Early intervention in neurodevelopmental disorders: underlying neural mechanisms

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ABBREVIATIONS

MRI	Magnetic Resonance Imaging
EI	Early Intervention
ICT	Information and Communications Technology
CT	CareToy

Neurodevelopmental disorders affect motor, cognitive, language, learning, and behavioural development with lifelong consequences. Early identification of infants at risk for neurodevelopmental disorders is a major prerequisite for intervention programmes. This ensures that interventions which aim to positively modify the natural history of these disorders can start in the first weeks or months of life. As indicated by recent scientific evidence, gene abnormalities or congenital brain lesions are not the sole determinants for the neurodevelopmental outcome of affected infants. In fact, environment and experience may modify brain development and improve the outcome in infants at risk for neurodevelopmental disorders. In this review, we analyse the complexity and sensitivity of the brain to environmental stimuli, highlighting clinical effects of early intervention, mainly reported so far in preterm infants, and summarizing the effects of enriched environment on human and animal models. Finally, we discuss some new approaches to early intervention, based on recent neurophysiological theories and new breakthroughs in biotechnologies for diagnosis and rehabilitation.

In the last decades several studies have explored and demonstrated the effects of environment and experience on brain development and plasticity. This review aims to (1) highlight some underlying neuronal and biological mechanisms of environmental enrichment both in animal and human models; (2) summarize the effects of early intervention in infants at risk for neurodevelopmental disorders and report their most representative results; and (3) explore the new breakthroughs of early intervention in the field of novel recent neurophysiological theories, and application of information and communication technologies.

NEURODEVELOPMENTAL DISORDERS: THE IMPORTANCE OF EARLY IDENTIFICATION AND INTERVENTION

Neurodevelopmental disorders are impairments of brain growth and development affecting several brain functions, and include cognitive, motor, language, learning, and behavioural disorders due to many causes – genetic, lesional, and environmental.[1] Infants at high risk for neurodevelopmental disorders can be identified early, i.e. in the first weeks or months of life, through careful clinical evaluation (i.e. developmental tests, neurological examination, observation of spontaneous movement patterns) combined with specific technical tools such as neuroimaging (cranial ultrasounds, brain magnetic resonance imaging [MRI]), neurophysiological tests (e.g. electroencephalography, evoked potentials), and genetic tests (karyotype, comparative genomic hybridization-microarray). The application of evidence-based recommendations or decision-making processes, which combine the use of clinical and technical tools at a proper point during development, is crucial for early detection of infants at risk for neurodevelopmental disorders by clinicians.

An example of early identification of infants at risk for cerebral palsy (CP), one of the most common neurodevelopmental disorders,[2] is the combined use of Prechtl's General Movement Assessment and brain MRI. In high-risk infants these techniques display high sensitivity and specificity starting from the first months of life (i.e. General Movement Assessment, 98% and 91% respectively; MRI performed at term 86–100% and 89–97% respectively), and therefore are important tools for predicting CP.[3]

As stated by the World Health Organization, identification of the infant at risk for a neurodevelopmental disorder is a crucial starting point to establish a close relationship between parents and health care providers and to provide early intervention (Fig. 1).[4] The goal of early intervention is to prevent or minimize motor, cognitive, emotional impairments in young children disadvantaged by biological or environmental risk factors.[5] Evidence suggests that brain development should be considered the result of the complex interaction between genes, social and physical environment thanks to the modulation of gene transcription and expression (epigenetic mechanisms).[6,7] In this framework, environment, social relationship, and parents have a

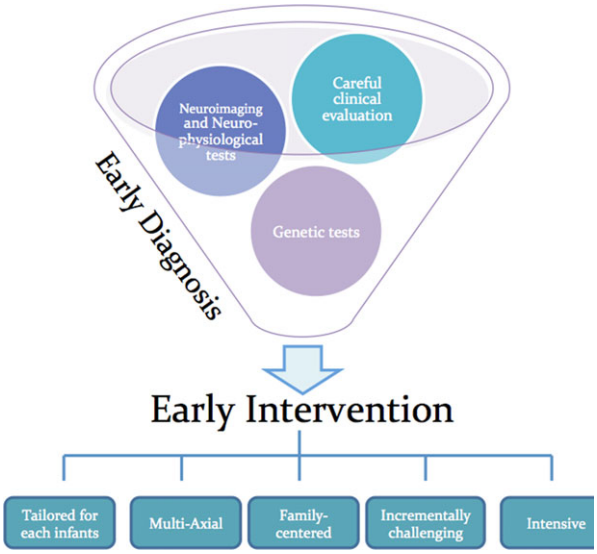

Figure 1: In the top section, infants at risk for neurodevelopmental disorders should be identified early through the use of specific diagnostic tools to initiate early intervention. In the bottom section, the main characteristics of early intervention are reported.

key role in early intervention. In particular, as highlighted in a recent review, parental involvement is a necessary requisite to transfer early intervention practices to daily life activities with positive effects on child development.[8] Moreover, parental education provides a positive impact not only in the parent–child interactions but also in the parental outcome (e.g. modifying their anxiety, depressive symptoms, and self-efficacy).[9]

A systematic Cochrane review carried out for preterm infants, who are at increased risk for neurodevelopmental disorders, shows evidence that early intervention in the first months of life has positive effects on early psychomotor development and parental involvement.[10] However, the heterogeneity of intensity, focus, setting, and participants in the studies limits the ability to identify the most effective intervention strategies.

INFANT BRAIN PLASTICITY: COMPLEXITY AND SENSITIVITY OF THE NEONATAL BRAIN TO ENVIRONMENTAL STIMULI

The term 'brain plasticity' refers to the capacity of the central nervous system to modify its structure and function. In the normal brain it is possible to distinguish three types of plasticity: experience-expectant, experience-independent, and experience-dependent. The complexity and sensitivity of the neonatal brain to environmental stimuli is referred to as experience-dependent plasticity, i.e. the modifications of structural and functional brain pathways in response to the 'rendezvous' between genes, environmental stimuli, and experiences. Extensive scientific literature has shown, both in animals and humans, that neuronal changes are related to behaviour.[6,7,11] Moreover, in the last decade, the new

What this paper adds

- Evidence is reported for the contribution of newer neurophysiological models and animal studies to EI programs
- ICT and biomechatronic tecniques can be of support for EI

term 'connectome' has been introduced by Sporns to label brain structural and functional connectivity in analogy to the human genome.[12] Connectome refers to a network of brain structural connections that are continually shaped by a host of mechanisms, from synaptic modifications to neuronal growth and structural plasticity, in conjunction with learning and experience. Much evidence from animal models suggests that structural arrangement of neuronal circuits, including connection topology, can undergo significant and rapid alterations both in dendritic and axonal compartments in response to environmental stimuli (e.g. sensory deprivation or changes in sensory input or motor learning).[6,7,11]

Even if this plasticity occurs throughout life, young brains show greater potentiality towards this phenomenon, thanks to prominent mechanisms of myelinization, creation, and sprouting of neural projections essential for brain development and modelling of cortical neuronal circuitries. Critical periods of brain plasticity are defined as those periods in which development of brain functional properties are strongly dependent and shaped by experience and environmental stimuli. Evidence of critical periods for visual, auditory, somatosensory systems, and cognitive functions has been largely demonstrated.[13]

EVIDENCE OF CLINICAL EFFECTS OF STANDARDIZED PROTOCOLS OF EARLY INTERVENTION FOR CHILDREN BORN PRETERM, IN THE NEONATAL INTENSIVE CARE UNITS AND POST-DISCHARGE

Early intervention could begin when infants are still in the Neonatal Intensive Care Unit, mainly by focussing on reduction/minimization of stress factors, or soon after Neonatal Intensive Care Unit discharge. Protocol examples that start in the Neonatal Intensive Care Unit or after discharge are Newborn Individualized Developmental Care and Assessment Program and Creating Opportunities for Parent Empowerment.[14,15]

Newborn Individualized Developmental Care and Assessment Program covers a range of strategies designed to reduce Neonatal Intensive Care Unit stress for high-risk infants. Systematic reviews have shown its variable short-term benefits and positive influence on brain function and motor development.[16] In addition, the Creating Opportunities for Parent Empowerment programme, designed to enhance parental coping for preterm infants, seems to show a positive effect on trained parents, assuming that facilitation of parental care can improve mental health outcomes and enhance parent–infant interaction.[15]

The main aim of early intervention programmes after hospital discharge is no longer the reduction of stress but to promote infant development. They are focussed on the

parent–infant relationship, infant development, or both, with the aim of improving the overall functional outcome of preterm infants. Interventions can include physiotherapy, occupational therapy, psychology, neurodevelopmental treatment, parent–infant relationship enhancement, infant stimulation, infant development, developmental care, and early intervention (education).

A Cochrane systematic review highlighted that these interventions are associated with positive effects more on a cognitive development level than a motor development one, but effects tend to disappear after preschool age.[10] However, as stated above, high heterogeneity among early intervention programmes (e.g. varied background and theoretical constructs, timing, duration, etc.) and lack of a high quality randomized controlled trial studies limit conclusions.

EFFECTS OF ENRICHED ENVIRONMENT IN ANIMAL MODELS AND RESULTS OF PARALLEL PILOT STUDIES IN INFANTS

It has been demonstrated that all animals show various forms of experience-dependent neuronal plasticity correlated with experience and learning. This kind of plasticity is related to gene expression and molecular cascades in response to the environment. Therefore, it reflects modifications of a basic phenotype shaped by experience and it could be a result of addition and/or pruning of synapses.[11]

The main animal model for studying the structural and molecular mechanisms underlying the effects of environment on brain is defined as the 'enriched environment' model. Enriched environment was described by Rosenzweig et al. as 'a combination of complex inanimate and social stimulation'.[17] Key enriched environment factors provide (1) a range of opportunities for visual, somatosensory, olfactory, and cognitive stimulation and (2) an increase of complexity in voluntary physical activity (see Fig. 2).

Based on this model, several studies have been performed on enriched environment animals (mainly mice) and have demonstrated that enriched environment enhances brain weight, neurogenesis, dendritic branching, synapse formation, and neuroanatomical components (e.g. brain weight, cortical thickness, and dendritic structure).[18–23] The experiences, especially if early, produce different effects on gene expression and brain plasticity. These various effects should be highly specific; for example, they are related to (1) the age; (2) the type and the intensity of stimuli; (3) the brain region (i.e. cortical region and cortical layer); (4) the direction of the changes (i.e. increasing or pruning of synapses); and (5) the structure of the brain (i.e. if it is normal or injured).[11]

All these effects might be mediated partially by epigenetic factors (e.g. chromatin remodelling, expression of mediators, such as insulin-like growth factor-1 and bone-derived neurotrophic factor). Moreover, it has been shown that enriched environment experience, compared with standard laboratory environment led to: (1) significant improvement in cognitive functions (e.g. learning and memory) in several laboratory behavioural tests; (2) reduction of progressive cognitive decline (neuroprotective effect); (3) attenuated or reversed sequelae of central nervous system insults such as seizures, ischaemia, infarct, cor-

Effects of environmental enrichment in animal models of neurodevelopmental disabilities

Disorder	Behavioural effects	Cellular effects	Molecular effects
Down Syndrome[18]	Improved cognitive (spatial learning and memory) and visual function recovery	Restored long-term synaptic plasticity in a neural circuit	Reduced inhibitory transmission, bringing GABA release in the synaptosomes
Fragile X Syndrome[19]	Rescued behavioral abnormalities displayed by adult Fmr1-KO mice: hyperactivity, social and cognitive deficits	Increased dendritic spine plasticity (especially in the hippocampal and amygdala)	Not determined
Rett Syndrome[20]	Ameliorated motor coordination and motor learning	Enhanced synaptic plasticity and regulation of synapse formation and stability in the cerebral and cerebellar cortex	Increased BDNF expression
Epilepsy[21-23]	Increased resistance to seizures; attenuated deficit in exploratory activity; improved learning and spatial memory	Decreased apoptosis; increased neurogenesis	Increased GDNF, BDNF, pCREB, ARC, HOMER1A and ERG1

Figure 2: Left: drawing from Berardi et al.[7], showing mice submitted to environmental enrichment that enhances sensory, cognitive, and motor stimulation on different brain areas, promoting neuronal activation, signalling, and plasticity throughout various brain regions. Right: table showing the effects of environmental enrichment and enhanced physical activity, as reported in published studies on some animal models of neurodevelopmental disorders. GABA, gamma-aminobutyric acid; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; pCREB, phosphorylated cyclic AMP responsive element-binding protein; ARC, activity-regulated cytoskeleton-associated protein; HOMER1A, a splice variant of the HOMER1 gene; ERG1, ether- à-go-go related gene 1.

tical lesions, and traumatic brain injury in animals, as well as in animal models of genetically rare neurodevelopmental disorders (see Fig. 2).[6,18] For a comprehensive analysis on this topic, we recommend the extensive reviews by Sale et al.[6] and Berardi et al.[7]

To summarize, strong 'bench' evidence of positive effects of enriched environment on brain plasticity, both in physiological and pathological conditions, has been suggested. Moreover, animal models allow us to speculate on cellular and molecular mechanisms underlying both behavioural and anatomical effects of enriched environment. For humans, enriched environment could represent a potential 'behavioural therapy'.

Recently a definition for enriched environment interventions in infants has been proposed by Morgan et al. that describes enriched environment as 'interventions aimed to enrich at least one of the motor, cognitive, sensory, or social aspects of the infant's environment for the purposes of promoting learning'.[24] However, we should be cautious about translating brilliant results obtained in animal models to humans.

Parallel studies carried out in different species with similar methodology could be of value. A study has been carried out in rat pups and in preterm infants, which explored the effects on brain development of tactile stimulation provided by licking/grooming in enriched environment animals and by body massage and multisensory stimulation in newborn infants, born preterm. Guzzetta et al. have demonstrated, for the first time, that body massage in human infants could influence brain development by accelerating maturation of electroencephalography activity, visual evoked potentials and visual acuity.[25] Furthermore, this study suggested that the environment acts by modulating the level of endogenous factors such as insulin-like growth factor-1, which regulate brain growth and the development of visual cortex. Similar effects and mechanisms were observed in the murine model.

Other studies exploring the effects of enriched environment in neurodevelopmental disorders have been carried out both in a mouse model of Down syndrome (Ts65Dn line) and in infants with Down syndrome. Begenisic et al. have shown that enriched environment (in terms of sensory-motor stimulation) can be successfully employed in the mouse model to favour recovery from cognitive impairment, decreased synaptic plasticity, and visual deficits.[18] Purpura et al. have reported positive effects on visual system development of multisensory intervention, including body massage, as previously described in preterm infants.[26]

NEW MODELLING OF EARLY INTERVENTION FOR DEVELOPMENTAL MOTOR DISORDERS, BASED ON UPDATED NEUROPHYSIOLOGICAL THEORIES

Recent neurophysiological evidence on motor control and learning has disclosed some interesting opportunities for rehabilitation. Discovery of mirror neuron system and its role in motor learning has recently revolutionized the field of upper limb rehabilitation. A novel paradigm defined 'action–observation training', based on observation of meaningful actions followed by execution, has been recently proposed and used with promising results in clinical studies, mainly on adult stroke patients.[27] Moreover, recent studies carried out on children with CP indicate positive effects on upper limb function. In particular, our group has recently published results of a randomized clinical trial using action–observation training, in children with unilateral CP, with encouraging results.[28] In addition, action–observation training is currently being investigated in two infant cohorts – typically developing or with asymmetric brain lesions – with the aim to provide evidence that action–observation training influences early development of reaching and grasping activities in typically developing infants and improves upper limb motor activity of infants with asymmetric brain lesions.[29]

CRITICAL POINTS FOR EARLY INTERVENTION PROGRAMMES: A ROLE FOR BIOMECHATRONIC TECHNIQUES?

Open issues questioning the effectiveness of early intervention programmes are heterogeneity of intensity, focus, setting, and participants in studies. However, clinical and experimental findings seem to indicate that, to be maximally effective, early intervention has to be early, intensive, active, tailored for each individual, and family-centred. Intervention programmes that fully satisfy these essential criteria are expensive, although economically justifiable if compared with costs of long-term disability. The possibility of creating a common family-centred home setting, which is able to quantitatively measure activities and progress and be remotely managed by rehabilitation staff, can represent a good solution. Therefore, biotechnologies and tele-rehabilitation could represent a promising approach to provide home early intervention programmes for a large number of infants, at a relatively low cost. In this field, neurodevelopmental engineering is a new ground-breaking interdisciplinary area, at the crossroads of developmental neuroscience and bioengineering, aiming to provide new methods and tools for quantitative analysis and modelling of human behaviour during typical and atypical neurodevelopment. It is mainly devoted to developing new clinical protocols and standards to help clinicians perform early diagnoses, functional evaluations, and interventions of neurodevelopmental disorders by providing new generations of educational and interactive toys that can provide quantitative measures, adequate stimuli, and support for psychomotor development. A variety of sensorized systems, such as toys able to measure grasp-force and grasping-shape, and other technology-assisted methods to obtain early diagnostic information for neurological disorders, are summarized in a recent review.[30]

Moreover, these new technologies have been proposed also for home rehabilitation. Our group is collaborating in a European research project, called CareToy (www.caretoy.eu), to clinically evaluate an intensive, individualized, home-based, family-centred early intervention programme

consisting of a new technological smart modular system, remotely monitored by a rehabilitation staff. The trial is being carried out on preterm infants and aims to assess the feasibility of Information and communication technologies as a challenging and innovative tool in the field of early intervention.[31]

These new frontiers in rehabilitation are completely in line with the guidelines of Convention on the Rights of Persons with Disabilities regarding the requirements of assistive technology and Information and communication technologies and the need to promote information and communication technologies policies and programmes in the field of rehabilitation, as stated in a recent research paper.[32] In this framework, the biomechatronic techniques, that is, techniques integrating aspects of biology, mechanics, and electronics, can open the possibility of managing early intervention in infants with neurodevelopmental disorders at home, far from the clinical centre, expanding the access of infants to early intervention in the near future.

CONCLUSIONS

Clinical studies on early intervention show promising but still inconclusive results, due mainly to their heterogeneity. Several animal studies and some parallel infant ones highlight mechanisms underlying effects of a positive and rich environment on development. Early detection and diagnosis of neurodevelopmental disorders is crucial in order to start early intervention, as soon as possible, optimize the use of limited resources for infants who need these resources most, to positively modify natural history of disorders. Early diagnosis is possible starting from the first months of life thanks to a careful clinical evaluation, which combines the use of genetic and neuroimaging tools. For this reason, common efforts need to be directed at identifying evidence-based recommendations for diagnosis and management of neurodevelopmental disorders. Moreover, as confirmed by clinical studies, parents should be involved in both processes (early diagnosis and intervention).

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