Evaluation of early stimulation programs for enhancing brain development

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Abstract
The term ‘early intervention’ designates educational and neuroprotection strategies aimed at enhancing brain development. Early educational strategies seek to take advantage of cerebral plasticity. Neuroprotection, a term initially used to characterize substances capable of preventing cell death, now encompasses all interventions that promote normal development and prevent disabilities, including organisational, therapeutic and environment-modifying measures, such as early stimulation programs. Early stimulation programs were first devised in the United States for vulnerable children in low-income families; positive effects were recorded regarding school failure rates and social problems. Programs have also been implemented in several countries for premature infants and low-birth-weight infants, who are at high risk for neurodevelopmental abnormalities. The programs target the child, the parents or both. The best evaluated programs are the NIDCAP (Newborn Individualized Developmental Care and Assessment Program) in Sweden for babies <1500 g in neonatal intensive care units and the longitudinal multisite program IHDP (Infant Health and Development Program) created in the United States for infants <37 weeks or <2500 g.

Conclusion: Although the NIDCAP and the IHDP targeted different populations, they produced similar effects in several regards: efficacy was greatest with programs involving both the parents and the child; long-term stimulation improved cognitive outcomes and child–parent interactions; cognition showed greater improvements than motor skills and larger benefits were obtained in families that combined several risk factors including low education attainment by the mothers.

EVALUATION OF EARLY STIMULATION PROGRAMS
Early stimulation programs have been developed in several countries in an attempt to minimize disabilities and to improve capabilities in children with—or at risk for—neurodevelopmental disorders. The broader term ‘early intervention’ encompasses all measures aimed at preventing perinatal disabilities, ensuring neuroprotection and providing optimal environmental conditions. This article focuses on valuations of early stimulation programs.

RATIONALE FOR EARLY STIMULATION PROGRAMS
Cerebral plasticity
Cerebral plasticity provides the rationale for early educational strategies. Special education therapy programs activate the plasticity of the developing brain. Plasticity varies with age. Studies of animal models have established that plasticity allows reorganization of cortical maps after early brain injury. Several underlying mechanisms have been described since the pioneering work on cat visual cortex conducted by Hubel and Wiesel in the 1960s and 1970s (1,2). The critical period is a time window during which a specific function develops normally, provided conditions are favourable, and the sensitive period is a time window during which abnormal conditions can modify the structure or function of a cortical region. Cortical plasticity has been described for the auditory, tactile, olfactory and motor systems. Plasticity, when it can occur, may have beneficial effects even if the developmental sequence it induces does not replicate the normal sequence. On the other hand, changes stemming from plasticity may be inappropriate if they result in new connections that fail to allow adaptive responses to the environment.

The innate-acquired interaction
The role for plasticity in correcting abnormal cognitive development is a crucial issue. Whether, and to what extent, plasticity can compensate for failure of cognitive functions...
to develop within the first few years of life has generated considerable attention. The crucial importance of developmental processes in the first few years has received support from data on the modulation of neuronal death (3), synaptic stabilization, axonal reorientation, axonal and dendritic budding and recruitment of transient projections (4–6), all of which depend on individual experience. However, delayed plasticity has been documented, and a high level of stimulation has been shown to correct early cognitive deficiencies (7) (Fig. 1).

Neuroprotection

The term ‘neuroprotection’ was first reserved for substances capable of protecting against neuron death. Now, ‘neuroprotection’ designates all the measures that promote normal brain development by preventing the occurrence of specific disorders. Neuroprotection includes organizational, therapeutic and environmental strategies. As an example, ‘in utero’ transfer to ensure that high-risk neonates are delivered in ‘level III’ facilities constitutes a key organizational measure that reduces the risk of neuromotor disability in preterm patients. In contrast, there is no convincing evidence to date that benefits are derived from caesarean section before or after labour, as compared to vaginal delivery.

To assist in designing neuroprotective treatments, animal models of neonatal brain injuries have been created. Advances have been made in identifying therapeutic strategies for protecting the developing brain or even reversing established brain lesions. Potentially neuroprotective substances act on the biological processes involved in cell death.

They include proinflammatory cytokine antagonists, membrane stabilizers, inhibitors of free-radical generation or of glutamate release, calcium-channel antagonists, NMDA glutamate receptor antagonists and anti-apoptotic agents. A major challenge faced by neuroprotective treatments aimed at preventing or minimizing brain damage in premature infants is the large number of risk factors and mechanisms responsible for brain lesions. In addition, the time of initiation of the cascade that leads to brain damage is not known, although it is probably antenatal. Poor specificity has been reported with both foetal stress markers (meconium-stained fluid and foetal heart rhythm disorders) at initiation of the cascade and signs of adjustment to extra-uterine life (Apgar score and metabolic acidosis). Finally, agents that are sufficiently safe to allow clinical trials have proved difficult to identify. As a result, there have been few treatment trials in humans. Some measure of improvement has been achieved using hypothermia for neonatal anoxia in full-term infants, maternal treatment with magnesium sulphate and fluorinated corticosteroids and postnatal nitric oxide in preterm babies. However, large multicentre trials are needed to further test these treatments.

Increasing awareness among paediatricians of the role for the environment in mental and cognitive development (the ‘acquired’ or ‘nurture’ component) has led to the creation of prevention programs. Targets of these programs include preservation of the mother–infant relationship and enhanced bonding, stress reduction in the hospital and individually tailored development-enhancing care in neonatal intensive care units.

OBJECTIVES, TARGETS AND RESULTS OF EARLY STIMULATION PROGRAMS

Early stimulation programs were developed for three target populations: children at high risk as a result of low socioeconomic status and limited stimulation at home, children with disorders known to induce developmental delay (e.g. Down syndrome) and children at risk as a result of preterm birth or low birth weight. Table 1 recapitulates the findings from the main controlled studies of these programs.

Low socioeconomic status

Studies have established that low socioeconomic status is a key determinant of development during the first 5 years. ‘Head Start’ programs were created in 1965 in the United States for low-income children and families. Several hundred thousand children benefit from the program each year. School failure and crime rates have fallen as a result. Increasing funding was allocated to ‘Head Start’ until the 1990s. Since 1990, support is also provided to parents; the effects of this additional measure have not yet been reported (8).

Disorders known to affect development

Two large meta-analyses deserve discussion. Simeonsson evaluated 27 studies published between 1975 and 1982. Subjective improvements were reported in 93% of the studies.
Table 1  The main controlled studies of early stimulation programs designed for various populations

<table>
<thead>
<tr>
<th>Target population</th>
<th>Where implemented</th>
<th>Reference</th>
<th>Description</th>
<th>Results in the early-stimulation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income</td>
<td></td>
<td>Majnemer 1998</td>
<td>Meta-analysis</td>
<td>“Head Start” programs started in 1965 in the US; several hundred thousand children/year; decreases in school dropout rates, crime rates, and welfare service use; long-term support needed to maintain effects.</td>
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<tr>
<td>Known disease</td>
<td></td>
<td>Hines et Bennet 1996</td>
<td>Improved cognitive function, better adjustment</td>
<td>Improvements in fine motor skills and self-sufficiency</td>
</tr>
<tr>
<td>Down syndrome</td>
<td></td>
<td>Parrette et Hourcade 1984</td>
<td>Quantitative motor assessments: limited effects; no qualitative assessments or evaluation of other functions.</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td></td>
<td>Parrette et Hourcade 1984</td>
<td></td>
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<tr>
<td>Preterm, VLBW</td>
<td>Hospital–home transition</td>
<td>Als 1994 USA, Sweden NIDCAP: individualized care for VLBW babies in NICUs; nurses deliver stimulation and adjust the program with the parents every 10 days.</td>
<td>Confirmation of results noted in 1986; improvements in respiratory and nutritional disorders, better weight gain, and shorter hospital stay. At 9 months corrected age, improvements in motor and cognitive Bayley scores.</td>
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<td></td>
<td></td>
<td>Achenbach 1993 USA Vermont Mother–Infant Transaction Program: Once a day on the last 7 days in the NICU, by the nurses, then four sessions at home over 3 months.</td>
<td>No short-term effects but better cognitive performance between 3 and 9 years of age.</td>
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<td></td>
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<td>Field 1980</td>
<td>Program for low-income teen-aged mothers with preterm babies.</td>
<td>Marked benefits. At 4 months, improvements in growth, mother–child interactions, and Denver scores; mothers had more realistic expectations. At 8 months, improved mental Bayley scores, decrease in reported behavioural disorders.</td>
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<tr>
<td></td>
<td></td>
<td>Ross 1984</td>
<td>Regular visits by nurse-occupational therapist</td>
<td>After 1 year, improved Bayley scores and decreased behavioural disorders.</td>
</tr>
</tbody>
</table>

NIDCAP = Newborn Individualized Developmental Care and Assessment Program; VLBW = very low birth weight; NICU = neonatal intensive care unit.

However, numerous methodological flaws were noted: the study populations were heterogeneous in terms of disabilities, many studies failed to include control groups, and statistical tests were used in only 59% of studies (9). Casto and Mastropieri assessed 74 studies of patients aged 0 to 5 years published between 1937 and 1984; however, most of the studies were done after 1970. Among the patients, 44% had mental deficiencies and 29% multiple disabilities. Early stimulation had limited effects that consisted chiefly in better access to services and valuable support to parents. Results were better with long-term programs that involved the parents (10).

Programs for patients with Down syndrome (11) were effective in improving cognitive capabilities, fine motor skills and self-sufficiency. In contrast, programs targeting patients with cerebral palsy have produced inconclusive effects. A meta-analysis of 18 studies (12) uncovered numerous methodological weaknesses (heterogeneous populations, small group sizes, unreliable measurements and absence of control groups for ethical reasons) that precluded definite conclusions.

**Preterm and low-birth-weight infants**

Several countries have implemented programs for preterm and low-birth-weight infants, who are at high risk for developmental deficiencies. These programs target the child, the family or both (13). They are initiated at the hospital, at hospital discharge to the infant’s home or as part of the post-hospital follow-up.

**Programs for neonatal care units**

Early programs designed for neonatal care units sought to correct the relative lack of stimulation to which preterm infants were exposed. They consisted in having nurses and occupational therapists supply sensory enrichment by multisensory stimulation, including tactile and kinaesthetic stimuli. Controlled studies showed benefits from this approach (14). Other programs were designed to reduce stress...
and to improve self-regulation by the infant; they were started by the nurses and transitioned gradually to the parents. Short-term improvements in development scores were obtained (15). The most extensively evaluated programs designed to reduce stress and improve self-regulation by infants are the Newborn Individualized Developmental Care and Assessment Programs (NIDCAP), which involve both the child and the parents. These programs were created in the United States then widely used in Sweden. They consist in individually tailored interventions for babies with birth weights of less than 1500 g who are admitted to neonatal intensive care units. The nurses stimulate the baby, periodically adjusting the program with the parents, minimizing discomfort and pain. NIDCAPs improve respiratory and nutritional disorders associated with preterm birth, improve weight gain and decrease hospital stay duration. Some studies also found beneficial effects at 3 years of age regarding motor and cognitive development, speech, mother–child interactions and parental stress (16,17) and behaviour (18). A 2002 meta-analysis of eight studies showed short-term benefits but failed to obtain conclusive evidence of long-term developmental improvements (19); however, the first in vivo evidence of enhanced brain function and structure due to the NIDCAP was recently reported. The study demonstrates through EEG coherence and white matter maturation tractography, that quality of experience before term may influence brain development significantly (20).

**Programs for the transition from hospital to home**

The Vermont Mother–Infant Transaction Program (21) is a well-known intervention for improving the adequacy of parent responses to signals given by the child. Daily sessions were provided by the nurses during the final week of hospitalization then four sessions at home over the first 3 months after discharge. Benefits were delayed, becoming significant after 3 years and being sustained until 9 years of age. These findings raise important questions about the optimal duration of follow-up care and the mechanisms of action of early stimulation programs.

**Programs for the post-hospital period**

Again, these programs may target the child, the family or both. Programs aimed at both the child and family seem more effective. A home-based parent training program for teenaged low-income mothers of preterm babies (22) produced improvements in the first 12 months including more realistic expectations on the part of the mothers, better mother–child interactions, improved growth and developmental scores at 4 and 8 months and fewer behavioural disorders. Similarly, a home-based program for premature babies of low-income families proved beneficial (23).

The limitations of studies of early stimulation programs must be borne in mind. Importantly, few data on long-term effects are available. Only the Vermont study collected data in school-aged children. Finally, all studies were conducted at a single site.

**Infant health and developmental program (IHDP)**

A careful analysis of the above-mentioned studies prompted the initiation in the early 1990s of a randomized clinical trial to assess a long-term intervention, the Infant Health and Development Program in the United States (Table 2). Eight sites recruited over 1000 babies born at or before 37 weeks’ gestational age and weighing no more than 2500 g at birth. The study patients had no severe health issues. They were divided into two groups based on birth weight (≤2000 g or ≥2000 g). Patients were allocated at random to conventional follow-up care or to an early stimulation program, from birth to 3 years of age. The early stimulation program included home visits by professionals, attendance of the child at a development centre (20 h/week) between the ages of 1 and 3 years and monthly meetings with the parents at the development centre. All patients received medical and developmental assessments (15,24,25). Cognitive and behavioural scores were similar in the two groups at 12 months but were significantly better in the intervention group at 24 and 36 months of age, when a 10-point IQ increase was found compared to controls. Effects were greater in the heavier infants (>2000 g at birth) and in infants whose parents had a high-school education or less and who were of ethnic minority status. Beneficial effects in the parents included a lower rate of depression and improved educational competence (Fig. 2).

In the heavier patients (2000–2500 g at birth), the intervention was associated with better cognitive scores (total and verbal IQs and receptive language) and behavioural scores at 5 years of age, compared to controls. No difference was found between the two groups for the patients who weighed less than 2000 g at birth. At 8 years of age, the heavier patients in the intervention group had better cognitive outcomes (total, verbal and performance IQs; receptive language and mathematic skills) compared to controls; however, there was no difference in behavioural scores (26–29,25,30).

**DISCUSSION**

Although the NIDCAP and the IHDP targeted different populations, they produced similar effects in several regards: efficacy was greatest with programs involving both the parents and the child; long-term stimulation improved cognitive outcomes and child–parent interactions; cognition showed greater improvements than motor skills and larger benefits were obtained in families that combined several risk factors including low education attainment by the mothers.

Two hypotheses can be put forward to explain the effects of early stimulation programs: early stimulation may compensate for the loss of exposure to stimulation from the family (tertiary prevention) and/or it may prevent the relative cognitive decline seen in controls. The optimal duration of early stimulation programs remains to be determined. Studies that showed beneficial effects of early stimulation raise questions about the best means of selecting high-risk groups. A preliminary step consists in improving and standardizing available tools for medical and developmental assessments in children.
Table 2 The main controlled studies of the methods and effects of the Infant Health and Development Program (IHDP)

<table>
<thead>
<tr>
<th>References</th>
<th>Description</th>
<th>Method</th>
<th>3-year results</th>
<th>5-year results</th>
<th>8-year results</th>
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<tbody>
<tr>
<td>McCarton 1995</td>
<td>8 sites</td>
<td>Early stimulation: - Home visits, 0–3 years (1/week for 1 year then 2/month for 2 years) for information on health and development - Development centre: 20 h/week starting at age 1 year - Parent groups: 1/month at the development centre</td>
<td>1. Cognitive effects: None detected at 12 mo, 10-point IQ increase at 24 and 36 mo. Subgroups: - Better results in 2000–2500 g BW group than in &lt;2000 g BW group - More effective when mothers had low educational attainment. 2. Social-emotional effects: 24 and 36 mo: decreased behavioural disorders reported by mothers. Subgroups: same as above. 3. Effects on parents. 12 mo: less maternal depression 36 mo: higher rate of employed mothers. 4. Educational capabilities: Improved at 30 and 36 mo</td>
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<tr>
<td>Brooks-Gunn 1993</td>
<td>985 babies &lt;37 WGA or &lt;2500 g BW</td>
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<tr>
<td>Brooks-Gunn 1994</td>
<td>Divided in 2 groups: &lt;2000 g BW (2/3) or 2000–2500 g BW (1/3)</td>
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<tr>
<td>McCarton 1997</td>
<td>In each BW group, 1/3 received the intervention and 1/3 conventional follow-up care</td>
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<tr>
<td>McCarton 1998</td>
<td>Medical and developmental assessments in all patients</td>
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<tr>
<td>McCormick 1998</td>
<td>Outpatient visits: 40 weeks then 4, 8, 12, 24, and 36 mo. Cognitive assessments: 12, 24, and 36 mo. Social and emotional assessments: 24, 30, and 36 mo</td>
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<td></td>
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<tr>
<td>Baumeister 1997</td>
<td>No serious health issues</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hill 2003</td>
<td>Ethnically heterogeneous groups</td>
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</table>

WGA = weeks’ gestational age; BW = birth weight; IQ = intelligence quotient; mo = months.

When seeking to define high-risk groups, studies of effective programs should be considered. For instance, patients who weighed less than 2000 g at birth derived limited benefits from the IHDP but showed large improvements with the NIDCAP until 2 years of age, although proof of sustained effects until the school age years is lacking. In the United States, each state creates its own definitions of high-risk groups. In addition to preterm infants, other groups at risk for developmental problems have been included. Early stimulation programs produced their largest effects in babies with multiple risk factors. In particular, low-income families were particularly likely to benefit. Therefore, in addition to very low-birth-weight infants and to babies born before 32 weeks’ gestational age, whose need for adapted follow-up care is well established, babies born between 32 and 36 weeks probably require special attention, as well as all infants with serious perinatal disorders (e.g. perinatal anoxia, prenatal maternal substance abuse, prenatal viral infection or perinatal meningitis, developmental brain defects, early epilepsy and metabolic disturbances), most notably those born to low-income families.

Further work is needed to determine the optimal timing of preventive measures. Clinical research will have to focus on the dates of onset of cognitive disturbances in preterm infants; on the impact of these disturbances on academic performance and on establishing priorities for the management of behavioural, visual, visuo-spatial, attentional and executive-function disorders.

CONCLUSION

Available data suggest that early intervention programs have positive effects, although scientific proof of efficacy is not available for all strategies. Efficacy was greatest with programs involving both the parents and the child; long-term stimulation improved cognitive outcomes and child–parent interactions. Recently, the first in vivo evidence of enhanced
brain function and structure was reported due to NIDCAP program. In addition, ethical considerations argue in favour of early support to the families. Families are now well informed, in particular via the Internet, and they are told earlier on about the risk of residual disturbances including neurological and psychological disabilities, that could increase anxiety level.

References