development of brain functions. Development of one brain area also depends on input from the other cortical area. Number of synapses that one neuron from prefrontal cortex area form is more than tens of thousands (up to 80.000) which confirms complexity of processing information in this part of telencephalon (Huttenlocher, 2002). That is why neuropil has highest thickness in this part of brain. Number of synapses that neurons form in other parts of the brain is lower. In the state of mental retardation dendritic arborization is lower comparing to normal healthy situation. Simulative surroundings induce increase of dendrites number and their size which means that arborization is higher. Balance between excitatory and inhibitory synapses is quite important for dendritic arborization and synaptogenesis. Besides, local conditions and different trophic factors could change purpose and function of certain neuron according to the theory of neuroplasticity. Together with development of synapses, fast development of brain functions occurs. Organized and proper time intervention applied in children with impairments could stimulate development of dendritic arborization and synaptogenesis, which further increase their biological potential.

Molecular mechanisms of brain plasticity encompass neurotrophins, NMDA receptors, the role of calcium ions and calcium channels, free radicals and lipid peroxides.

- *Neurotrophins* belong to a family of secretory proteins that promote neuronal survival and differentiation, but also have essential roles in neuronal survival and synaptic plasticity (Sheng & Kim, 2002). The local and synapse-specific modulation, together with preference in active neurons/synapses, proposes that neurotrophins must mainly regulate active synapses with little or no effect on nearby less active synapses (Thoenen, 1995).
- *NMDA* (N-methyl-D-aspartate) *receptor* and AMPA (a – amino – 3 – hydroxy–5 – methyl – 4 – isoxazole propionate) – type glutamate receptor activation are engaged in synapse formation and stabilization. The NMDA-type glutamate receptor plays a special role in this process because it involves synchronized stimulation by glutamate and membrane depolarization caused by stimulation of adjacent excitatory receptors. Synapses are shaped by the balance of excitatory and inhibitory pathways entering the brain from primary sensory modalities such as hearing, vision and somatosensory sensation, as well as by the activity of intrinsic circuits. These pathways use glutamate as their neurotransmitter. Increased AMPA receptor numbers are also associated with synaptic plasticity (Kulak & Sobaniec, 2004).
- Long-term potentiation (LTP) known as cellular mechanism of learning and memory is defined as a long-term enhancement of synaptic strength resulting from repeated activation of that synapse. In several regions of the brain, LTP has been shown to involve activation of glutamate receptors and calcium influx into the dendrite of the post-synaptic neuron. Facts also suggest that calcium release from endoplasmatic reticulum (ER) stores can promote LTP (Kulak & Sobaniec, 2004).

- *Free radicals (FR) and lipid peroxides (LP)* are the byproducts of cellular metabolism that have been associated with neurodegeneration, however a relation between FR and modulation of synaptic plasticity has been proposed. High concentrations of FR attenuate synaptic transmission and LTP, while superoxide radicals are proposed to be engaged in LTP induction (Knapp & Klann, 2002).

Biological foundation for early intervention could be found at the level of molecular mechanisms. Neutrophines, NMDA and AMPA receptors, free radicals and lipid peroxides are some of the actors in this process.

Discovery of neurogenesis in hypocampus of adult brain at the end of XX century (Eriksson et al., 1998) changed our attitudes concerning neuroplasticity in adults. Before this discovery it was believed that number of neurons that humans get at birth declines during the life period. Today, it is estimated that number of newly formed neurons in adult person per one day is about few thousands. There is hypothesis that newly formed neurons: increase capacity of memorizing, decrease interference between remembered data and add information about the time, but that they also regulate stress situations. It is believed that antidepressants act by increasing hippocampal neurogenesis. Similar effects comes from physical training, learning, changing of environment, ad potentially even health diet. In contrary, stress decrease the number of newly formed neurons, as well as sleep deprivation, through mechanism of glucocorticoid increase. Neurogenesis could improve plasticity of the brain and therefore to regulate our behaviour (Castren, 2005, Павловић, 2012). These data broaden possibility for early intervention in adults and invalid persons. In the case of acquired invalidity that occurred during productive life period, early intervention is applied as early as possible.

"Neuronal recycling" hypothesis (Dehaene et al., 2004) implies to certain limitation of primate brain architecture which is under genetic control with limited variability and plasticity. This means that every cultural object must find own neuronal niche among already existed. The brain adapts to our cultural environment through "recycling" or modifying purpose of already established cortical substrate or its genetic predisposition. Features of our neuronal apparatus (brain architecture) will determine the speed and easiness of cultural learning. Some brain structures for speech are activated through short oral sentences in babies only three months old (Dehaene-Lambertz et al, 2002). This model is compatible with theory of socio-cultural development made by Vygotsky (Vygotsky, 1996) that point to necessity of inclusion of children with developmental impairments in their age groups. Brain plasticity is determined by structure rearrangements and it is present during whole life period (Richardson et Price, 2009). New skills that are adopted induce structural modifications that are present while the skills are used. Influence of speech on brain structures begin very early in life and continue through life. Reading is skill that is adopted consciously; it changes brain structures and demands coordination of different brain areas. Text is recognized as different type of stimulus out other visual stimuli. Importance of speech for development of cognition was previously discussed by Vygotsky (1977) and Piaget (2005). This characteristic of the brain we could consider as capacity of children with impairment to develop while they are under organized influence from environment regardless they are in educational system, social care or health care system. Our

experiences show that absence of stimulation and systematic training in children with impairments and invalid adults leads to behavioural and functional regression as a consequence of probably biological regression.

Developmental aspects of brain plasticity

Developmental impairments in children could be motor impairments and psychological impairments. It is estimated that about 7,9% of children under 18 years old have some impairment that decrease they capabilities. From this number about 29,5% of children have learning difficulties, 6-7% mental retardation, 13,1% impairment of speech, 6,3% some emotional disorders etc (Osmon et al., 2008). Brain development starts during fetal development and continues after birth, but also encompass adolescence. Myelinisation, synaptogenesis, and synapse modification in subcortical grey matter, limbic and prefrontal structures continues till third decade of life (Snyder, 2006). Neuropsychological problems in childhood and adolescence are therefore specific because developmental factors are still persistent. Damage that was introduced early in life does not always show effects immediately because all brain structure are not formed, neither their functions. Therefore, certain dysfunctions are not present until specific period of life. On the other hand, brain plasticity that is specific for development of the child enables under certain conditions compensation of present dysfunctions. Brain plasticity during developmental period enables recovery after injuries based on three mechanisms (Kolb & Whishaw, 2003): 1. reorganization of rest undamaged or less damaged neural circuits which leads to recovery but also to development of disturbed function; 2. creation of new neural circuits in preserved brain structures and in some cortical areas; 3. creation of new neurons and glial cells that exchange damaged brain cells (these cells are produced by stem cell that persist in some brain regions through adult period).

Brain plasticity and motor skills

The cellular mechanisms responsible for neural plasticity in humans are still under dynamic investigation. There are four different mechanisms of motor cortex plasticity. A change in the balance of excitation and inhibition that can happen very quickly is the first one. Second mechanism, that is also quick, is based on strengthening or weakening of existing synapses, in processes such as long-term potentiation or long-term depression. A third process is a change in neuronal membrane excitability, and the fourth, that require most of the time, is anatomical changes.

Two research groups working on motor systems demonstrated that after deafferentation of a limb reorganization of the sensory and motor cortex may occur (Donoghue, 1990; Merzenich et al, 1984). Furthermore, deafferented cortex did not stay idle but was taken over by body representation adjacent to the deafferented body part. Research group of Hallett (Hallett et al., 1999) demonstrated that motor cortex representation of the muscles proximal to the amputation had expanded into the area of the motor representation of amputated part.

Mano et al. (1995), showed that projections from the biceps region of the motor cortex can be directed to the spinal cord neurons of intercostal nerves in patients with brachial plexus avulsion upon the intercostal nerve is anastomosed to the musculocutaneous nerve. What is more, they have demonstrated that the biceps can eventually be controlled separately from respiration, which demonstrates that control of the spinal neurons has been completely altered as a result of the brain plasticity.

Motor function in the limb contralateral to the excised hemisphere experiences a substantial degree of recovery, particularly when surgery is performed at early age. Ipsilateral and contralateral representations in the remaining hemisphere are topographically differentiated; ipsilateral representations have a more anterior and lateral scalp distribution, which suggests that the normal ipsilateral representation has become more influential in these patients and is likely to have contributed to the recovery (Hallett et al, 1999).

It seems that there is a continuous combat for the control of each neuron among its various inputs, therefore the purpose of each neuron or neuron pool will be determined by the dominant inputs resulting from several dynamic processes. For example Hallett et al. (1999) showed that cortical representation for the reading finger in proficient Braille readers is enlarged at the expense of the representation of other fingers. The same investigators also demonstrated the rapid modulation in motor cortical outputs in relation to preceding activity. In addition, theory of cross modal plasticity demonstrated that cortical areas normally reserved for one type of sensor modality that is deprived (i.e. vision) might be activated by other presented sensory modalities (i.e. tactile) (Sadato et al, 1998).

Application of described principles of brain plasticity should be feasible to progress process of spontaneous recovery. For example, use of arm is critical for establishing and maintaining cortical representation of that limb. In physical therapy and early intervention certain balance between accomplishing tasks of daily living and improving functions of injured limb should be established.

Motor activity directly influence sensomotoric representation in the brain as well as senso-motoric pathways that are in direction connection with brain. That is why motor activities lead to establishment of stabile synaptic connections, formation of sensomotoric pathways and enlargement of area of sensomotoric representation. This benefit also stands for children with impairments during their growth and development. It is important to point that organization of motor learning and performance of motor activities are different between certain types of impairment. Does this leads to different effects on brain biology should be further investigated.

Brain plasticity and cognition

Brain development and plasticity could be defined as complementary, but relatively independent processes. Development of normal brain is strictly defined by genetic factors, genes that are expressed in both neurons and glial cell, which are strongly influenced by input from the surroundings of an individual. In the case of insult or injury the system has the capacity to react flexibly, thus circumventing functional deficit.

Out of many cognitive functions it seems that for humans *language* has an essential function. This claim is supported by the fact that under conditions of early brain insult, it is preferentially supported at the expense of other (specifically visuospatial) functions. If there is injury to traditional left hemisphere language areas, homologous areas of the right hemisphere are recruited for language, thus "crowding" out spatial functions that normally would have been mediated by these areas (Teuber, 1974). Alternative to the hypothesis of crowding is the notion of functional redundancy, which proposes that early in development there may be multiple language-specific neural systems. Therefore, if the primary language system is injured or lost, these secondary systems are available to mediate language (Stiles, 2000).

Speech production could be routine, automated, and the one that needs special engagement. Speech also encompass learning and processes of neuronal plasticity, especially during childhood, at the time that vocal apparatus of the child is formed. Vygotsky and Piaget were also discussing importance of speech for cognitive development. It is well known that children with impairments have also problems in speech and language development. The nature of these impairments is different and require specific treatment. Together with development of speech and language, cognitive functions will further develop and enable formation and preservation of social contacts.

Visual stimulation implies stimulation of receptors in the eye; neural pathways; and analytical centres in occipital region of the cortex. If this stimulation is further supported with explanations or instructions then other processes like perception, remembering, thinking etc are activated. Engagement with music has important positive developmental effect on brain functions, especially on language skills (Bidelman & Alain, 2015). There are some indications that these neuroplastic causes have long effect even during old age. It is demonstrated that musical education slowdown decrease of auditory processing in older people. This effect could be observed in phonetic capabilities and more precise cortical responses on speech (Bidelman & Alain, 2015). Musical education affects neural mechanisms of phonetic information processing. This knowledge has consequences on application of intensive early stimulation of the brain. Musicotherapy, therefore could be used in therapy during whole life period, including also in psychogeriatric patients.

Neuroplasticity and developmental impairments

Neuroplasticity during childhood and adolescence

Brain development starts during embryonic development, but continues after birth and during adolescence. Myelinisation, synaptogenesis and modification of synapses in the areas of subcortical grey matter, lymbic system and prefrontal cortex continues until third decade of life period (Snyder, 2006).

Neural processes included in plasticity are neurogenesis, apoptosis and synaptic plasticity dependent on activity. As a result of plasticity children are more capable for adoption of different knowledge and skills comparing to adults (Johnston, 2009). This phenomenon is present during learning of foreign languages, learning to play musical

instruments and during motor learning specific for sport skills, as well as during recovery from brain lesions.

During development brain experience affects intensive growth of synapses that later further develop or regress (Johnston, 2009). The choice between wanted and unwanted synapses occurs according to interaction and experience with the surroundings. Early development of synapses is especially intensive in occipital region of the brain. The similar process later occurs in parietal, temporal and frontal region of cortex. This changes correlate with development of behaviour in children.

Dysfunctions of plasticity are quite often in neurological disorders of children (Johnston, 2004). Child's brain is superior in plasticity comparing to the brain of an adult because of more intensive neurogenesis, more effective apoptosis, dendritic arborization and adaptation. Therefore, children and adolescents are capable to learn foreign language without accent and to recover much faster from brain injuries.

Most of the brain structures have neuroplastic potential in early postnatal period. After this critical period, neuroplastic potential decrease. Increased number of stimuli from environment leads to increase in serotonin transmission and increase of number of neurons that produce BDNF. As a consequence the level of neurogenesis in the brain is increased. These processes have important implications on development of brain functions in children with impairments. Also, these processes are important for early treatment in special education and rehabilitation.

Developmental disabilities and brain plasticity

Brain plasticity might be related to several disorders in children: cerebral palsy, epilepsy, hypoxic-ischemic encephalopathy, neurofibromatosis, sclerosis tuberose, phragile x syndrome, developmental types of intellectual disorders, cretinism, Coffin-Lowry syndrome, Rett syndrome.

Children with developmental disabilities have certain potential for brain plasticity that is determined by their biological features. Also, on behavioral and functional level there are some potential for further development.

Down syndrome

Down syndrome is consequence of chromosome 21 triplication, and this is the most frequent type of intellectual disability. Murine model of this syndrome showed decreased number of neurons in cerebellum and hippocampus (Insausti et al., 1998). This model also demonstrated reduced dendrite sprouting and changed anatomy of all neuron extensions (Necchi et al., 2008). Disturbance in neurotrophic factors leads to degeneration of basal telencephalon that is main source of cholinergic innervations of the brain. The same process might be observed in patients with Alzheimer's disease that develops in all Down syndrome patients after they get older than 40 years (Павловић, 2008). Total effect of these processes is preponderance of inhibition in neuronal circuits of temporal area with permanent disturbance of synaptic plasticity (Baroncelli et al., 2011). Potential therapy would be decreasing of brain inhibition.

Autistic spectrum disorders

Autistic spectrum disorder has heterogeneous etiology. Common feature for all forms of autistic spectrum disorder is dysfunction in domain of communication, social interactions, behaviour and sometimes in cognition (Павловић, 2014). Several genetic factors are related to development of autistic spectrum disorder mostly. Mostly they are under control of genes that codes for different subunits of GABA receptors and genes that are responsible for control of maturation of synapses. Personal experience is less important. Dysfunction is present at neural circuits that control social cognition and behaviour, emotion, speech, and thinking (Baroncelli et al., 2011). In large number of patients autism is followed with epilepsy which points on disbalance of glutamatergic excitatory in GABA inhibitory system. Hyperactivity of amigdala was detected with increased and non-effective neuroplasticity. Due to this effect synaptogenesis and fine synaptic adaptation necessary for normal development were affected.

Dyslexia

Dyslexia is relatively frequent specific disorder of learning skills (Павловић, 2014). It was demonstrated that children with dyslexia have pathological variability of sensor and cognitive aspects of hearing (Hornickel et al., 2012). Devices that help in stability of hearing perception improve acoustic attention and clearness of pronounced words. Application of these devices in classroom during one year significantly improved reading skills and phonological discrimination in children with dyslexia.

Cerebral palsy

Cerebral palsy is long life neurological disorder that affects primarily motor functions, usually more from one side (Reid et al., 2015). Physical therapy, occupational therapy, speech and language therapy, along with adaptive equipment, are popular forms of treatment for children with cerebral palsy. Used within a coordinated, comprehensive treatment plan, therapy plays a vital role in managing the physical impairment while optimizing mobility. Critical period for application of therapy are first years of development when brain plasticity has highest capacity (Reid et al., 2015). Neuroimiging might be used for monitoring of therapy.

Cerebral palsy of children has different causes, but they all directs to lesions in brain structures and brain functions (Павловић, 2014). Normal development in these children is not usual because of impossible performance and learning of movements or because of its significant limitation (Lee et al., 2014). Cortical plasticity is absent in the part of the brain that controls movement of dysfunctional extremity, therefore dysfunction further enlarge. New methods of rehabilitation as comprehensive hand repetitive intensive strengthening training system enable encouragement of neuroplasticity in children with spastic hemiplegic form of cerebral palsy in children. Functionality of these methods is demonstrated using functional magnetic resonance. It was also showed that muscles improve in structure and function as a effect of the therapy. The same effects were observed in healthy adolescents that had physical training comparing to the other group of adolescents with sedentary habits (Pareja-

Galeano et al., 2013). In this study different neurotrophic factors were followed: brain-derived neurotrophic factor (BDNF), serum insulin-like growth factor-1 (IGF-1), cAMP response element-binding (CREB) and activation in peripheral blood mononuclear cells – PBMCs. Levels of BDNF and IGF-1 were significantly higher in adolescents on intensive physical training programme comparing to adolescents with sedentary habits. Early learning of skills has positive structural consequences in grey matter of children. The same might be observed in children with cerebral palsy (Johnston, 2009).

Hearing impairment

There are several scientific reports showing that children with hearing impairments demonstrate faster speech development if they were diagnosed and habilitated before they reach 6 months old comparing to other group of children with the same impairments diagnosed and habilitated in later period of life. If child with hearing impairment younger than 6 months starts with the therapy like amplification; voice and speech therapy; and habilitation therapy; then significant improve might be expected. There are several benefits that results from this therapy. Chances for normal development of the child increase and negative effects of late diagnostics like total hearing loss are eliminated. Moreover, chances that child will attend regular school are higher therefore costs of education decrease. Later diagnostic of hearing impairment could have serious consequences on child's development (Finitzo & Diefendorf, 1997; Gopnik, Meltzoff & Kuhl, 1999; Kuhl et al., 1992; Sininger, Doyle & Moore, 1999; Vohr et al., 1998; Watkin, 1996).

Researchers from Garvan Institute of Medical Research from Australia investigated structural changes in auditory cortex at congenitally deaf animal models. They studied effects of early intervention on brain. Upon cochlear implantation performed on these animals it was detected that reestablishment of auditory nerve activity with electric stimulation leads to almost total normalization of previous dysfunctions in auditory cortex. Therefore, reestablishment of auditory nerve function through electric stimulation of cochlear implant recovers cortical changes that are consequences of deafness (Ryugo, 2015).

Colucci (2012), concluded that there are three major types of morphological changes that are results from neuroplasticity. First, synaptogenesis and sprouting are processes that further improve formation on new synapses between neurons. Pruning occurs when stimulus is inhibited. The rule "use it or lose it" here applies not only on function but also on morphological changes of auditory cortex of the brain. Relations between neurons could be reorganized and re-established if there is appropriate stimuli in next few weeks. Second, neuron migration enables adequate rewiring between neurons. This is specialized process that have important role in formation of tonotopic organization of whole auditory system. Finally, there is neurogenesis or formation of new neurons in fetal and early postnatal period. Unfortunately, neurogenesis is not specificity of adult period. Early cochlear implantation enables development of newly formed neurons in auditory system and improves establishment of synapses. For that reason, it is clear that negative effects of sensory deprivation could be avoided and that is main precondition for process of learning and habilitation (Colucci, 2012).

Sensitive period for development of central auditory system is at the time when central auditory pathways have high potential for plasticity. Late auditory evoked potentials P300 demonstrate that children that obtained their cochlear implants up to 3,5 years age old have normal latent period, while children that obtained implants up to 7 years old have abnormal latent period (Scherf et al., 2006). Absence of typical auditory experience brings to serious changes in deeper layers of cortex. Secondary auditory areas could be totally or partially reattached from primary areas and they are not more able to enable cognitive "top-down" modulation. Reattachment of primary and secondary areas could enable to secondary areas to become more accessible to other modalities, i.e. sight (Scherf et al., 2006).

Development of whole auditory system, and especially auditory centres in the brain, is possible only at children with normal hearing. Potential for development of auditory centres decrease with the age of the child and depends on sound stimuli. Upon the first year of life synaptogenesis significantly decrease in auditory centres. Late intervention or late cochlear implantation therefore has no full effect. Children with long time auditory deprivation are succesible to significant reorganization of auditory cortex that is responsible for speech perception. One of the consequences of this reorganization is integration of combined auditory and visual information that could be disturbed upon cochlear implantation.

Visual impairment

Largest part of perception from outside of the body comes through sense of seeing. About 90% of information from outside world we get from this sense and that is why is sense of seeing key factor for physical, spiritual, and intellectual development. Visual cortex of adult person show several manifestation of plasticity, at first place possibility of perceptive learning and adaptation.

Early bilateral sensory deprivation (i.e. congenital cataract) changes structure and function of cortex and late surgical operation of cataract doesn't recover sightseeing. An early surgical intervention is necessary for normal functional development of sightseeing. Surgical operation should be made latest at 8 weeks of life time, at the time when development of occipital cortex has highest potential. Negative effects of plasticity are lost of vision on strabic eye or at unilateral loss of sight during critical period of development. Although, there are quite good methods for correction of optic anomalies, sense of seeing is in largest part determined with interaction between retina and brain. It is considered that brain plasticity, as well as neural networks, are shaped during sensitive period and stabilized during further normal brain development (Bavelier et al., 2010).

After discovery of so called critical period in early postnatal development, it was considered for long time that all features of cortical neurons from visual cortex are definitive in adult period. Hubel and Wiesel found that balance of information that comes from both eyes could be disturbed with simple closing of the eyes. They detected this effect only in first few months of the life. Experiment was performed on cats of different age, and these authors detected that cats with surgically closed right eye demonstrate significant decrease in number of neurons of striate visual cortex. They observed change

in number of neurons only in cats that where between 4 and 8 weeks old, while older and adult cats did not show any effect (Hubel & Wiesel, 1970). Also, different visual stimuli expressed during early childhood, as it is in strabismus or congenital cataract, leads to permanent impairments of vision known as amblyopia (Lewis & Maurer, 2009). These paired stimuli also lead to destruction of typical binocularly organized talamocortical neuron connections (Bavelier et al., 2010). One could ask is amblyopia reversible?

Study of Rahi and his colleagues showed interesting example of incredible plasticity of visual cortex. They demonstrated that in adults with monocular amblyopia lost of sight on "healthy" eye leads to improvement of vision on impaired eye (Rahi et al., 2002). It is assumed that neuron connections in amblyopic eye are preserved but weakened or inhibited, therefore lost of "healthy" eye leads to reactivation of neuron connections (Bavelier et al., 2010). The question that comes from results of the experiment is could we use this phenomenon in clinical practice. The healthy eye could be closed in certain period of time and that might have positive effect on dysfunctional eye. Monocular deprivation is example of neuroplasticity showing that neurons of visual cortex overthrow dominancy on the eye that is opened. Nevertheless, mechanism of this phenomenon is not clear yet. Study of Restani and associates demonstrated that significant role in this phenomenon play neuron connections of corpus callosum. They showed that suppression of callosal connections in rats during monocular deprivation decrease possibility of overthrow of dominancy to opened eye (Restani et al., 2009). This is another proof that plasticity is not phenomenon that is characteristic only for cortex. Significant role in this process is played by neuron synapses.

Early correction is of importance in all types of visual impairments like strabismus, congenital cataract etc. Without early corrections amblyopia occurs because of disturbed development of occipital cortex. Children with higher IQ have higher potential for neuroplasticity with extended time for synapses growth, with initially thicker cortex especially in prefrontal regions (Shaw et al., 2006). What could have negative effect is that child's brain is more sensitive on sensory deprivation comparing to the brain of adults.

Perceptual learning represents one of the main form of neuroplasticity that is defined as improvement in performing tasks after certain experience concerning that task was obtained. In experimental studies perceptual learning of visual system is investigated through different visual functions as: orientation in space; following of movements or geometrical shapes; movement of objects; or through complex functions as recognition of human faces. Bays and associates investigated changes in electric activity of the brain using electroencephalography. They found some alterations in electric activity of alpha waves during activation by stimulus of perceptual visual learning. These alterations show that as a consequence of neuroplasticity not only structural but also functional changes in brain tissue occur (Bays et al., 2015).

Li and associates studied effect of playing video games on inducement of visual system plasticity in adults with ambyopia on one eye. They demonstrated that playing video games in time of 40-80 hours (maximum 2 hours per day) using only dysfunctional eye improves basic visual functions. Improvement was detected in visual acuity for 33%, space attention for 37%, and stereopsy for 54% (Li et al., 2011). Based on this and some other studies many methods were introduced in therapy of

shortsightedness as subcutaneous injections of strychnine; application of blinking red and blue light; application of rotating grid; electric stimulation; direct transcranial magnetic stimulation; and pharmacological methods. They are all based on activation of neuroplasticity. Although some of the preliminary results looks promising it is necessary to perform more randomized prospective studies (Li et al., 2011; Maya Vetencourt et al., 2008; Thompson et al., 2008).

Neuroplasticity and neurological disorder in adults

Neurodegenerative disorders

Neuroplasticity also leads to destabilization of neuronal connections and without control of this process plasticity becomes excessive and as a result pathological destabilization and disease may occur (i.e. dystonia). Control of synapses is performed through homeostatic synaptic scaling that stabilize neuronal activity and neuronal network during longer periods of inactivity or hyperactivity.

According to the theory of retrogenesis fibres of gray matter that are last in process of myelinisation are usually first during degeneration as a consequence of aging or disease and this leads to cognitive fall (Brickman et al., 2012). This process was anticipated in XIX century by theory of John Huhlings Jackson about hierarchical dissolution of functions (Павловић, 2012). There are several studies that proofs this theory in model of patients with dementia as well as in model of "normal" aging (Brickman et al., 2012). Measurements of status of grey matter made on magnetic resonance (fractional anisotropy, radial diffusivity) further verify theory of retrogenesis. Physical training showed positive results on neurodegenerative diseases through reduce of degenerative and inflammatory processes (Svensson et al., 2015). The same processes were investigated in Parkinson disease, stroke and dementia. Physical training acts by mechanism of releasing neurotrophic factors, anti-inflammatory cytokines and decrease of pro-inflammatory cytokines. Parkinson disease has effects on motor, emotional and cognitive domain (Павловић, 2008). Programmes of physical training for patients with Parkinson disease include training of motor skills that support cognitive mechanisms of motor learning (Petzinger et al., 2013). Learning is supported by specific instructions that improve movement that were previously performed without conscience. Aerobic exercises sustain blood flow as well as neuroplasticity by increase secretion of neurotrophic factors.

Patients with Alzheimer's disease showed on magnetic resonance micro-structural alterations of grey matter that are probably consequences of primary and secondary degeneration of cortical neurons (Alves et al., 2015). According to the theory of retrogenesis progression of brain aging and progression of Alzheimer's disease occur by inverse form in children (Rubial-Álvarez et al., 2013). Aerobic physical training leads to increase in production of neurotrophic factors and this process occurs even in patients with Alzheimer's disease. Programme of adapted games also showed effective in decrease of agitation in patients that suffer from Alzheimer's disease (Venturelli et al., 2012).

Traumatic brain injuries

Traumatic brain injuries have as a consequence lost of brain tissue mass, brain cells as well as white matter (Tomaszczyk et al., 2014). These effects decrease brain reserve, accelerate brain aging and induce neurodegeneration. Lack of stimulation from the environment and decreased activity, also have effect on brain aging. These processes leads to negative neuroplasticity.

Brain ischemia

One of the most frequent diseases is brain ischemia or cerebral ischemia. Brain ischemia is leading cause of invalidity in older ages. Beside thrombolysis that is performed in most acute phase of the disease, there is no specific therapy (Felling & Song, 2015). Neuroplasticity occurs upon brain ischemia when different processes like axon growth, synaptogenesis and neurogenesis start. These processes form structural substrate for spontaneous recovery. Neuroprotective mechanisms are important in acute phase but also in the phase of recovery. Their increase is one of the most important tasks of recovery and secondary prevention of cerebral stroke (Павловић, 2012). Epigenetic mechanisms are important in neuroplasticity after brain ischemia (Felling & Song, 2015). Aerobic training is important for stimulation of meuroplasticity after brain ischemia. Intensive physical training of moderate to high intensity acts positive on brain through increased production of brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), nerve growth factor (NGF) and synaptogenesis (Ploughman et al, 2015). Moderate physical training is more effective for dendritic sprouting.

Recovery from cerebral ischemia is at the beginning of that process faster, then slower and could take even few years. Therapy with hyperbaric oxygen could encourage neuroplasticity in some patients with neurological sequels of cerebral ischemia (Efrati et al, 2013). In one prospective randomized controlled study it was demonstrated that therapy with hyperbaric oxygen has positive effect on neurological functions and quality of life in treated patients.

Aphasia is quite often in cerebral ischemia with mechanical injuries. Acquired aphasia is the cause of trauma on dominant brain hemisphere (Павловић, 2012). Recovery depends on the cause, type of aphasia and brain reserve. Functional neuroimaging enabled monitoring of the active brain and some of the changes that follow neuroplasticity. It was demonstrated that successful recovery from aphasia is under influence of speech and language therapy and depends on improvement of functions in left hemisphere (Marcotte et al., 2013). Rehabilitation is mainly dependant on degree of injury in Broca's area and precentral gyrus. Adaptive brain plasticity is expressed individually.

Anosmia is also present in neurological disorders. Anosmia is dysfunction of sense of smell that is quite often and difficult to treat. Rehabilitation is performed by sensomotoric act of smelling without real smell. Recovery is based on mechanisms of neuroplasticity (Kollndorfer et al., 2014). This mechanism is demonstrated by functional magnetic resonance. Olfactory training induced neuron reorganization.

Neuroplasticity and aging

Aging

As a consequence of physiological aging brain of an older person demonstrate decline of cognitive functions. This phenomenon was thought to be caused by necrotic or apoptotic death of certain number of neurons, at first place in neocortex. Nowadays, it is best explained by loss of synapses and neural connections, but not as a loss of whole neurons (Bishop et al., 2010). From the global prospective an aging brain shows volumetric reduction of both grey and white matter, that is more advanced in anterior than posterior brain regions, reaching a maximum in the prefrontal cortex. Considerable neuronal losses can occur in subcortical centres of an aging brain, but they can be balanced by a volume increase and enhancement of function of the some remaining neurons. Massive neuronal loss is one of main characteristics of progressive neurological disorders such as Alzheimer's dementia. Surprisingly, it seems that cognitive decline in normal aging brain correlates more with reduction of white matter than with that of grey matter. This is due to degeneration of axons and their sheaths, as well as a breakdown of some myelin sheaths with preservation of axons (Berlucchi, 2011).

Therefore, any intellectual and physical stimulation or systematic physical training of older person could contribute to reestablishment of synaptic connections and increase of cognitive functions.

Cognitive reserve

Cognitive reserve is the model that has been build up to explain how it is that some elderly people with widespread neuropathology correlated with dementia show little in the way of cognitive decline. Cognitive reserve is related both to the process of brain plasticity and brain aging. Simply, it describes resistance of the brain to dysfunction. Sometimes cognitive performance is quite below the level supposed for the amount of pathology found, but more often someone with a substantial load of pathology had nonetheless performed cognitively within the normal range. Nevertheless, association cortex, hippocampus and the parts of the brain that these are connected to have been considered as well developed and nourished brain with an abundance of synapses and healthy neurons, which provides structure for cognitive reserve.

However, the relationship between cognitive reserve and its architectural neural basis is not clear. Synapse loss, minicolumn change and total brain size have shown some of the clearest morphological relationships with functional deficits in ageing and dementia (Esiri, 2012). On the other hand, older adults are capable of counteracting age-related neural decline through plastic reorganization on the structural level, such as alterations of dendritic arborisation, synaptic remodelling, axonal sprouting, neurite extension, synaptogenesis, and neurogenesis (Mesulam, 1999). Furthermore, de la Monte suggested that white matter atrophy may precede whole brain atrophy in ageing brains (de la Monte, 1989).

Early intervention and neuroplasticity

Neural plasticity and *cognitive reserve* may play crucial role in the process of recovery and rehabilitation. The accomplishment of the recovery depends on the active participation of individual disabled patients, on their awareness of and insight into their disabilities, and on their attention to the rehabilitating procedures and their motivation to comply with them (Berlucchi, 2011). Brain lesions cause less impairment in individuals with high IQ and advanced education than in individuals with low intelligence and poor education (Wilson, 2003), which could be explained using concept of cognitive reserve. In order to establish reference for the practice of neuropsychological rehabilitation Zangwill affirmed that a strict scientific rationale of rehabilitation is in the understanding of the mechanisms whereby the brain adjusts itself in reaction to injury to its parts (Berlucchi, 2011).

Zangwill distinguished *compensation*, a reorganisation of behaviour aimed at minimizing or circumventing a particular disability, from substitution, the accomplishment of a task by a new method totally different from that naturally employed by the intact brain in the performance of the same task. Substitution was determined as a special form of compensation in which the new method of completing a task is expanded by training over and above what patients can achieve on their own initiative. Today it is accepted that during process of restitution damaged but surviving neurons can re-establish some functional connections due to processes of axonal and dendritic sprouting and synaptogenesis, perhaps akin to those occurring during the developmental growth of the brain (Berlucchi, 2011). Without any doubts, younger and growing brain has a greater potential for compensating for damage and a higher ability for correcting dysfunctions.

Brain plasticity could be affected using specially formed exercises; virtual reality; medicines; transcranial stimulation; somatosensor stimulation. Benzodiazepines and baklofen increase inhibition of cortex (Johnston, 2009).

CONCLUSION REMARKS

Neuroplasticity is natural process that is disturbed in children with impairments and in invalid adults. Studies in medicine and especially in clinical medicine demonstrated that brain has potential to adapt and to perform functional reorganization. Neuroplasticity is feature of central nervous system that is detected in children and in adults, with certain specificity that is consequence of different biological potential. Neuroplasticity is always under huge influent of environment and external stimuli. Therefore, neuroplasticity could have significant role in early intervention in children and adults. We should have in mind that different morphological structure of the brain responsible for motor functions, cognitive functions, vision and hearing demonstrate certain specificity in the process of neuroplasticity.

Medical research in the field of neuroplasticity is further supported with data obtained in experimental work from biological sciences. Processes on cellular, molecular and biochemical level are enabled by stimulation of NMDA and AMPA receptors, neutrophines,

free radicals, cytokines etc. They all play significant role in synaptognesis, denedritic sprouting and axon growth that make morphological foundation for establishment of motor and cognitive functions. Increased stimulation from environment leads to increase of number of neurons that produce BDNF which further stimulate neurogenesis in the brain and decrease GABA induced inhibition in cortex.

Early intervention will have full effect in special education and rehabilitation only if it is applied well-timed. In other way the effects will be reduced.

We can define as necessary for correct early intervention: defining optimal time period for beginning of early intervention in children with impairments and invalid adults; composition of protocol for methods of stimulation and systemic exercise; to use these measures in connection with prospective biological potentials.

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