Molecular mechanisms of brain plasticity: neurophysiologic and neuroimaging studies in the developing patients

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Abstract

The term plasticity, derived from the Greek word "plaistikos" meaning "to form" refers to the brain's ability to learn, remember and forget as well as its capacity to reorganize and recover from injury. There are four major types of plasticity: adaptive plasticity, impaired plasticity, excessive plasticity, and the 'Achilles heel' of the developing brain. Mechanisms of plasticity include: a change in the balance of excitation and inhibition; a long-term potentiation (LTP) or long-term depression (LTD); a change in neuronal membrane excitability; the anatomical changes-formation of new axon terminals and new synapses. Mechanisms for plasticity include activity-dependent refinement of neuronal connections and synaptic plasticity as a substrate for learning and memory. The molecular mechanisms for these processes were described in view of the current investigations. Authors presented: the role of calcium ions, calcium channels, NMDA receptors, free radicals, lipid peroxides and neurotrophins in the plasticity of developing brain. The utility of the neurophysiologic and MRI techniques were described in the determination of brain reorganization and repair in patients with cerebral palsy. Authors discussed their results on quntatative EEG and spectroscopy MRI studies in children with cerebral palsy. They have shown the existence of two processes in brain: brain damage and recovery.

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Received 12.07.2004 Accepted 18.07.2004

Key words: brain, plasticity, children.

Introduction

The term plasticity, derived from the Greek word "plaistikos" meaning "to form" refers to the brain's ability to learn, remember and forget as well as its capacity to reorganize and recover from injury [1]. Children have enhanced capacity for learning and memory compared to adults as reflected in their ability to learn a second language, play musical instruments or become proficient in complicated sports such as golf or tennis. Children also have remarkable ability to recover from early brain injuries as demonstrated by their ability to recover receptive language after left hemispherectomy performed for epilepsy as late as the second decade [2]. Mechanisms of plasticity include: first, a change in the balance of excitation and inhibition; second, a long-term potentiation (LTP) or long-term depression (LTD); third, a change in neuronal membrane excitability; fourth, the anatomical changes, which need a longer period of time. Specific anatomical changes include formation of new axon terminals and new synapses.

In the 1980s and 1990s, a great deal of excitement was generated by new insights into new novel mechanisms of brain damage during hypoxia/ischemia [3,4]. It has been well known that hypoxia/ischemia lasting more than a few minutes can cause irreversible brain damage. Further research has indicated that reperfusion may cause more damage than simple hypoxia [4-6]. The mechanism of reperfusion injury is thought to involve the production of free oxygen radicals. The free radicals induce a chain reaction leading to a breakdown of the neuronal cell membrane (necrotic cell death). Further, free radicals are generated, causing a damage in the original cell that spreads to neighboring cells [5,6]. The brain uses glucose as its primary energy source. Glutamic acid, or glutamate, is a common metabolite of glucose metabolism. Glutamate is involved in several metabolic processes in the brain. It plays a role as a precursor for the inhibitory neurotransmitter, γ-amino butyric

acid (GABA). Elevated levels of glutamate were associated with increased brain activity. Furthermore, glutamate-induced excitotoxicity is a major mechanism by which neuronal loss may occur [6,7].

This review describes molecular mechanisms of brain plasticity and neurophysiological and magnetic resonance imaging studies in children with cerebral palsy.

Role of calcium ions (Ca^{2+})

Ca^{2+} is a regulator of metabolic pathways and serves important functions as a second messenger, thus the free cytosolic Ca^{2+} concentration must be tightly regulated at round 10^{-7}M. Ca^{2+} influx occurs by voltage dependent calcium channels (VDCCs) and receptor-operated calcium channels (ROCCs), while release form the endoplasmatic reticulum is triggered by inositol triphosphate [4,5,8]. Efflux of Ca^{2+} occurs by a high affinity-low capacity ATPase (calmodulin-dependent) and by a low affinity-high capacity, electrogenic Na^{+}/Ca^{2+} exchanger. Ca^{2+}-binding proteins buffer any Ca^{2+} entering the cell, or release within the cell. When Ca^{2+} concentrations increase, mitochondria become important in calcium storage. The Ca^{2+} sequestration process is dependent on ATP and during ischemia Ca^{2+} concentration within the cell rises [6,8,9].

The channels may be opened by the occupation of associated receptors (ROCCs) or by changes in membrane potential including those occurring with depolarization (VDCCs). The L-type Ca^{2+} channel is composed of five different polypeptide subunits, each with different molecular masses. The existence of this channel type has been demonstrated in many regions of the central nervous system (CNS) such as the cortex, hippocampus, cerebellum, and spinal cord.

The N (high-threshold inactivating) and T (low) type Ca^{2+} currents have also been documented. The T-type current could contribute to rhythmic firing of veretebrate neurons and the N or L-type currents could be involved in the release of neurotransmitters [10,12].

In general, it is thought that the blockade of T-type Ca^{2+} channels is associated with efficacy in treating absence seizures, while blockage of high voltage-activated (L-type) Ca^{2+} channels seems to be associated with control of partial seizures with or without secondary generalization [11-13]. More importantly, elevated levels of intracellular Ca^{2+} are thought to activate numerous Ca^{2+}-dependent processes that lead to cell death. Blockage of Ca^{2+} channels may play a key role in preventing these progressions [3,10,12].

L-type Ca^{2+} channels are expressed by particular cell types in the spinal sensorimotor network. They provide distinct non-linear conversions of synaptic input to axonal output. Several features suggest a major role in spinal motor function. The unusually slow kinetics is well adapted to provide the driving potential for the firing patterns that regulate the muscle activity of posture and locomotion. This arguably reduces the computational load on the premotor network [14]. Motor behaviour is the concerted action of hundreds of muscles. The study of postsynaptic properties mediated by L-type Ca^{2+} channels in spinal neurons has revealed mechanisms that may provide functional plasticity on a time scale from hundreds of milliseconds to tens of seconds [15].

Long-lasting changes in the structure and function of synapses occur in response to environmental stimuli in many regions of the nervous system during child and adult life.

The synaptic plasticity is a process called long-term potentiation (LTP) that is believed to be a cellular mechanism of learning and memory [16]. LTP is defined as a long-term enhancement of synaptic strength resulting from repeated activation of that synapse. In several regions of the brain, including the hippocampus, LTP has been shown to require activation of glutamate receptors and calcium influx into the dendrite of the post-synaptic neuron. Evidence also suggests that calcium release from endoplasmatic reticulum (ER) stores can promote LTP. And LTP can be modified by changes in ATP production and release. During LTP, mitochondrial calcium pump activity increases [17] and changes in mitochondrial gene expression occur [18]. Current findings suggest that such changes in mitochondria play an important role in the process of LTP. Calcineurin (CaN) exerts a powerful effect on a variety of signaling-proteins within neurons. Depending upon the strength, duration, and site of a Ca^{2+} stimulus, CaN may either increase or decrease synaptic efficacy and cell excitability, through modulation of ion channels, neurotransmitter receptors, cytoskeletal proteins, kinases, other phosphatases, and transcription factors. Thus, in response to multiple forms of synaptic stimulation, CaN initiates both short- and long-term changes on neuronal function, which ultimately translate to behavioral modification and neuroplasticity [17].

Role of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors

Developing neuronal connections are shaped by the balance of excitatory and inhibitory pathways entering the brain from primary sensory modalities such as vision, hearing and somatosensory sensation as well as by the activity of intrinsic circuits [16,18]. Most of these pathways use glutamate as their neurotransmitter, and active pathways are likely to gain influence compared with quieter ones according to their pattern of activation of glutamate receptors. Over-production of synapses during the postnatal period results in the 2 year old toddler having twice as many synapses in cerebral cortex as adults, and excessive synapses are pruned until approximately 16 years of age [19]. During this period, synaptic connections are refined through activity at excitatory synapses that use glutamate as their neurotransmitter [20]. Activity at glutamate synapses contributes to the loss of many synapses and the preservation of synapses that fire together repeatedly [21]. Both NMDA (N-methyl-D-aspartate) and AMPA (a-amino-3-hydroxy--5-methyl-4-isoxazole propionate)-type glutamate receptor activation is involved in synapse formation and stabilization. The NMDA-type glutamate receptor plays a special role in this process because it requires simultaneous stimulation by glutamate and membrane depolarization caused by stimulation of adjacent excitatory receptors [21]. Persistent coincident

firing of neurons leads to Ca^{2+} entry through NMDA receptors into post-synaptic neurons and release of trophic factors that support that synaptic connections [22]. Enhanced function of the immature NMDA receptor during postnatal development contributes to enhanced plasticity at this time [19,21,23]. Activation of NMDA channels allows Ca^{2+} to flux into neurons, activating protein kinases such as CaMKinase II and IV and production of neurotrophins such as brain-derived neurotrophic factor (BDNF). The growth factors such as BDNF, acetylcholine and serotonin receptors, and neurotransmitters that stimulate adenyl cyclase and protein kinase A all play roles in activation of gene transcription involved in neuronal plasticity [23,24]. Influx of Ca^{2+} through NMDA receptors plays an important role in LTP, formation of memories, and plasticity of neuronal circuits through downstream phosphorylation of transcription factors such as CREB (cyclic AMP response element binding protein transcription factor) as well as through indirect activation of transcription through the Ras-MAP kinase cascade [23].

AMPA receptor expression is also linked to synaptic morphology [24,28]. Synapses smaller than 180 nm across have been found to contain only NMDA receptors; above this size, the number of immunohistochemically detectable AMPA receptors increases linearly with synaptic diameter [29]. Increased AMPA receptor numbers are also associated with synaptic plasticity.

In the fetus or premature infant, expression of non-NMDA type glutamate receptors on immature oligodendroglia, during a critical window in development, makes them vulnerable to glutamate-mediated cell death leading to periventricular leukomalacia (PVL) [24]. Later in gestation, the enhanced function of immature NMDA receptors contributes to the selective vulnerability of neuronal circuits in the thalamus, basal ganglia and cerebral cortex to near-total asphyxia.

Free radicals (FR) and lipid peroxides (LP)

Free radicals (FR) and lipid peroxides (LP) are the byproducts of cellular metabolism that have been implicated in neurodegeneration, age-associated cognitive, memory impairments, ischemia and epilepsy [6,9,25-27,29]. Thus far, FR and LP have been treated as harmful agents that cause damage to macromolecules through nucleophillic attack [25]. However, there are recent indications that FR and LP may have an important role as signaling molecules that are used by cells as second messengers for altering the redox state of specific molecules that affect their functions [27,28]. These regulatory roles can only occur under physiologically significant concentrations of FR, which are strictly regulated in vivo by a myriad of antioxidant molecules. Recently, a link between FR and modulation of synaptic plasticity has been proposed; high concentrations of FR attenuate synaptic transmission and LTP [29]. On the other hand, superoxide radicals are proposed to be involved in LTP induction [30].

Nitric oxide (NO) is involved in the pathophysiology of brain ischaemia as well as in the formation of activity dependent synaptic plasticity. Accordingly, inhibition of nitric oxide synthase (NOS) attenuates anoxic LTP in the brain and this effect can be blocked by L-arginine (a substrate of NOS) [16].

PVL in the premature infant is a distinctive lesion of cerebral white matter associated with much of this adverse neurologic outcome. The pathogenesis of cerebral white matter injury in the premature infant is not entirely clear, although ischaemia-reperfusion and infection/inflammation appear to be important [31]. The unique nature of this neuropathological lesion in the premature infant is to relate in part to an exquisite vulnerability of the immature oligodendrocyte to FR and LP damages [31]. In two model systems of free radical accumulation, the early differentiating oligodendrocyte has been shown to be exquisitely vulnerable to FR attack [31]. Moreover, this immature form, the so-called preoligodendrocyte, has been shown recently to account for 90% of the total population of oligodendrocytes in cerebral white matter of infants under the gestational age of 31 week [32], the period when the premature infant is most at risk for white matter injury.

Neurotrophins

Neurotrophins belong to a family of secretory proteins that include nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and NT-4/5. Neurotrophins promote neuronal survival and differentiation, but it has become increasingly clear that they also have essential roles in neuronal survival and synaptic plasticity [22,33]. The expression of BDNF mRNA and the secretion of BDNF protein are tightly regulated by neuronal activity. Exogenous BDNF enhances transmission at the developing neuromuscular junction and at various central excitatory synapses [34]. Furthermore, endogenous BDNF, supports the survival, the growth of dendrites and axons, including glutamatergic neurons [35,36]. At cellular levels, the expression of BDNF mRNA is enhanced when the non-NMDA-type glutamate receptor is activated [37,38] and suppressed when GABA-A receptor is activated [39]. Cholinergic afferent inputs to the cortex and hippocampus also increase the levels of BDNF mRNA [37]. An important finding was that the enhancement of BDNF gene expression requires an increase in intracellular calcium concentrations [36] possibly by Ca^{2+} influx through L-type Ca^{2+} channels or NMDA receptors [38,39].

The local and synapse-specific modulation, together with preference in active neurons/synapses, suggests that neurotrophins must preferentially regulate active synapses with little or no effect on nearby less active synapses [37]. Moreover, both BDNF and NT-4 regulate cortical development. Specifically, exogenous application of BDNF regulates pyramidal neuron dendritic growth [40], whereas endogenous BDNF is necessary for differentiation of cortical interneurons [41].

Neurogenesis

Mechanisms that account for enhanced brain plasticity during childhood include persistence of neurogenesis in certain parts of the brain during the postnatal period, deletion of neurons through apoptosis or programmed cell death, proliferation and pruning of synapses, and activity-dependent

refinement of synaptic connections [3]. The presence of primitive ipsilateral non-pyramidal pathways can also contribute to plasticity as occurs in recovery of walking and body steering activity after injury to one hemisphere [4]. If damage to the corticomotoneuronal system occurs in adulthood, great difficulty follows in learning new or relearning former sequences of skilled movements [5], emphasizing the role of the corticomotoneuronal system in the acquisition and maintenance of skill. When lesions occur in the perinatal period, not only is learning of skilled movements severely impaired, but the development of alpha-motor neurons and their afferent segmental reflex control is secondarily disrupted [6,7]. This implies a further role for the corticomotoneuronal system in man: activity dependent regulation of the development of spinal motor centres.

In animals, it has been demonstrated that exercise increases the number of new neurons [49]. Neurotrophins might mediate this effect. Exercise increases levels of BDNF in the hippocampus and BDNF promotes the survival of newly differentiated neurons. Exercise increases brain uptake of circulating IGF-1, a factor that promotes neuronal differentiation of progenitor cells and increases hippocampal BDNF gene expression [49,50]. In addition, Fibroblast growth factors (FGF-2) which stimulates proliferation and differentiation of hippocampal cells, and there is increased in hippocampal astrocytes after exercise [51]. Thus, exercise activates a number of factors that converge on neurogenesis.

There are four major types of plasticity: adaptive plasticity, impaired plasticity, excessive plasticity, and the 'Achilles heel' of the developing brain [42]. Adaptive plasticity refers to the changes in neuronal circuitry that enhance a special skill with practice or allow the brain to adapt or compensate for injuries or changes in sensory input. Impaired plasticity refers to situations in which genetic or acquired disorders disrupt molecular plasticity pathways (genetic and acquired disorders that cause cognitive impairment). In contrast, excessive plasticity in the developing brain can lead to disability through reorganization of new, maladaptive neuronal circuits that cause neurologic disorders such as partial seizures following mesial temporal sclerosis or focal dystonia. Plasticity becomes the brain's 'Achilles heel' in situations such as energy failure or status epilepticus when excitatory mechanisms designed to enable plasticity become over-stimulated, resulting in excitotoxic neuronal damage.

More recent studies have concentrated on the recovery and plasticity in the stroke patients [43-46]. A small number of the investigations have been performed on children with cerebral palsy (CP) [47,48].

Cerebral palsy

The CP prevalence is increasing, more premature infants survive because of better neonatal care [52]. Spastic diplegia is the commonest form of CP as a results of injury to the PVL, which occurs only during a temporal window of development that ends at 30-32 weeks PCA. A characteristic feature of PVL is disruption of corticospinal axons, while the cortical pyramidal projection neurons are left intact and subsequently make aberrant intracortical axonal projections [53]. The rapidly expanding understanding of CNS axonal regeneration indicates that with early intervention there are realistic prospects of inducing corticospinal axons to re-grow through the cystic areas of PVL and to find their appropriate targets [54]. Myelin is inhibitory to axonal growth but this should not pose an encumbrance to axonal regrowth, since the corticospinal tract is poorly myelinated before term [55,56]. Recently, it has been demonstrated that corticospinal axons are actively growing, innervating spinal cord and expressing growth-associated protein-43 (GAP43) during this period and are thus likely to have a high degree of plasticity. Interventions providing early regeneration of corticospinal projections and reinnervation of the spinal cord in preterm babies with PVL would be likely to reduce disability, not only by re-establishing the cortical input to spinal motor centres but also by facilitating their subsequent normal development.

There are a few tools to study brain plasticity. Recently, neural plasticity can be measure evaluated validly with transcranial magnetic stimulation techniques (TMS), mapping EEG and functional magnetic resonance imagines (fMRI).

EMG studies

Carr and colleagues [57] studied the central motor reorganization in subjects with hemiplegic CP. The cortico-spinal projections were investigated using focal magnetic stimulation of the motor cortex. Reflex pathways were examined with digital nerve stimulation. In 64% of the patients, there was evidence for reorganization of central motor pathways. The clinical and neurophysiological findings revealed two different forms of reorganization. In both forms focal magnetic stimulation demonstrated novel ipsilateral motor pathways from the undamaged motor cortex to the hemiplegic hand. Ipsilateral projections were not demonstrated from the damaged motor cortex. In these subjects cross-correlation analysis and reflex testing suggested that corticospinal axons had branched abnormally and projected bilaterally to homologous motor neuron pools on both sides of the spinal cord. It was demonstrated that good function of the hemiplegic hand was associated with the presence of EMG responses in that hand following magnetic stimulation of the contralateral motor cortex. When EMG responses were absent, hand function was poor unless the subject had intense mirror movements.

Transcranial magnetic stimulation (TMS), functional MRI (fMRI) studies

In the motor an sensory system, TMS studies demonstrated cortical plasticity in CP patients [58-60]. Maegaki and colleagues [58] investigated central motor reorganization for the arm and leg muscles in spastic and athetoid CP patients with bilateral cerebral lesions using TMS. On computer tomography and MRI, bilateral PVL were observed in all spastic patients with preterm birth. Ipsilateral responses were more common among CP patients, especially in TMS of the less damaged hemisphere

in patients with marked asymmetries in brain damage. The cortical mapping of the sites of highest excitability demonstrated that the abductor pollicis brevis and biceps brachii sites in CP patients were nearly identical to those of the normal subjects. These results suggest that ipsilateral motor pathways were reinforced in both spastic and athetoid CP patients, and that a lateral shift of the motor cortical area for the leg muscle may occur in spastic CP patients with preterm birth.

Thickbroom et al. [59] used TMS and fMRI to investigate cortical motor and sensory areas in children with hemiplegic CP. Both TMS and fMRI demonstrated a normal contralateral motor and sensory projection between the unaffected hand and the cerebral hemisphere. However, in the case of the affected hand, the TMS results indicated either a purely ipsilateral projection or a bilateral projection in which the ipsilateral pathway had the lower motor threshold, whereas passive movement resulted in fMRI activation in the contralateral hemisphere. A significant fast-conducting corticomotor projection to the affected hand from the ipsilateral hemisphere was demonstrated. Also, the predominant afferent projection from the hand was directed to the affected contralateral hemisphere, resulting in an interhemispheric dissociation between afferent kinesthetic inputs and efferent corticomotor output. The authors [59] have concluded that there are differences in the organization of sensory and motor pathways in CP. They have also suggested that the motor dysfunction experienced by these subjects could be due to an impairment of sensorimotor integration at cortical level as a result of reorganization in the motor system.

In another study, Staudt and colleagues [60] have evaluated the impact of different lesion extents on the type of reorganization induced in young adult patients with congenital hemiparesis. The severity of structural damage to hand motor projections of the corticospinal tract was assessed on semi-coronal MRI reconstructions along anatomical landmarks of corticospinal tract somatotopy. The functional integrity of these crossed corticospinal projections in the affected hemisphere, as well as the presence of any abnormal ipsilateral projections to the paretic hand, was examined by TMS. The cortical activation during simple voluntary hand movements was studied by functional MRI (fMRI). Patients with small lesions and only mild hand motor impairment possessed intact crossed corticospinal projections to the paretic hand, whereas no motor response could be elicited by TMS of the affected hemisphere in those with large lesions and more severe hand motor impairment. Evidence for compensatory recruitment of the unaffected hemisphere was found in both subgroups. In the small lesion group, fMRI demonstrated ipsilateral activation of premotor areas, without any abnormal projections to the paretic hand originating from these sites. In the large lesion group, such abnormal ipsilateral projections to the paretic hand were indeed found, and fMRI confirmed cortical activation of an abnormal ipsilateral hand motor representation in the primary sensorimotor region of the unaffected hemisphere. They concluded [60] that the type of corticospinal reorganization depends on the extent of the brain lesion.

Coherence EEG studies

The EEG changes in CP patients generally reported are non-specific [61,62]. On the other hand a quantitative EEG (power spectra and coherence) provides objective measures in the search for global or focal abnormality which, if present, may signal an underlying organic process [63,64]. The coherence is function of frequency [65]. Coherence is an amplitude independent measure of phase synchrony between EEG signals, reflecting functional interregional coupling and depending mainly on structural connections [64,65]. The coherence values are interpreted in terms of various connectivity between brain structures [66]. Coherence has been found to vary with numerous diseases states. Certain regions and frequency range increases in coherence in multi-infarct dementia, AIDS and mild head injury, while it decreases in Alzheimer's disease and depression [66-68].

Koeda et al. [69] have evaluated EEG spectral power density, interhemispheric (ICoh) and intrahemispheric (HCoh) coherence, and asymmetry of coherence between the right and left hemispheres in twelve children with spastic diplegia (SD). No significant differences in EEG spectral power density were observed in these patients. The authors noted lower ICoh at the occipital pair for the alpha band and a higher value at the frontal pair for the theta band in SD children. Higher HCoh in SD was pronounced in the left hemisphere for the delta, theta, and beta bands. On the other hand, there were no higher values in the control group. Higher HCoh asymmetry was exhibited in the left hemisphere in the control group, while very little asymmetry was found in the SD group. We suggest that these neurophysiologic abnormalities in preterm SD children correspond neuroanatomically to the callosal thinning and neuropsychologically to the visuoperceptual impairments. These findings are agreement with our results [70]. In our previous report on MRI findings in CP patients, we have observed callosal thinning more expressed in the tetraplegic patients than in SD ones [70].

We have studied the quantatative and coherence EEG on the lager group of patients with spastic diplegia [71]. A group of twenty-nine children with SD was studied. EEG records were compared to healthy children with normal EEGs. For every subject, twenty artifact-free EEG epochs, each of 2 s duration, were selected for spectral analysis and coherence functions. Significant decrease of power alpha at occipital derivations was demonstrated in children with SD in comparison to the control group. On the other hand, there was an increase in theta power and delta bands almost in all leads. Significant decrease of ICoh coherence values in children with SD for the alpha and delta bands in frontal and central leads, as compared with controls, were observed (*Fig. 4*). However, higher ICoh coherence values were detected at frontal, central, parietal and occipital leads for the alpha, theta and beta1 bands. Lower HCoh coherence values in the patients at temporal-occipital derivations were noted. In contrast, we have also detected higher HCoh values at temporal and temporal-occipital derivations for delta and beta bands. The presented results support anatomic-neurophysiologic abnormalities and the existence of compensatory mechanisms in children with SD.

Figure 1. **Patient aged 7, spastic diplegia, hyperintensity changes in thalamus (white arrows) (MRI-T2). (Kułak et al., 2004 [70])**

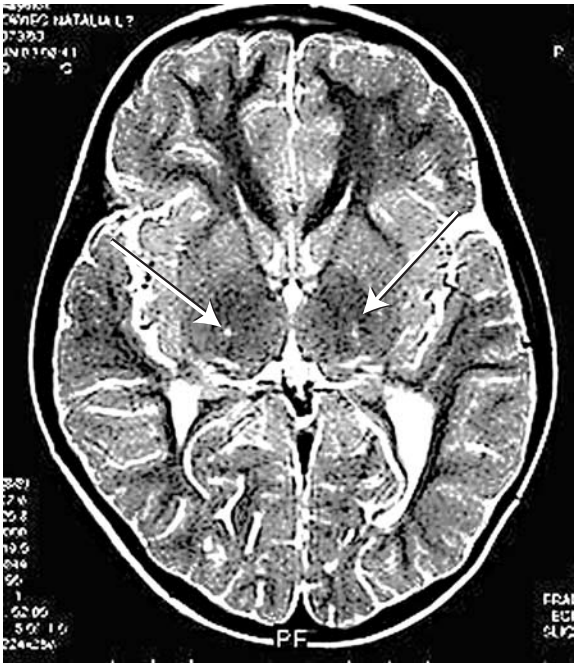


Figure 2. **Patient aged 11, with spastic CP tetraplegia. Paraventricular leukomalacia with hyperintensive changes in frontal and parietal lobes – black arrows, with wide sulci of cortex and enlargement of ventriculi (MRI-FLAIR). (Kułak et al., 2004 [70])**

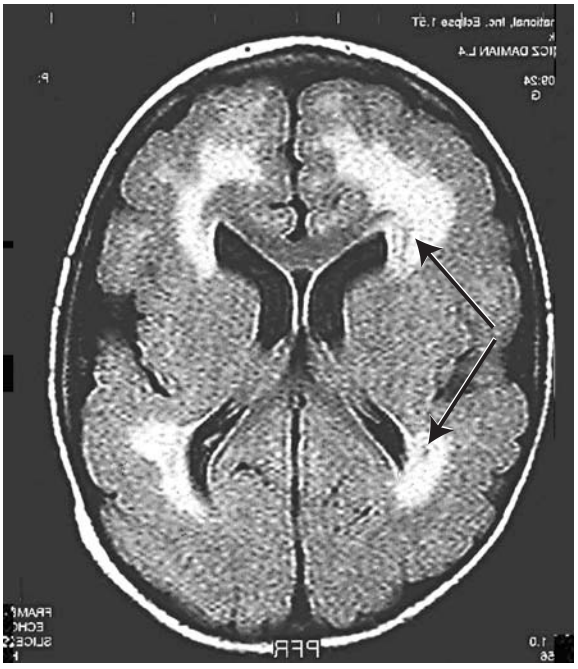
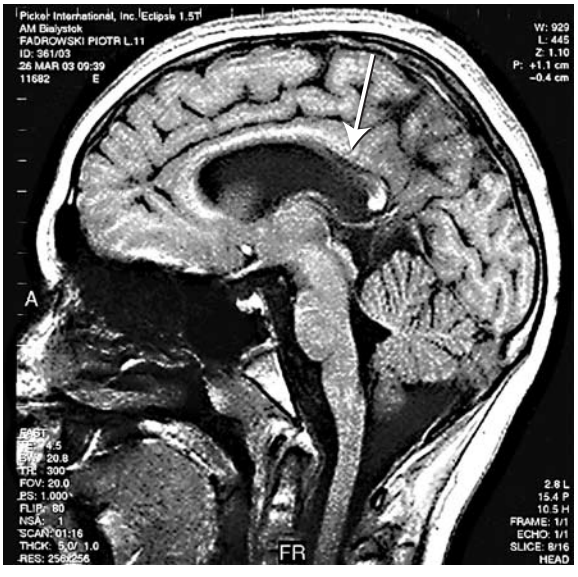


Figure 3. **Patient aged 11, with spastic CP tetraplegia. Thinning of corpus callosum – white arrow. Wide sulci of cortex and enlargement of ventriculi (MRI-T2).(Kułak et al., 2004 [70])**



Hemiparetic cerebral palsy (HCP) is a form of CP. HCP often predicts which patients will develop cognitive disabilities and/or unprovoked seizures. Children whose hemiparesis involves the upper limb to a greater extent than the lower one (arm-dominant hemiparesis) are much more likely to experience learning difficulties than those whose clinical pattern is leg-dominant. Patients with arm-dominant hemiparesis tend to have relatively large lesions involving cortex and subcortical white matter (e.g. major arterial territory infarcts, porencephaly, schizencephaly, polymicrogyria, cortical and subcortical atrophy) and would therefore be more likely to develop learning difficulties and epilepsy.

We have analyzed the spectral and coherence EEG in children with spastic hemiplegia [72]. A group of fourteen children with right hemiparetic cerebral palsy (RHCP), ranging from 6-14 years of age was studied. The second group consisted of twelve children with left hemiparetic cerebral palsy (LHCP) of similar age. In this study we have found significant differences in the distribution of the alpha, theta, delta and beta rhythm between HCP and control children over the left and right hemisphere. There were highly significant differences between the HCP and controls in the distribution of the theta rhythm over left hemisphere. The lower ICoh at the temporal, parietal and occipital derivations in the alpha band implies hypoconnectivity between the right and left hemispheres and suggests hemistructural brain lesion (*Fig. 5*). The HCoh asymmetry, which implies relative hypoconnectivity within the left hemisphere, as compared with the right one, suggests that functional hemispheric differentiation may be diminished. Our results suggest a possible increase in the plasticity of the brain in children with CP. We postulate that the rehabilitation efficacy of children with CP can be measured by EEG coherence.

***Figure 4*. Differences of interhemispheric (ICoh) and intrahemispheric (HCoh) in children with spastic diplegia (SD). Solid lines indicate significantly lower ICohs and HCoh in SD children compared to normal subjects. Dashes indicate significantly higher ICohs and HCoh in SD children compared to the control group (Kułak et al., 2003 [71])**

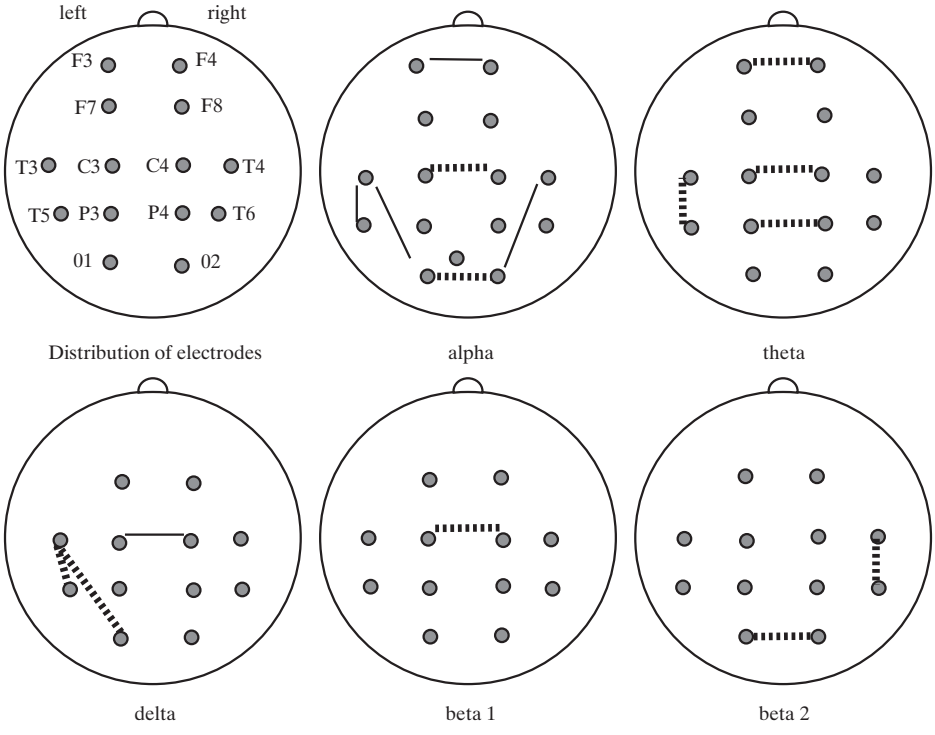


***Figure 5*. Differences of HCoh between right hemiparetic cerebral plasy (RHCP) children and the control group. Solid lines indicate significantly lower HCohs in HCP children compared to normal subjects. Dashes indicate significantly higher HCohs in RHCP children compared to the control group (Kułak et al., 2004 [72])**

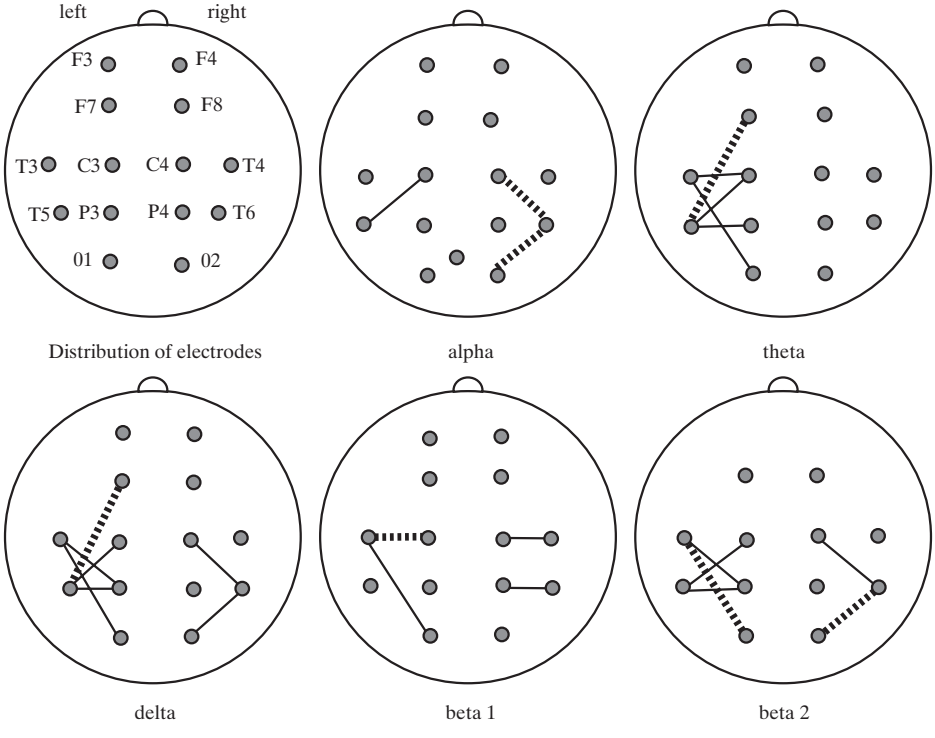


Table 1. **Metabolites ratios in the left basal ganglia in children with spastic diplegia (SD) and control group (X ± Standard Deviation) (Kułak et al., 2004, [77])**

Metabolites	SD group, n=19	Control group, n=19	t value	p value
NAA/Cr	1.63 ± 0.18	1.99 ± 0.16	t= 5.95	p<0.001
NAA/Cho	1.98± 0.26	2.17 ± 0.17	t=2.58	p<0.05
NAA/mI	3.08 ± 0.68	3.84 ± 0.70	t= 3.33	p<0.01
Cr/NAA	0.59 ± 0.06	0.49 ± 0.02	t=5.43	p<0.001
Cr/Cho	1.15 ± 0.13	1.06 ± 0.10	t= 2.11	p<0.05
Cr/mI	1.87 ± 0.38	1.92 ± 0.37	t=0.45	NS
Cho/NAA	0.51 ± 0.06	0.47 ± 0.04	t=2.28	p<0.05
Cho/Cr	0.87 ± 0.09	0.95 ± 0.10	t=2.31	p<0.05
Cho/mI	1.59 ±0.33	1.81 ± 0.27	t=2.17	p<0.05
mI/NAA	0.33 ± 0.07	0.26 + 0.04	t=3.55	p<0.01
mI/Cr	0.58 ± 0.13	0.53 ± 0.07	t=1.43	NS
mI/Cho	0.66 ± 0.66	0.57 ± 0.11	t=1.62	NS

two tailed t-test, NS – not significant; N-acetylaspartate (NAA), creatine (CR), choline (Cho), myo-inositol (mI)

MRI and MRS

Proton magnetic resonance spectroscopy (^{1}H MRS) is widely applied in the determination and differentiation of brain tumors, hypoxia, post radiotherapy changes and other lesions mimicking neoplasm-like abscesses [73,74]. ^{1}H MRS has proved to be a useful tool for the early evaluation of brain injury in asphyxiated neonates [75]. The basal ganglia, and more specifically the corpus striatum, play a central role in the feedback loop that modulates cerebral cortical function [76]. Disruption of corticostriatal pathways seems to be of particular importance with regard to neurobehavioral abnormalities. This is highly relevant in CP children because, for several reasons the basal ganglia are vulnerable to injury during a restricted period in brain development. High lactate (Lac) levels and low N-acetylaspartate (NAA) levels are the most common findings. A fall in the NAA/choline (Cho) ratio also indicates an adverse prognosis. NAA is a neuronal marker, the other metabolites can be viewed as cerebral indicators of energy metabolism creatine (Cr) and of cytoplasmic Lac and mitochondrial glutamate-glutamine (Glx) redox state. Myo-Inositol (mI) is a precursor for the phosphatidylinositol second messenger system, regulates osmotic processes within the brain and takes part in mood states. We used ^{1}HMRS to children with SD to determine the metabolite profile of SD children in the basal ganglia, and the relationship of this profile with motor and mental development [77]. ^{1}H-MR spectroscopy single-voxel (8 cm^3) located in the left basal ganglia (thalamus, capsula interna) from an axial section was applied. Seventeen SD children had hypoxic-ischaemic lesions with patterns of PVL (see *Fig. 1*, *2* and *3*) subcortical lesions or cortical infarction in MR. Two patients had normal MR scans. The reduced ratios of NAA/Cr, NAA/Cho, NAA/mI, Cho/NAA, Cho/Cr and Cho/mI of SD children and controls in the basal ganglia differed significantly (*Tab. 1*). On the other hand, we noted increased ratios of Cr/NAA, Cr/Cho and mI/NAA in the SD patients as compared with the controls. NAA/mI ratios were positively correlated with the severity scale of CP in SD children. Cr/NAA ratios were significantly correlated with the mental retardation in SD patients. In this study, we found reduced values of NAA and Cho in the basal ganglia in SD children. This may be indicative of neuronal loss subsequent to an anoxic episode during the prenatal or perinatal periods. After all, elevated Cr values in SD children may reflect an increase in the metabolism in the basal ganglia and the existence of compensatory mechanisms-plasticity. And increased mI/NAA ratios suggest the existence of gliosis in the examined patients. Only in one study [78] of Krägeloh-Mann et al., ^{1}H MRS was performed on two children with dyskinetic CP. They found a decrease in NAA/Cr and Cho/Cr ratios in the basal ganglia. To our knowledge, no HMRS study has been conducted in children with SD. We postulate that HMRS may be a useful technique in the determination of plasticity processes in the brain.

Conclusions

Children with cerebral palsy have remarkable ability to recover from early brain injuries. Mechanisms of brain plasticity include: a change in the balance of excitation and inhibition; a long-term potentiation or long-term depression; a change in neuronal membrane excitability; the anatomical changes, which need a longer period of time.

The molecular mechanisms of brain plasticity are under intensive researches. Calcium ions, calcium channels, NMDA receptors, free radicals, lipid peroxides and neurotrophins play a major role in these processes. At present, the neurophysiologic and MRI techniques are able to disclose the plasticity in children with cerebral palsy. Quntitative EEG and spectroscopy magnetic resonance are useful tools in the determination of plastic changes in children with cerebral palsy.

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