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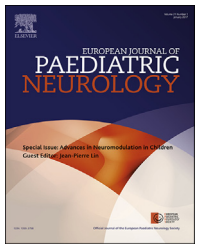

Review article

Cerebral plasticity: Windows of opportunity in the developing brain

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ABSTRACT

Background: Neuroplasticity refers to the inherently dynamic biological capacity of the central nervous system (CNS) to undergo maturation, change structurally and functionally in response to experience and to adapt following injury. This malleability is achieved by modulating subsets of genetic, molecular and cellular mechanisms that influence the dynamics of synaptic connections and neural circuitry formation culminating in gain or loss of behavior or function. Neuroplasticity in the healthy developing brain exhibits a heterochronus cortex-specific developmental profile and is heightened during "critical and sensitive periods" of pre and postnatal brain development that enable the construction and consolidation of experience-dependent structural and functional brain connections.

Purpose: In this review, our primary goal is to highlight the essential role of neuroplasticity in brain development, and to draw attention to the complex relationship between different levels of the developing nervous system that are subjected to plasticity in health and disease. Another goal of this review is to explore the relationship between plasticity responses of the developing brain and how they are influenced by critical and sensitive periods of brain development. Finally, we aim to motivate researchers in the pediatric neuromodulation field to build on the current knowledge of normal and abnormal neuroplasticity, especially synaptic plasticity, and their dependence on "critical or sensitive periods" of neural development to inform the design, timing and sequencing of neuromodulatory interventions in order to enhance and optimize their translational applications in childhood disorders of the brain.

Methods: literature review.

Results: We discuss in details five patterns of neuroplasticity expressed by the developing brain: 1) developmental plasticity which is further classified into normal and impaired developmental plasticity as seen in syndromic autism spectrum disorders, 2) adaptive (experience-dependent) plasticity following intense motor skill training, 3) reactive plasticity to pre and post natal CNS injury or sensory deprivation, 4) excessive plasticity (loss of

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homeostatic regulation) as seen in dystonia and refractory epilepsy, 6) and finally, plasticity as the brain's "Achilles tendon" which induces brain vulnerability under certain conditions such as hypoxic ischemic encephalopathy and epileptic encephalopathy syndromes. We then explore the unique feature of "time-sensitive heightened plasticity responses" in the developing brain in the in the context of neuromodulation.

Conclusion: The different patterns of neuroplasticity and the unique feature of heightened plasticity during critical and sensitive periods are important concepts for researchers and clinicians in the field of pediatric neurology and neurodevelopmental disabilities. These concepts need to be examined systematically in the context of pediatric neuromodulation. We propose that critical and sensitive periods of brain development in health and disease can create "windows of opportunity" for neuromodulatory interventions that are not commonly seen in adult brain and probably augment plasticity responses and improve clinical outcomes.

Contents

1. Introduction

When it comes to the development of the young brain, "The only constant is change", *Heraclitus of Ephesus a Greek philosopher (c.535 BC – 475 BC)*. Neuroplasticity is a complex process that is heightened during time-sensitive periods of pre and postnatal brain development and continues, albeit to a lesser degree, throughout adolescence and adulthood. Neuroplasticity refers to the inherently dynamic biological capacity of the central nervous system (CNS) to undergo maturation, change structurally and functionally in response to experience and to adapt following injury. This malleability is achieved by modulating subsets of genetic, molecular and cellular mechanisms that influence the dynamics of synaptic connections and neural circuitry formation culminating in gain or loss of behavior or function.[1] The endpoint of plasticity, however, is not always beneficial and can lead to significant maladaptive outcomes depending on the nature and extent of the neuropathogenic process, the stage of neurodevelopment during which it occurs as well as the integrity of homeostatic regulatory mechanisms.[2]

Patterns of abnormal neuroplasticity have been recently recognized as core pathologies in many congenital and acquired pediatric disorders of CNS such as neonatal hypoxic