Review Article • DOI: 10.2478/s13380-011-0006-5 • Translational Neuroscience • 2(1) • 2011 • 33-42

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EARLY BRAIN INJURY AND PLASTICITY: REORGANIZATION AND FUNCTIONAL RECOVERY

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Abstract

One of the most remarkable observations in developmental neuroscience is the plasticity of the developing brain. Although recent findings suggest that the developing brain possesses substantial compensatory potential, the mechanisms of reorganization and its limitations remain largely unknown. This review includes studies elucidating the complexities of brain reorganization in response to early brain injury. It describes the factors influencing the pattern and degree of brain plasticity, provides insight into the patterns of reorganization in different brain systems and offers guidelines for clinicians in the field of neurorehabilitation. This knowledge is crucial in clinical work when designing the appropriate type and timing of interventions for children with early brain injuries.

Keywords

• Early Brain Injury • Plasticity • Reorganization • Functional Outcome • Rehabilitation • Timely Appropriate Interventions

Received 25 February 2011
accepted 04 March 2011

1. Introduction

There are two main structural processes in which the central nervous system maintains function after damage. They are regeneration and compensatory plasticity. Regeneration involves the process in which the cut axon begins to regrow from the damaged end and elongates through or around damaged tissue in order to reconnect with deafferented targets. The process of compensatory plasticity is quite different. Here the undamaged neurons grow new axonal connections to deafferented targets. It is interesting that this new axonal growth can be quite distant from the original injury site. It is assumed that these two types of recovery share a similar molecular basis [1].

The term plasticity refers to the brain's ability to learn, remember and forget as well as its capacity to reorganize and recover from injury [2]. It is enhanced in the developing brain and its basic mechanisms include neurogenesis, apoptosis or programmed cell death and activity-dependent synaptic plasticity [3]. During the second trimester of fetal life neurogenesis and apoptosis are carefully controlled processes that ensure a proper number of neurons in each brain region. Animal studies indicate that there is a marked overproduction of neurons in the fetus compared to the final number in the mature brain [4]. This overproduction of neurons could be adaptive for the brain by creating a reservoir that is available to repair injury in the fetus [5]. The changes in the strength of synapses and reorganization of neuronal networks also play important roles in brain plasticity. An early postnatal burst of synaptogenesis, followed by activity-dependent pruning of excessive synapses are characteristic of the developing brain [6]. This phenomenon may contribute to cortical plasticity by providing an excess of synapses to be selected based on experience during childhood [5].

The immature central nervous system responds to injury with a remarkable re-routing of neuronal pathways from undamaged areas to re-innervate denervated areas. This lesion-induced plasticity following early brain injury occurs in all systems studied so far, including the visual, auditory, sensorimotor and limbic systems [7]. This continuous process allows remodelling of neurosynaptic maps [8], while the organization of neuronal networks are "under construction" in the developing brain. The better functional outcome often seen after early brain injury as compared to the same injuries sustained in adulthood, is thought to be underlined by this new pathway formation. This observation has fueled the plasticity hypothesis [9,10]. Plasticity perspectives are underpinned by the assumption that the young brain is less functionally committed than the adult brain, and so it may be more easily reorganized following injury. It is thought that plasticity is maximal in early development when the central nervous system is less rigidly specialized [11,12] and synapse connections remain unspecified. Such flexibility is an advantage for the reorganization of functions.

In contrast, an early vulnerability approach sees this lack of specialization as a disadvantage, suggesting that early brain injury can lead to maladaptive recovering [13]. Hebb [14,15] argued that plasticity theories

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have ignored the possibility that brain injury will have different consequences at different developmental stages.

Despite the evidence that the developing brain has a capacity for neural restitution via neural regrowth or anatomical reorganization [13,16], there is ongoing controversy as to the implications of these processes. Full recovery may be limited by inappropriately established connections [16] resulting in dysfunctional behaviour, or by a "crowding effect" [17] where the functions of damaged tissue are diverted or "crowded" into the remaining areas of healthy brain tissue leading to a general depression of all abilities.

This plasticity-vulnerability debate sets plasticity in the immature central nervous system as a controversial issue in developing neuroscience. However, it is important to stress, as mentioned by Meeks and his colleagues, that "cerebral vulnerability and plasticity are mutually exclusive alternatives: a full understanding of the effects of brain injury requires both" [18]. These factors play a role at each new stage of development following early brain damage.

The purpose of this review is to illustrate the complexities of brain reorganization in response to early brain injury and to highlight the factors influencing the pattern and degree of brain plasticity. Furthermore, this review aims to present implications for rehabilitation and guidelines for establishing timely and appropriate interventions.

2. Factors influencing brain plasticity

The ability of the developing brain to reorganize after injury involves a complex interplay among various factors within a biopsychosocial context [19]. The biological factors include the severity of the brain injury and specific injury factors, such as lesion size. It would be naive to discuss lesion size without considering topography of the lesion. The location of the brain lesion clearly affects the pattern of recovery. Other relevant domains include the maturational state of a particular brain system when it is injured. An important factor which strongly influences the ability of brain reorganization, and one that has received little attention [20], is the integrity of neuronal circuits surrounding and contralateral to the lesion at the time of injury. The psychosocial resources include the support of family and community and the role of rehabilitation treatment (Figure 1).

2.1. Extent and topography of lesions

Current findings suggest that extent and location of brain injury are likely to predict severity of residual impairment [21-23]. Bond Chapman's discourse studies in early brain injury have shown a strong association between long-term outcome and injury variables, such as size and site of lesion [24-26]. Larger lesions were related to poorer outcomes on both discourse measures and cognitive measures of planning, problem solving and memory [27]. Concerning lesion focus, children with lesions in the frontal regions performed lower on discourse tasks than children matched for severity but with lesions outside the frontal regions [24,28]; while children with left frontal lesions showed reduced word fluency [29].

Furthermore, poorer cognitive and discourse outcomes have also been associated with subcortical lesions [27]. Both anterograde and retrograde neural connections can be interrupted with subcortical lesions, leading to degeneration of regions distal to the injury. It is also possible that very early subcortical injury is particularly detrimental to cognitive development because it disrupts later cortical and white matter maturation [19]. This explanation is consistent with evidence that the normal development of early-maturing brain regions is essential for the normal development of late-maturing brain regions [30,31]. Consistent with existing literature [32,33], Westmaccott and colleagues [34] found that combined cortical and subcortical lesions were more detrimental to cognitive outcome than injury affecting either cortical or subcortical tissue alone. This effect remained significant even after the authors factored in the contribution of lesion size.

Concerning motor outcome, Holmström and associates [35] found that the extent and location of the lesion is a strong predictor of hand function in children with unilateral cerebral palsy. Children with a severe degree of white-matter loss or with basal-ganglia/thalamus involvement had more impaired hand function. It appears that the capacity of the developing brain to reorganize after injury is diminished with combined lesions to cortical and subcortical areas.

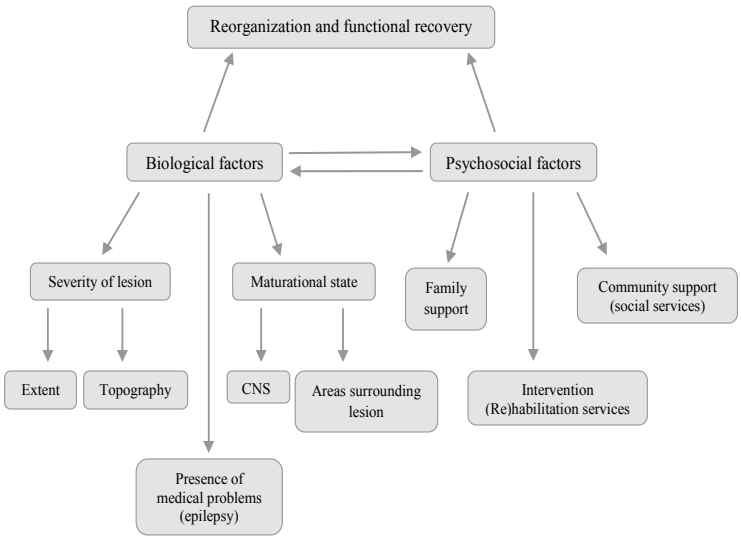

Figure 1. Factors influencing reorganization and functional recovery following early brain injury.

2.2. Timing of early brain injury

The developmental stage of the child at the time of injury is a dimension with major controversy regarding its potential impact on functional outcomes. At the core of this debate is the "plasticity" versus "early vulnerability" theories which dispute whether the immature brain has a greater capacity for recovery than the mature brain.

In order to study the impact of age at injury, it is necessary to compare outcomes associated with brain injury sustained at different time points. This is particularly essential for skills which demonstrate developmental trajectories across timeframes [33]. Thus, most studies which have examined the impact of age at brain injury have focused on cognitive outcomes. Findings have been inconsistent, likely due to within-study and between-study heterogeneity in terms of etiology, age at assessment, lesion size and location, the specific cognitive skill in question and the cognitive measures used [34]. Some authors have found that the first two years of life to be the period of highest vulnerability [36], others have found the poorest outcome to be when lesions occur between 1 month and 5 years of age [37], and still others have found no clear relationship between age at injury and cognitive outcome [32]. These contradictions suggest that multiple factors interact with the patient's age at the time of brain injury on cognitive outcomes, leading to the assumption that developmental plasticity may not be understood along the sole dimension of age and that age serves as a moderator but not as a predictor of outcome [21].

In the largest study of cognitive outcomes following pediatric brain injury, Westmacott and colleagues [34] found that an earlier age at the time of injury was associated with weaker cognitive performance overall, but the relationship was modulated by lesion size. Subcortical lesions (basal ganglia and/or thalamus) in the perinatal period appear to be particularly detrimental to future cognitive outcomes. Children in whom subcortical injury occurred before the age of 28 days performed significantly more poorly than children in whom a similar stroke occurred later on in life. In the case of cortical injury, they found that the period of greatest vulnerability appears to be between 1 month and 5 years of age. Cortical injury during this period was associated with significantly weaker cognitive skills than when compared with earlier or later cortical injury. These findings show that there is an earlier period of peak vulnerability for subcortical than for cortical injuries, indicating that vulnerability is dependent upon lesion location. As subcortical structures are developing earlier than cortical structures [38], these results are in concordance with the notion that developmental "windows" with an increased intensity of events are vulnerable periods [39]. Finally, combined cortical-subcortical injury was associated with weak performance on all cognitive measures, regardless of age at injury. It can be proposed that the relationship between age at injury and cognitve outcomes is non-linear and modulated by variables such as lesion type, lesion location and the specific cognitive skills in question [40].

Recent studies have shown significant correlation between the gestational age at the time of insult and the reorganization efficacy of the ipsilateral corticospinal tracts. [41,42]. Staudt and colleagues [41] demonstrated more efficient reorganization for hand function in children with congenital brain lesions in the first and second trimester versus the early third trimester versus the late third trimester. These findings were confirmed in a study by Feys [43].

Therefore, while timing of early brain injury determines the nature of impairment; the extent and location of injury are likely to predict its severity [23].

3. Reorganization of cerebral systems

Highly localized functions of the cerebral cortex can become remapped across the cortical surface as a result of early injury. Remapping produces a different brain and the key element of this reorganization is the enormous potential of immature neurons to modify connections and to contribute to neural compensations that will result in relatively normally organized behaviors [44]. Two competing views of brain plasticity and reorganization have emerged in research literature as a result of conflicting findings. The plasticity approach is supported by evidence of better recovery of "essential" motor and language functions in very young children with focal brain injuries compared with older children and adults [45]. Recent functional neuroimaging findings have begun to delineate possible mechanisms for this cerebral reorganization associated with successful development of language and/or motor function [46,47]. However, evidence exists demonstrating that injured immature brain is limited in its capacity to compensate and support the development of higher-level cognitive skills [48]. This suggests that reorganization after early brain injury is not always associated with positive or adaptive long-term outcomes for higher-level cognitive skills, giving rise to the early vulnerability hypothesis [39].

Developing systems are progressively adaptive and the final reorganization of the brain will reflect an alternative developmental pathway. The route or direction of our clinical work should be focused on "defining the multiple, alternative patterns of brain reorganization that can arise following early injury, and not on identifying a typical profile of functional reorganization" [49].

3.1. Motor system

The motor cortex and/or corticospinal tract is a common site of brain injury in the prenatal and perinatal period [50]. Lesions at such an early stage may lead to substantial reorganization of the corticospinal system during subsequent development [51,52]. The normally transient existence of ipsilateral corticospinal projections provide the basis for motor reorganization following early brain injury. Possible mechanisms include the development of new ipsilateral corticospinal projections, double-crossing of contralateral corticospinal fibres and the reinforcement of existing ipsilateral corticospinal pathways [53].

Since prenatal lesions occur during the period when ipsilateral and contralateral corticospinal motor projections compete for synapse space with spinal alpha-motorneurons, extensive lesions can influence neuronal activity of the crossing projections from the affected hemisphere and give them a "disadvantageous" position [54]. Thus during

this phase, the ipsilateral projections from the unaffected hemisphere may exceed the contralateral projections in terms of neuronal activity, which will lead to the withdrawal of contralateral projections and the maintenance of ipsilateral projections. As a result, the unaffected hemisphere becomes equipped with fast-conducting ipsilateral projections to the paretic limbs [41,57]. The presence of ipsilateral corticospinal projections in the reorganization of the motor system has also been demonstrated in a fMRI study in patients with perinatal unilateral brain injury. Finger movements of the affected hand produced widespread activation of the intact ipsilateral, hemisphere [57].

Studies involving children who have suffered perinatal brain damage have shown different patterns of corticospinal system development after unilateral and bilateral lesions to the corticospinal tract. In children with unilateral perinatal lesions, progressive loss of response from the affected hemisphere was associated with the rapid development of the contralateral and ipsilateral corticospinal projections from the unaffected hemisphere [50]. In contrast, subjects with extensive bilateral perinatal lesions had an essentially normal pattern of development of the corticospinal projection (fast conducting contralateral and slower conducting ipsilateral corticospinal projection from both hemispheres) [50,51]. Eyre [50] suggests that activity-dependent competition for spinal synaptic space between the contralateral projections from one hemisphere and the ipsilateral corticospinal projections from the other, can provide an explanation for these findings. The evidence for such competition is provided by Martin in studies involving cats [52]. When a neuron's activity in one sensorimotor cortex is inhibited during development, it fails to maintain contralateral endings in the spinal cord and its synaptic space is taken over by increased ipsilateral terminations from the normally active hemisphere [58,59]. When both sensorimotor cortices are inhibited, the normal pattern of ipsilateral and contralateral terminations is maintained from both hemispheres [60]. Salimi and Martin [61] have also shown that unilateral electrical stimulation of the corticospinal tract during development will lead to persistence of the ipsilateral endings from the stimulated hemisphere and to a loss of contralateral ones from the non-stimulated side.

When considering the functions based on such ipsilateral projections on the control of paretic hands, great variability is found. Some patients show a useful grasp function, but near normal function has never been reported with only ipsilateral motor control [41,62]. Some patients cannot use their paretic hand for active grasping although the existence of such fast-conducting pathways is confirmed. This variability can be attributed to the maturational stage of the central nervous system at the time when the injury occurred. Staudt maintains that the earlier the brain lesion occurs in development, the better the functional outcomes of a paretic hand [41]. Thus, many children with brain injury acquired around or after term birth will develop no useful hand function although ipsilateral tracts are maintained [41,55]. To summarize, when the corticospinal reorganization occurs very early in development, the abnormal ipsilateral projections can establish appropriate networks required for effective hand control. When reorganization occurs relatively late, ipsilateral projections cannot establish appropriate networks, which will result in greater motor disability of hand [54].

3.2. Somatosensory system

It is hypothesized that intra-hemispheric reorganization is the main compensatory mechanism of the sensory system. A magnetoencephalography study by Staudt involving patients with periventricular lesions revealed that primary somatosensory representations (S1) of a paretic hand was preserved in its original topography in the Rolandic region of the affected hemisphere [54]. This confirms that afferent thalamo-cortical somatosensory projections had "detoured" the lesion to reach their original cortical destination area in the post-central gyrus. It should be noted that thalamo-cortical projections reach their cortical destination sites only during the third trimester of pregnancy [63] and thus these projections are often not primarily damaged in the case of periventricular brain injuries.

Functionally, such patients typically show none or only few somatosensory deficits which is in contrast to the marked motor dysfunction [64]. Patients display so-called "hemispheric dissociation" [54] between a contralaterally preserved primary somatosensory (S1) and an ipsilaterally reorganized primary motor (M1) representation of the paretic hand. As intra-hemispheric interconnections between primary sensory and motor cortex are considered crucial for the quality of motor performance and for the degree of recovery following focal lesions [65], this should be considered during the planning of interventional strategies.

3.3. Language

In terms of language, it is now accepted that even large lesions of left hemisphere can be nearly fully compensated if the insult occurs during the prenatal or perinatal period; whereby the right hemisphere takes over the development of language functions [66]. This reorganization pattern occurs in areas homotopic to the classical language zones in the left hemispheres of healthy subjects [67,68]. The threshold for shifting the future language dominance to the right hemisphere is apparently low [47]. This can occur even in the absence of direct cortical damage in subcortical lesions, and correlates with left facial motor tract involvement, suggesting that impairment of speech motor output from the left hemisphere can induce an inter-hemispheric reorganization of productive language functions [69]. Accordingly, no such shift was observed for a function which does not depend on motor output, that is, the perception of speech [70]. Patients with large left-hemispheric lesions display a hemispheric dissociation between a left hemispherically preserved perception region and a right hemispherically reorganized production of speech region. This parallels findings observed in the sensorimotor system.

This language reorganization relies on the inborn ability of the intact right hemisphere to acquire language dominance, which is based on an initially bilateral processing of lingusitic

information [47]. Therefore the architecture of the resulting right-hemispheric language network is almost an exact mirror image of the normal distribution of language zones in healthy individuals.

Patients with such language reorganization are typically slower in the early phases of language development [71], but often have normal verbal intelligence quotients. However, more recent studies have found that deficits in higher-level aspects of language processing (discourse, complex syntax, making inferences) emerge later on in development [72,73].

Such right-hemispheric language networks lead to deficits in visuospatial and visuoconstructive functions [74]. This is known as the crowding effect, a term first described by Teuber [75] in adults with brain injury and later by Carlsson and colleagues [76] in children with hemiplegia. This phenomenon postulates that the right hemisphere has difficulties with the mediation of both verbal and nonverbal functions, which causes visuospatial impairment due to language dominance.

Although several mechanism of this language reorganization have been described, most studies to date have focused on unilateral lesions. Since many mechanisms of reorganization observed after unilateral lesions involve homotopic areas in the unaffected hemisphere, it would be beneficial to research this process in the case of bilateral lesions.

3.4. Visual system

Periventricular leukomalacia (PVL), a common lesion in preterm infants, is primarily localized in the parietooccipital area. Therefore, it serves as a proper model to study the impact of early lesions on vision and visuoperception [77,78]. The parietooocipital periventricular lesions lead to long-term disturbances in visual perception, even when relatively small. Pavlova and colleagues [78] found that even mild PVL, not leading to damage of the primary visual system, causes deficits in biological motion detection. It seems that subcortical lesions interfere with functions of secondary visual brain areas. Although these lesions are acquired very early in brain development (early third trimester), they cannot easily be compensated [77]. As the gestational age associated with highest incidence of PVL coincides with the peak of subplate development [79], this lack of compensation is expected. Namely, it is known that subplate neurons are required for normal visual cortical development.

3.5. Cognition

Hebb [14] concluded that for cognitive skills, early brain injury may be more detrimental than late brain injury; while cognitive development depends upon the functional integrity of particular cerebral structures at certain stages of development. Thus, if a cerebral region is damaged during a critical stage of cognitive development, reorganization will not be able to compensate for the damage [31,80,81]. This cascade of neurobiological events can result in cumulative or emerging deficits in higher-level cognitive skills [34].

Ballantyne et al. [82] examined the stability of cognitive abilities during development in children with perinatal injury. They found no evidence of decline in cognitive function over time. The results of this study indicate that the brain is able to compensate after early injury and maintain a steady rate of development. This is in concordance with the findings of a longitudinal study of intellectual development in children with congenital hemiplegia [83].

4. Implications for rehabilitation

Because of enhanced plasticity mechanisms, the developing brain is under the strong influence of the environment, and the structure of certain brain circuits can change in response to environmental stimuli [53]. The idea that experience might modify the organization of neural circuits is at the core of Hebb's neuropsychological theory on the organization of behaviour [15]. Hebb states that the structure of cortical neurons is influenced by various types of sensorimotor experience.

Activity-dependent mechanisms which are at the core of developmental interventional strategies, may have a significant impact on the degree of functional recovery [84]. Environmental enrichment holds the promise of being extremely valuable in neuroscience rehabilitation [85]. Prolonged in vivo imaging of neurons in rodent cerebral cortex indicates that sensory experience drives the continuous sprouting and retraction of synapses located on dendritic spines to remodel neural circuits [86]. Similar mechanisms are probably responsible for enhanced excitability in cerebral cortex that has been documented following short periods of motor skill training using the hands or lower legs [87]. Kolb and Gibb [31] also summarized that interventions of complex housing and tactile stimulation experiences soon after early lesions in rats, generally led to improved behavioural outcomes correlated with selective anatomical measures.

There is a general correlation between behavioral development and temporal periods of dynamic change in synaptic number in specific cortical regions [5]. It is widely accepted that placing a patch over an eye with good vision to reverse unilateral amblyopia, related to strabismus, is less effective after 12 years of age. This is the same time when the number of synapses in the occipital lobes is rapidly declining [88]. This suggests that for the acquisition of certain skills, there is a window of therapeutic opportunity, which needs to be timely recognized for achieving functional recovery.

Sensory input augmentation and somatosensory training have been utilized by therapists with the belief that these interventions promote plasticity and recovery. Scientific evidence from animal models has shown that representation within the somatosensory cortex are use-dependent [89,90]. With this in mind, it should be supposed that children with brain injuries may be able to improve their somatosensory responsiveness and organization via appropriately implemented interventions. These neurophysiological changes might lead to the enhancement of motor control and improved ability to learn new motor skills [91].

These interventions can enhance recovery if they are designed to take advantage of the brain's intrinsic plasticity mechanisms. Nevertheless, the efficacy of an intervention is dependent on a number of factors, including age at the time of injury, size and topography of the brain lesion, maturational state of the brain, the integrity of brain areas surrounding the lesion, and the presence and duration of other medical problems [92-95]. When considering

the timing and type of intervention, the ontogenetic neural timetable [96,97] and the developmental window for a certain neural system [98] should be consulted (Figure 2).

It is important to emphasize that intervention implementation in children at neurodevelopmental risk should be adapted to the infant's age. In a systematic review of the effects of early intervention on motor development, Blau-Hospers and Hadders-Algra [99] demonstrated that the type of intervention most beneficial for infants at preterm age differs from the type that is most effective in infants who have reached term gestational age. The implementation of active forms of intervention prior to term age appears to be a source of stress. Research on rodents showed that stress during early development (equivalent to the second half of human gestation) can result in unfavourable changes in catecholaminergic content of the cortical and subcortical regions [100]. Therefore it has been suggested by Blau-Hospers and Hadders-Algra that interventions prior to 40-44 weeks should focus on mimicking the intrauterine environment.

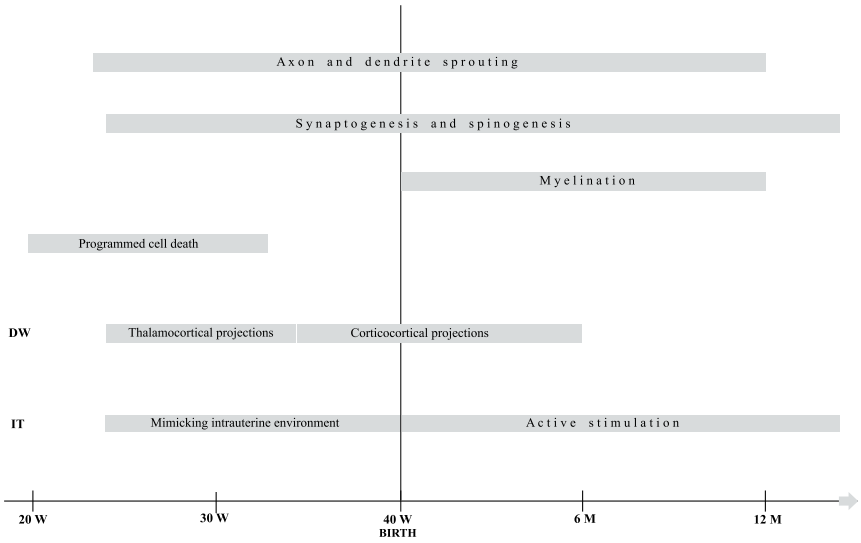

Figure 2. The most intensive neurogenetic events during human preterm and postnatal period, the developmental "window" for structural-functional plasticity of neural systems and appropriate type of interventions (W=weeks PMA, M=postnatal months, IT=intervention type, DW=developmental window). The scheme is modified according to Graaf-Peters and Hadders-Algra, 2006 and Judaš et al, 2011.

5. Conclusion

There is a great capacity for functional reorganization following early brain injury in developing human brain, but there are also limitations. Those limitations are quite apparent in the motor system, where even small periventricular lesions can cause hand motor dysfunction. The maintenance of ipsilateral corticospinal tracts in these patients has a certain but incomplete, functional role. The important message for clinicians is that it is possible for children with ipsilateral projections to develop fairly good hand function. This is in contrast with the language system, in which patients normal verbal IQ scores advocates its superior efficacy of reorganization. Despite differences in the efficacy of reorganization of motor and language system, mechanisms of their reorganizationn are similar. In both systems the contralesional hemisphere takes over the functions and, as stressed by Staudt [70], "it occurs always in cortical areas homotopic to the areas harboring the respective functions in the healthy brain". Interestingly, imaging studies suggest that productive/motor functions and perceptive/sensory functions are reorganized by different forms of neuroplasticity. Thus patients with large lesions show hemispheric dissociations between motor functions (interhemispherically reorganized in the contralesional hemisphere) and sensory functions (intrahemispherically reorganized in the ipsilesional hemisphere). This advocates for different reorganizational patterns between afferent and efferent functions in the developing human brain, related to their specific maturation timetables [63,95], suggesting that different stages of brain development may be critical for different functions. It can be rather stated that precise time is better, than earlier is better.

Concerning higher-level and later developing skills, it is clear that increased neural plasticity does not necessarily translate into better functional outcomes. As early biological injury may disturb the development of neural networks that support the acquisition of later developing skills, it is important to be aware that time does not always equal recovery in developing children [48]. Thus, children with early injuries may "grow into" their cognitive, linguistic and behavioral deficits as the injured brain matures [19,101]. It is therefore crucial for clinicans to observe these children at later stages of development to ensure any late-emerging deficits are detected.

Finally, there is a question of the functional significance of cortical plasticity. It is evident that recovery after injury involves a reorganization of the brain; however, the structural and functional changes that follow an injury may not necessarily prove to be adaptive, but instead may be disruptive to normal development [19]. As a consequence, plasticity after injury may occur at a cost; that is, this reorganization process may "crowd" the development of later-developing skills.

6. Future directions

Understanding the mechanisms responsible for brain plasticity and how they can be influenced to improve outcomes after brain injuries are areas of knowledge important for all neuroscience clinicians. An accurate structural and functional characterization of brain injury by neuroimaging techniques, would be highly valuable in defining optimal rehabilitation strategies [102]. This is particularly critical in the context of recent evidence that early experience (rehabilitation) has a strong influence on brain development [84].

Future research should be aimed to identify the mechanisms underlying the inherent

plasticity of a developing brain and to determine how these mechanisms can be manipulated to promote optimal recovery. A special focus should be established in answering the following questions: Can brain adaptability be given a boost with enriched stimulation? Can the structural and functional changes in brain be altered in adaptive ways with appropriate interventions? Can these interventions enhance neural connections and serve as a stopgap to avoid late-emerging deficits [19]? If yes, which type of interventions should we apply and more importantly, when is the most appropriate time to implement interventions in order to improve functional outcome?

To fully understand the effects of early brain injury, it is crucial to take a developmental approach. Increasing our knowledge about the effects of early injury on development and how these effects may change with age, has important theoretical implications concerning the limits and extent of functional plasticity. In addition, this knowledge may have important practical implications for planning interventions for children with early brain injury, even for those who appear to be functioning well at early stages of development.

Acknowledgements

I gratefully acknowledge the critical comments of assistant Professor Dr. M Heffer-Lauc on a previous version of the manuscript.

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