Neurophysiologic studies of brain plasticity in children with cerebral palsy

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Abstract

The 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-formation of new axon terminals and new synapses. There are few tools for brain plasticity investigations. The utility of the neurophysiologic in the determination of brain reorganization and repair in patients with cerebral palsy (CP) are described. The authors discuss also their results of quantitative EEG, visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs) in children with CP. They showed the existence of brain reorganization and repair in children with CP.

Key words: brain plasticity, cerebral palsy, EEG, visual evoked potentials, somatosensory evoked potentials.

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 [1,2]. Children have a 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 [3]. 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.

In the 1980s and 1990s, a great deal of excitement was generated by new insights into new mechanisms of brain damage during hypoxia/ischemia [4-6]. It was well known that hypoxia/ischemia lasting more than a few minutes could cause irreversible brain damage. Further research indicated that reperfusion might cause more damage than simple hypoxia [6,7]. 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 damage in the original cell that spreads to neighboring cells [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 are associated with increased brain activity. Furthermore, glutamate-induced excitotoxicity is a major mechanism by which neuronal loss may occur [7,8].

Cerebral palsy

Cerebral palsy (CP) is a chronic disorder of movement and posture caused by non-progressive damage to the developing brain, which occurs prenatally, perinatally or postnatally. Patients with CP may have some problems other than this motor impairment; mental retardation, epilepsy and sensory disturbance [9-12]. CP prevalence is increasing since more premature infants survive because of better neonatal care [9,12]. Spastic diplegia is the commonest form of CP as a results of injury to the periventricular leukomalacia (PVL) ring a temporal window of development that ends at 30-32 weeks [12]. A characteristic feature of PVL is the disruption of corticospinal axons, while the

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cortical pyramidal projection neurons are left intact and subsequently make aberrant intracortical axonal projections [13]. The rapidly expanding understanding of CNS axonal regeneration indicates that with early intervention there are realistic prospects of inducing corticospinal axons to regrow through the cystic areas of PVL and to find their appropriate targets [13]. Myelin is inhibitory to axonal growth but this should not pose an encumbrance to axonal regrow, since the corticospinal tract is poorly myelinated before term [14,15]. Recently, it has been demonstrated [16] that corticospinal axons are actively growing, innervating the spinal cord and expressing 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 centers but also by facilitating their subsequent normal development.

There are few tools for brain plasticity investigations. Recently, it has been made possible for neural plasticity to be measured validly with transcranial magnetic stimulation techniques (TMS), and mapping EEG.

More recent studies have concentrated on the recovery and plasticity in the stroke patients [17,18,19,20]. Few investigations have been performed on children with cerebral palsy [21,22].

This review describes neurophysiological imaging studies of brain plasticity in children with CP.

EMG studies

Carr and colleagues [16] studied the central motor reorganization in subjects with hemiplegic CP. The corticospinal projections were investigated by using focal magnetic stimulation of the motor cortex. Reflex pathways were examined with digital nerve stimulation. In 64% of the patients, there was evidence of 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.

Coherence EEG studies

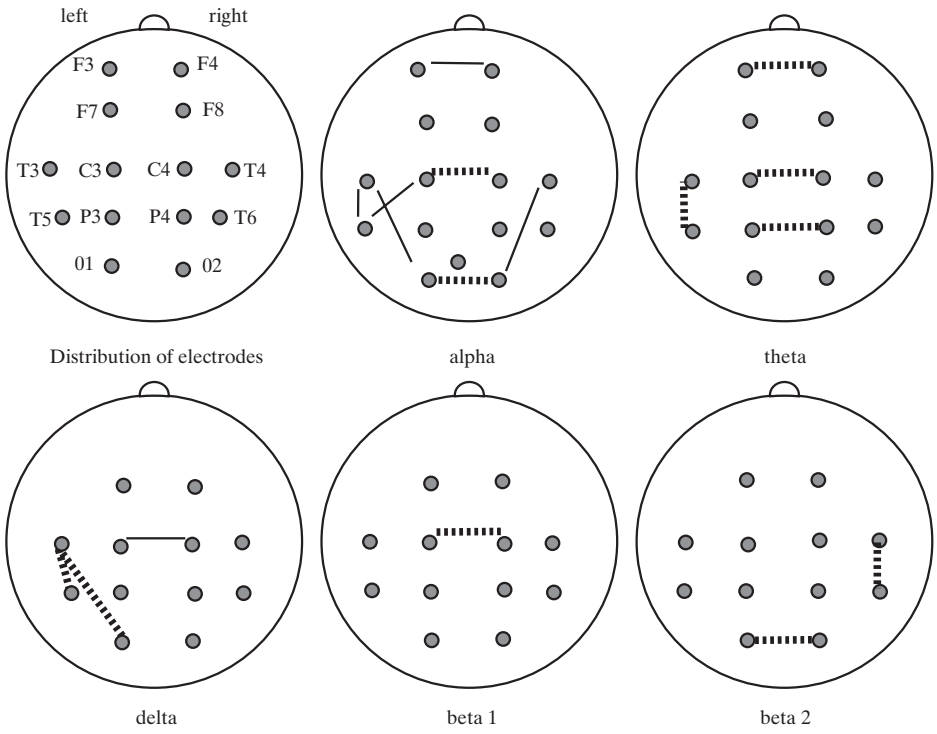
The EEG changes in CP patients generally reported are non-specific [10,23]. On the other hand a quantitative EEG (power spectra and coherence) provides objective measures in the search for global or focal abnormality which, if present, may signal an underlying organic process [24]. The coherence is a function of frequency [25]. Coherence is an amplitude independent measure of phase synchrony between EEG signals, reflecting functional interregional coupling and depending mainly on structural connections. The coherence values are interpreted in terms of differences in connectivity between brain structures [26]. Coherence has been found to vary with numerous disease states. Certain regions and frequency range increase in coherence in multi-infarct dementia, AIDS and mild head injury, while the decreases in Alzheimer's disease and depression [27,28].

Koeda and Takeshita [29] 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 were found in EEG spectral power density in these patients. A lower ICoh values 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. They suggested that these neurophysiologic abnormalities in preterm SD children corresponded neuroanatomically to callosal thinning and neuropsychologically to the visuoperceptual impairments. These findings are in agreement with our results [30].

We investigated the quantitative and coherence EEG on a larger group of patients with SD [10]. A group of twenty-nine children with SD was studied. EEG records were compared with 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. A significant decrease in power alpha at occipital derivations was demonstrated in the children with SD as compared with the control group. On the other hand, there was an increase of theta power and delta bands almost in all the leads. A significant decrease in ICoh coherence values in children with SD for the alpha and delta bands in the frontal and central leads as compared with the controls was observed (*Fig. 1*). In contrast, higher ICoh coherence values were detected at the frontal, central, parietal and occipital leads for the alpha, theta and beta 1 bands. Lower HCoh coherence values were noted in the patients at the temporal-occipital derivations. In contrast, we also detected higher HCoh values at the temporal and temporal-occipital derivations for the delta and beta bands. The results presented confirm the presence of anatomic-neurophysiologic abnormalities and the existence of compensatory mechanisms in children with SD.

Hemiparetic cerebral palsy (HCP) is one of the form of CP [9]. HCP often predicts which patients will develop cognitive disabilities and/or unprovoked seizures. We investigated the spectral and coherence EEG in children with spastic hemiplegia [30]. 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 a similar age. In this study we found significant differences in the distribution of the alpha,

Figure 1. **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) [10]**



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 the 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. The HCoh asymmetry, which implies relative hypoconnectivity within the left hemisphere as compared with the right, 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.

Visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs) studies

Most studies [31,32] have proved VEPs to be accurate predictors of the outcome in term infants with hypoxic-ischemic encephalopathy. However, there are few reports [32] on VEPs in children with CP. More recently, Costa et al. [33] evaluated grating acuity in children with CP by sweep VEPs and found a high correlation between the grating acuity and the motor impairment classified by The Gross Motor Function Classification System. More recently, serial recordings have been performed in order to get information on the course of diseases or on intervention effects. Mild SEP abnormalities have been demonstrated not only in direct focal lesions of the cortex, but also as a consequence of lesions of other brain structures functionally linked to sensorimotor cortical areas [34]. SEPs have been shown to be of prognostic value after brain injury [34,35].

We evaluated VEPs and SEPs on 20 children with spastic CP, and 42 healthy children as controls [36]. All MR scans were obtained using a 1.5 T MR scanner. We found a significant difference in the latencies P100 between the CP and controls. No correlations between increased P100 latencies and asphyxia, prematurity, the CP severity, MRI findings and mental retardation were noted. A significant difference of N13-N20 conductions (SEPs) between the subjects with CP and the control group was found (*Tab. 1*). Furthermore, SEPs were positively correlated with mental retardation in CP children. It has been suggested that VEP latencies are valuable estimators of neuronal injury and even predictors of later intellectual performance [37]. In our study, latencies of VEPs were increased more frequently in the CP patients with alterations in the optic radiation by MRI.

In summary, children with CP have a remarkable ability to recover from early brain injures. At present the neurophysiologic techniques are able to present the plasticity in children with cerebral palsy. Quantitative EEG, VEP and SEP can be useful tools in the determination of these plasticities in children with CP. The authors have demonstrated the existence of two processes in the brain: damage and recovery.

***Table 1*. Somatosensory evoked potentials (SEPs) in children with cerebral palsy (CP) (n=20) and controls (n=42). Kułak et al., 2005 [36]**

CP		Controls	
Left stimulation/Latencies (ms)			
N9	9.14±0.99	N9	9.38±0.76
N13	12.04±1.12	N13	12.29±0.95
N20	17.93±1.50	N20	18.09±0.99
N25	21.32±1.62	N25	22.41±1.99
Right stimulation /Latencies (ms)			
N9	9.18±0.97	N9	9.41±0.72
N13	12.06±1.28	N13	12.32±1.03
N20	17.96±1.65	N20	18.41±1.06
N25	21.76±1.89	N25	22.61±2.12
Left stimulation/Conductions (ms)			
N9-N13	2.64±0.32	N9-N13	2.86±0.38
N13-N20	6.36±1.08*	N13-N20	5.75±0.29
Right stimulation/Conductions (ms)			
N9-N13	2.70±0.40	N9-N13	2.94±0.52
N13-N20	6.44±1.01*	N13-N20	5.85±0.64

* $p<0.05$ vs controls

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