DISCUSSION OF DEVELOPMENTAL PLASTICITY: FACTORS AFFECTING COGNITIVE OUTCOME AFTER PEDIATRIC TRAUMATIC BRAIN INJURY

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Current research on plasticity has altered the over simplistic view of greater capacity in the developing brain after injury. In another paper in this issue, Dennis provides a model to elucidate the complexity of the multiple factors that influence recovery after brain injury in children. The authors present a brief summary of findings from their longitudinal research in neurobehavioral recovery after traumatic brain injury in children and adolescents that elaborates on the framework of Dennis. The discussion highlights the psychobiological factors that interact to define developmental plasticity and outlines promising directions for future research to elucidate and promote long-term recovery in pediatric brain-injured populations. © 2000 by Elsevier Science Inc.

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INTRODUCTION

Stein, Brailowsky, and Will (1995) defined plasticity as the capacity of the brain to adapt to the dings, dents, and major insults that alter it. Plasticity refers to the adaptive structural and functional changes that occur in the brain after lesions and during development (Buchwald, 1990) and is often inferred from performance on functional outcome measures (Edeline, 1999). Dennis presents examples representing a broad spectrum of brain etiologic factors that tempers long-standing theories of greater plasticity in children as compared with adolescents or adults. She makes an emphatic point that developmental plasticity could not be understood along the sole dimension of age because many deficits do not disappear with age. Clearly, some impairments in
young children increase in severity over time after injury. In addition, new deficits may emerge at later stages after injury. Therefore, age serves as a moderator but not as a predictor of outcome.

The ability of a young brain to adapt after injury unfolds in a protracted course where a number of critical factors play a role at each new stage of development into adulthood. Dennis conceptualizes the plasticity and reorganization after brain injury within a psychobiological context involving multiple factors, some endogenous and others exogenous. Specifically, recovery after brain injury in children involves a complex interplay among diverse factors such as the biological pathophysiology of the brain injury, the developmental stage at the time of injury, the amount of time after injury, and the child’s reserve or psychosocial resources. The psychosocial resources include phenomena such as the child’s premorbid abilities; clinical course of new skills acquisition; support of family, school, and peers; and the role of rehabilitation.

INSIGHTS FROM PEDIATRIC TRAUMATIC BRAIN INJURY STUDIES

In this section, we summarize evidence from our work and others that supports Dennis’s framework. Salient findings from studies of discourse, verbal fluency, and working memory are highlighted to elucidate the complex factors that may either enhance or exacerbate long-term recovery. A schematic for the diverse interdependent systems that influence developmental brain plasticity is illustrated in Figure 1. In closing, we suggest future directions for research and clinical care in understanding and promoting recovery from acquired brain injury in children.

Biological Insult

Congruent with the work of Chugani, Muller, and Chugani (1996), our research has shown that developmental brain plasticity is associated with a number of factors related to the severity of the brain injury and specific injury factors such as size and topography of the brain lesion. Other relevant domains include the maturational stage of the brain system and the integrity of neuronal circuits surrounding the lesions at the time of injury. One of the most robust findings from our discourse studies in pediatric brain injury has been a strong association between long-term outcome of discourse abilities and injury severity (Chapman et al., 1992; Chapman, Levin, Matejka, Harward, & Kufera, 1995; Chapman, Levin, Wanek, Weyrauch, & Kufera, 1998). Injury severity was derived from multiple variables including depth of coma, coma duration, length of posttraumatic amnesia, and findings on structural brain imaging measures. Severe brain injuries in children and adolescents were related
to lower discourse performance (Chapman, 1995). In reviewing individual cases, however, severity of initial injury did not always correspond to degree of recovery, because some children with severe brain injuries showed relatively good recovery. This discrepancy for individual cases suggests that the variable of injury severity is more an indicator rather than predictor (Chapman et al., 1995).

We found that other injury variables, such as size and site of lesion, also influenced recovery after brain injury. As expected, larger lesions were related to poorer outcome on both discourse measures and other cognitive measures of planning, problem solving, and memory (Culhane, 1993; Levin et al., 1993). With regard to lesion focus, children with injuries to the frontal regions performed lower on discourse tasks than children matched for severity but with lesions outside the frontal regions (Chapman, 1995; Chapman et al., 1992; Culhane, 1993). Children with left frontal lesions also showed reduced word fluency (Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, submitted). Poorer cognitive and discourse outcomes have also been associated with subcortical lesions identified on magnetic resonance imaging (Levin et al., 1993; Levin, Devous, & Chapman, 1995). With subcortical lesions, neural connections both anterograde and retrograde may be interrupted, causing degeneration of regions distal to the injury.
It is interesting to note that the motor cortex has shown the largest potential for postlesional plasticity in children (Hertz-Pannier, 1999). Interhemispheric compensation occurs in most cases of large motor cortex lesions, and intrahemispheric compensation occurs with small lesions.

Injuries to frontal cortex may be detrimental in the developing brain because of the extended period of maturation and the developing complex neural pathways that are prematurely disconnected. Myelination of the sensory and motor areas of the brain is completed by age 2, whereas myelination in the frontal region continues throughout young adulthood (Reinis & Goldman, 1980). Myelin sheath covers the axons of neurons and provides signal conductivity required for impulse speed and efficiency. When a developing child has a frontal lesion, myelination is not only interrupted but may also be prevented from further formation, inhibiting adaptability of the developing brain. In terms of the complex neural networks, the frontal cortex receives projection fibers from the mediodorsal nucleus of the thalamus and has reciprocal connections both with lower levels of the brain and the basal ganglia, brain stem nuclei, hippocampus, and thalamus (Booth et al., 1999; Pennington, 1994). External input, forming information pathways from the posterior cortex, and information from internal states originating in the limbic system also converge in the frontal lobes (Lezak, 1983). When injuries sever the complex frontal network at any junction, regions distal to the injury are disrupted as indicated on functional brain imaging measures such as single photon emission computed tomography (SPECT; Chapman, 1996; Levin et al., 1995). Later maturation of frontal pathways may explain, in part, why frontal and subcortical white matter lesions can impede developmental plasticity.

Cognitive Stage of Child at Injury

Brain maturation and cognitive development are finely tuned. For example, a relationship between cycles of cognitive development and electrical brain wave (measured by electroencephalogram) growth has been identified by Case, Kurland, and Goldberg (1982). As a child’s intellectual development moves to a higher level of cognitive processing, cycles of electroencephalograph patterns change. As cognitive processing, such as working memory, expands mental demand during cycles of cognitive growth, electroencephalograph data suggests that new short-distance cortical connections are formed and controlled by the frontal lobes (Thatcher, 1991, 1992).

Two sides of the plasticity issue can be considered regarding the effects of cognitive stage of the child at time of injury. On the one hand, it has been proposed that prognosis is better for an early brain injury as compared with a later injury. From another perspective, prognosis could be less favorable if the injury occurred before later cognitive stages are achieved or before the brain has
reached mature neural connections. Whereas research can be cited to support either perspective, our research and others lend support for the latter view that an early injury could increase the difficulty in acquiring later cognitive stages.

With regard to discourse function, a younger age at injury has a more deleterious impact on long-term recovery. Five years of age represents a critical stage when basic narrative structure is generally acquired. Children injured before 5 years of age were found to have lower discourse scores than children matched for severity and age-at-test. However, the latter comparison group was injured after 5 years of age (Chapman et al., 1998). The greater vulnerability of early injuries was notable given the longer recovery interval for this early-injury group. Similarly, children with earlier age-at-injury performed consistently lower on verbal fluency measures than children injured at later ages (Levin et al., submitted).

Studies of working memory add further support to the importance of developmental cognitive stage at time of injury. Luciana and Nelson (1998) examined normal children aged 4 to 8 years of age performing various working memory tasks (e.g., spatial working memory, Tower of London sequential planning task). Findings showed a general age-related progression in ability levels of frontal lobe tasks, with 4-year olds performing worse than 5- to 7-year olds on all measures. Eight-year olds were superior to younger children in their ability to solve complex problems but had not yet reached adult levels of performance on the most difficult items of the Spatial Working Memory and Tower of London tasks. Conclusions stated that the development of cognitive functions such as working memory proceed dimensionally starting with refinement of basic perceptual and sensorimotor functions and culminating with the biological maturation of neural networks that integrate complex cognitive processing demands. In McKinnon’s (1999) study of pediatric brain injury, children with frontal lobe damage performed significantly poorer on a working memory dual task that required simultaneous processing of verbal and spatial components as compared with control participants. What was interesting in this latter study was that the children with frontal lesions had acquired the skills to perform within normal limits when the tasks were performed separately. This pattern is related to the challenge level of the task and is discussed later.

The possibility of reduced plasticity with earlier-age brain injuries for later emerging cognitive functions needs further verification. However, the preliminary evidence suggests that adaptability of the brain to recover previously acquired skills contrasts with the greater plasticity that occurs in acquiring new skills at later stages of development. Younger children use different cognitive strategies than older children in organizing discourse information. For example, normally developing children are less able to engage in gestalt level processing during interpretation of connected language and discourse. As more complex discourse processing skills are expected to develop, children with early injuries may fail to acquire later-developing, more efficient types of in-
formation processing strategies (Brookshire, Chapman, Song, & Levin, in press; Chapman, Levin, & Lawyer, 1999). Perhaps disruption in the supporting neural functional network may impede later emerging skill acquisition.

**Age and Lesion Focus**

An intriguing pattern that emerged from our previous research was a disparity in the relationship between age at injury and lesion focus. Specifically, frontal lobe injuries were more likely to produce specific cognitive-linguistic deficits in older-injured than in younger-injured children. Frontal lobe effects were reported for later injured children in separate studies of discourse function (Chapman et al., 1992; Chapman, Watkins, Gustafson, Levin, & Kufera, 1997) and for verbal fluency measures (Levin et al., submitted), but not for younger injured children (less than 8 years of age at injury).

One hypothesis that has been offered to explain the age-related frontal effects is that children with early frontal injuries may grow into their lesions, showing specific lesion effects only at later ages of brain maturation and cognitive development. Examining two cases, Anderson, Antoine, Damasio, Tranel, and Damasio (1999) found that early-onset lesions in prefrontal cortex caused long-term behavioral deficits. Both patients who were studied as young adults in their 20s had focal damage in infancy to prefrontal regions associated with moral development, and had no evidence of damage in other brain regions. The issue raised by the two cases was whether brain plasticity during development would compensate for the early damage. As adults, both individuals failed to acquire social conduct and moral rules. The researchers suggested that this sociocognitive ability had been permanently impaired by frontal lobe damage occurring before the age of 16 months.

Because this was a retrospective study, the precise age when the symptoms of impaired socialization emerged was unclear, although the behaviors were established as long standing. This preliminary evidence suggests that acquisition of stage-dependent cognitive reasoning purportedly subserved by frontal networks may be guarded when a frontal injury has occurred early in development. Whereas both children showed relatively good recovery in general abilities at the early stage of development, case history revealed consistent difficulties at later stages with moral reasoning. That is, these two children failed to acquire skills requiring abstract reasoning and reflecting on behavior at a stage when moral judgment should have normally appeared.

These results from Anderson and colleagues (1999) support the view that children may appear to function normally after frontal damage until they reach an age when frontal skills are more apparent. These two cases suggest that plasticity can be less compensatory for a younger child who has not yet acquired certain skills than for that of older injured children or adults. In older children and adults, they may have difficulty executing appropriate moral be-
behavior after frontal lobe damage, but they nonetheless are able to show they have the knowledge of appropriate behavior on judgment tasks.

**Time Since Onset and Challenge Level of Tasks**

At this stage of our knowledge, we have clear evidence that the brain can compensate for early injuries as shown in recovery of certain cognitive abilities. In our longitudinal study of more than 400 children with closed head injury, most children with severe injuries regardless of age at injury showed relatively good recovery of basic language, vocabulary, and syntactic abilities. This dramatic recovery typically occurred within 3 months of injury even after severe injuries. The recovery of the formal aspects of language (i.e., semantics, syntax) may be achieved through the recruitment of new sets of nerve cells to substitute for those injured. Perhaps these functions can be readily subserved and adapted for by other brain regions.

As discussed earlier, the picture of language recovery is not straightforward because plasticity for later emerging skills of discourse function may be more guarded after early injuries. We have documented later emerging discourse deficits some 3 years and more after injury in young children with severe closed head injuries (Chapman et al., 1998, 1999). In contrast to recovery in basic language skills, children and adolescents with severe brain injuries failed to acquire new skills related to organization of discourse and connected language commensurate with normally developing peers or later-injured children. This evidence of relatively good recovery of basic language skills with poorer discourse outcomes after severe brain injury supports Dennis’s claim that the challenge level of the task directly impacts conclusions drawn regarding brain plasticity. The evidence that children with frontal injuries performed similarly to normal control children on separate tasks of verbal digit span and spatial tracking, but significantly lower on simultaneous tasks (McKinnon, 1999), adds further support for the relevance for challenge tasks in understanding developmental plasticity.

With regard to time since onset of brain injury, the evidence warns against prematurely judging full recovery in children who are still developing. The clinical problem is that if these children are not observed at later stages of development, emergent problems may go undetected (Chapman, 1997). The possibility of disability increasing over time validates Dennis’s warning that time does not always equal recovery in developing children. Thus early biological injury may perturb development of the neural networks that support acquisition of later cognitive stages. As alluded to earlier, children with early injuries may “grow into” their cognitive, linguistic, and behavioral deficits as the injured brain matures (Bates, Reilly, & Marchman, 1992; Ewing-Cobbs, Levin, Eisenberg, & Fletcher, 1987). The issue of developmental plasticity continues to unfold over many years requiring long-term assessment of brain
adaptability to address adequately the child’s level of functioning at each new stage of development. Many children may “hit a brick wall” at new stages if the underlying brain systems are injured before a particular skill acquisition.

**Exogenous Factors**

The constellation of endogenous and exogenous factors influencing long-term outcome of traumatic brain injury is shown in Figure 1. Each constituent in the flow chart can affect outcome in either a positive or negative way. In this paper, we focused on the biological factors primarily because we know more about this domain and less about how environmental factors influence plasticity. Nonetheless, evidence from animal studies has shown a direct influence of enriched stimulation on adaptability of the brain (Greenough & Klintsova, 1999). In humans, studies have documented the vital role of exogenous factors such as family emotional and physical support, an extensive social network, and stimulating personal activities in the outcome after brain injury in children (Taylor et al., 1995). In addition, interventions by speech-language pathologists, neuropsychologists, professionals in the school setting, and psychiatrists are proposed as avenues for influencing the brain’s ability to compensate for losses. If the various factors have a positive influence, they may alleviate stress levels, which is important to the child’s overall well being and can impact the neurochemistry in the brain. Without positive exogenous factors, emotional stress can exacerbate the recovery process. For example, if the child is anxious or depressed, these factors can retard long-term recovery.

**FUTURE DIRECTIONS**

Plasticity in children involves a complex interaction of endogenous factors, such as the specifics of the brain injury and the stage of the child at the time of injury, and exogenous factors, such as the child’s environment and supporting systems. It is clear that recovery may be enhanced or exacerbated by any combination of these factors. Understanding developmental plasticity requires a long-term perspective that must be explored over time as the brain elaborates and the child reaches more complex cognitive stages.

Future research will be directed toward a number of relevant issues. First, one goal is to link how exogenous factors (such as treatments involving either cognitive-linguistic interventions or drug trials using neuromodulators such as serotonin or dopamine) impact endogenous factors. Can brain adaptability be given a boost with enriched stimulation or appropriate drug regimens in children? In addition, there is a strong impetus to identify which mechanisms are part of the inherent plasticity of a younger brain and to determine how these mechanisms can be manipulated to promote recovery perhaps at all ages. Evidence continues to
accrue that the child’s brain possesses biological plasticity or capacity for repair that may be greater than the adult brain (Chugani et al., 1996).

However, injuries to the developing brain have also been shown to disrupt the normal maturational processes (Levin et al., 2000). The structural and functional changes that follow an injury may not necessarily prove to be adaptive, but instead may be disruptive to normal development. Greenough and Klintsova (1999) suggested that the plasticity after injury may occur at a cost. For example, increased neural connections emerging after injury may not correspond to improved functioning. Perhaps reorganization of specific function that was once subserved by the injured brain network will be taken over by surrounding or cross-hemispheric, uninjured brain regions. This reorganization may “crowd” and hinder development of later-developing abilities that would have been controlled by these now “claimed” brain regions. Research must address whether the structural and functional changes in brain can be altered in adaptive rather than disruptive ways with appropriate interventions. For example, can more timely interventions enhance neural connections and serve as a stopgap to avoid later emerging deficits? Along these same lines, there is a need to determine an appropriate time line for determining when to intervene to promote optimal recovery. Recent advances in functional brain imaging may allow us to undertake studies to clarify the direct effects of neurobehavioral and neuropharmacologic treatments on brain reorganization after injury. The recent evidence that new brain cells are made daily combined with previous data showing the brain’s ability to regenerate and adapt after brain injury provides us with great hope for the future of manipulating neuroplasticity to improve the long-term outcome for our patients.

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