Cognitive Recovery in Socially Deprived Young Children: The Bucharest Early Intervention Project
Charles A. Nelson, III, *et al.*
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from neuronal synchrony. Synchrony may have contributed to these effects, and lack of synchrony during another epoch may have resulted in an absent effect [see, however, (*14*)].

Lack of synchrony was unlikely to account for absent effects when the highly significant effects were consistent with monosynaptic connections (onset latency > 5 ms and PWHM < 9 ms, lower right quadrants). Particularly for the eight SpikeTA effects in the lower right quadrant of Fig. 3C (from eight different neurons recorded in eight different sessions, three in monkey E and five in monkey W), the loss of throughput that resulted in absent effects cannot be attributed simply to lower neuron firing rate, lower ongoing EMG, and/or loss of synchronized inputs. Additional factors may have changed the throughput from these M1 neurons to their target muscles.

Although M1 output, particularly that from CM cells, dominates control of distal upper extremity musculature during voluntary activity, our results show that the throughput from individual M1 neurons to muscle activity can be changed rapidly and dramatically. For about half of the neuron-muscle pairs that produced highly significant SpikeTA effects, throughput evident during some behavioral epochs was absent during other epochs. In most cases, differences in intracortical excitability and the resulting changes in excitation of motoneuron pools—reflected by the firing rate of the trigger neuron, the level of ongoing EMG activity, and/or synchrony in the SpikeTA effect—contributed to the presence of effective throughput during some behavioral epochs and not others.

In about 10% (8 of 82) of cases, however, none of these factors could account for the presence versus absence of throughput from the M1 neuron to the muscle's EMG activity. We therefore speculate that three subcortical factors may have contributed as well. First, some SpikeTA effects may be mediated through disynaptic linkages that involve rubrospinal neurons, reticulospinal neurons, or spinal interneurons (*20*–*22*). Such effects may have been blocked during some epochs by inactivity of the interposed neuron. This mechanism seems likely for suppressive effects, all of which are mediated through inhibitory interneurons, and may have contributed to the absence of some facilitative effects as well. Second, single CM cell EPSPs in motoneurons may be relatively small (*23*, *24*). Within motoneuron dendrites, small synaptic inputs may have been amplified by persistent inward currents during some behavioral epochs but not during others (*25*). Third, the synaptic input from an M1 neuron to a motoneuron pool commonly is assumed to remain constant. Although synaptic efficacy might be altered by presynaptic inhibition, available evidence indicates that this mechanism does not affect corticospinal terminals (*26*, *27*). Plastic changes can occur in spinal cord synapses (*28*), however, and dendritic spines have been observed to be remodeled over minutes (*29*). We therefore speculate that the efficacy of CM synapses on motoneurons might have changed in some behavioral epochs. Subcortical factors such as these, which might have played a role in the 10% of cases lacking differences in intracortical excitability, also could have contributed to the rapid change in throughput in many of the other 90%.

Our findings indicate that M1 neurons, even those with relatively direct connections to α-motoneurons, are not always effective in driving their target motoneurons. Rather, throughput can be changed rapidly such that an individual M1 neuron, which is ineffective in eliciting motoneuron discharge during certain motor behaviors, does elicit discharge of the same motoneurons during other behaviors.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5858/1934/DC1
Materials and Methods
Figs. S1 and S2
Table S1
References

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Cognitive Recovery in Socially Deprived Young Children: The Bucharest Early Intervention Project

Charles A. Nelson III,[1]* Charles H. Zeanah,[2] Nathan A. Fox,[3] Peter J. Marshall,[4] Anna T. Smyke,[2] Donald Guthrie[5]

In a randomized controlled trial, we compared abandoned children reared in institutions to abandoned children placed in institutions but then moved to foster care. Young children living in institutions were randomly assigned to continued institutional care or to placement in foster care, and their cognitive development was tracked through 54 months of age. The cognitive outcome of children who remained in the institution was markedly below that of never-institutionalized children and children taken out of the institution and placed into foster care. The improved cognitive outcomes we observed at 42 and 54 months were most marked for the youngest children placed in foster care. These results point to the negative sequelae of early institutionalization, suggest a possible sensitive period in cognitive development, and underscore the advantages of family placements for young abandoned children.

For normal development, mammalian brains require an optimal level of environmental input, a so-called "expectable" environment (*1*, *2*). Examples of an expectable environment might include exposure to patterned light information, normal language exposure, and access to responsive caregivers. Unfortunately, not all children are exposed to such environments. Institutional settings vary both within and between countries, but many are characterized by unfavorable caregiver-to-child ratios; highly regimented routines (e.g., all children eat, sleep, and toilet at the same time); impoverished sensory, cognitive, and linguistic stimulation; and unresponsive caregiving practices. These issues af-

[1]Harvard Medical School and Children's Hospital, Boston, MA 02215, USA. [2]Tulane University Health Sciences Center, New Orleans, LA 70112, USA. [3]University of Maryland, College Park, MD 20742, USA. [4]Temple University, Philadelphia, PA 19122, USA. [5]University of California, Los Angeles, CA 90095, USA.

*To whom correspondence should be addressed. E-mail: charles.nelson@childrens.harvard.edu

fecting early development have implications for the millions of children throughout the world who begin their lives in adverse circumstances, such as those who have been maltreated or abandoned or whose parents have died.

Although the effects of early psychosocial deprivation on brain development has been examined extensively in animal models (*3*, *4*), the effects of similar deprivation on humans are less clear. Evidence suggests that children reared in institutions suffer from a variety of neurobiological and behavioral sequelae compared to never-institutionalized children. Children reared in institutions showed reduced metabolic activity in regions of the temporal and frontal cortices (*5*), and cortico-cortico connections between these regions were reduced in number (*6*). In addition, children reared in institutions have shown delays or deviations in a variety of behavioral domains, such as intelligence quotient (IQ), attachment, language, or social-emotional development (*7*–*10*).

This literature on the effects of early institutional care suffers from methodological limitations, particularly selection bias: In nonrandomized studies, a biased sample (e.g., healthier children or more psychologically competent children) may be adopted into families while others remain in institutions. These nonrandom factors make it difficult to attribute differences in behavioral characteristics of children reared in or out of institutional settings to the different environments in which the children were reared.

An additional unanswered question is the importance of timing of environmental enhancement in producing recovery from early deprivation. From the perspectives of both developmental brain plasticity and social policy, a vital question is whether there may be sensitive periods after which recovery becomes significantly more difficult. The Bucharest Early Intervention Project (BEIP) was designed, in part, to address the issue of timing of intervention on remediation of cognitive delay as a result of early deprivation. To address this issue, we designed a randomized controlled trial of foster care versus institutional care for young children who had been abandoned at or shortly after birth and placed in institutions. We avoided the selection bias of previous studies (*11*–*15*) by random assignment of children to the two groups. We assessed the children before the start of intervention, while they were still living in institutions, followed by randomization to continued institutional care or to placement in a foster family and longitudinal follow-up assessments of their cognitive development as assessed by standardized intelligence tests. We also assessed the timing of intervention on this outcome in early childhood.

We assessed three groups of children: an initial group of children abandoned at birth and then studied extensively with a battery of measures. Half of these children were then randomly assigned to foster care (foster care group, FCG) and the other half to continued institutional care (institutional group, IG). A third group consisted of children being reared with their biological families in the greater Bucharest community (never-institutionalized group, NIG).

Participants in institutions comprised 187 children less than 31 months of age and residing in any of the six institutions for young abandoned children in Bucharest, Romania (*16*). These children were initially screened with a pediatric and neurological exam, growth measurements, auditory assessment, and assessment of physical abnormalities. We excluded 51 children from the original sample for medical reasons, including genetic syndromes, frank signs of fetal alcohol syndrome (based largely on facial dysmorphology), and microcephaly (*17*). Thus, the final sample at baseline consisted of 136 children. Weight for age, height for age, weight for height, and head circumference for age were all lower in the IG than in the NIG.

The NIG comprised 80 children who were born at the same maternity hospitals as the institutionalized children. They were recruited from community pediatric clinics, were living with their biological parents, had no history of institutional care, and were matched on age and gender to the institutionalized sample. The final sample of the NIG consisted of 72 children (eight families declined further participation after initial recruitment into the study). All fell within 2 SD of the mean for physical growth (weight, length, and occipitofrontal circumference).

Birth records of the children in institutions were limited, allowing derivation of gestational age data for only 112 children; the length of gestation ranged from 30 to 42 weeks (mean = 37.2 weeks, SD = 2.2 weeks). Birth weight (available for 117 cases) ranged from 900 g to 4150 g (mean = 2767 g, SD = 609 g) and was significantly different from that of the NIG (mean = 3338 g, SD = 467 g), $t(187) = 6.8$, $P < 0.001$.

After initial assessment of all children in both institution and comparison samples, 68 children from the institutions (33 males and 35 females) were randomly assigned to remain in institutional care and were designated the IG (institutional group), and 68 (34 males and 34 females) were randomly assigned to foster care and were designated the FCG (foster care group). Randomization was implemented by assigning each child a number (1 to 136) written on a piece of paper. These papers were then placed in a hat and then drawn from the hat at random. The first number pulled from the hat was assigned to the IG, the next randomly drawn number was assigned to the FCG, and so on, until all children had been assigned to the IG or the FCG. The two sets of twins in the study were each on the same piece of paper and thus placed together.

Because government-sponsored foster care was limited to about one family when our study commenced, we created our own foster care program (*18*, *19*). After extensive advertising followed by screening, we recruited 56 foster families into the project. A total of 46% were single-parent families (widowed, divorced, or never married), and foster care mothers ranged in age from 30 to 66 years (mean = 48 years); all mothers had at least a high school education.

After random assignment, the average age for children at placement in foster care was 21 months. Cognitive development was assessed at

Table 1. DQ and IQ at 42 and 54 months of age.

Evaluation	*N*	Mean DQ and IQ	SD	SE
		IG		
42 months	57	77.1	13.3	1.8
54 months	51	73.3	13.1	1.8
		FCG		
42 months	61	85.7	14.2	1.8
54 months	59	81.0	18.5	2.4
		NIG		
42 months	52	103.4	11.8	1.6
54 months	45	109.3	21.2	3.2

Table 2. DQ and IQ of FCG by entry age group. η indicates effect size in multiples of the pooled standard deviation, and Y is younger than and O is older than age cutoff at entry to foster care.

Age cutoff	42 months (BSID-II)					54 months (WPSSI-R)				
	Y	O	*t*(59)	η	*P*	Y	O	*t*(57)	η	*P*
20 months	93.5	82.6	2.82	0.81	0.007	84.3	79.6	0.87	0.25	0.39
22 months	90.4	83.0	2.01	0.54	0.051	83.2	79.7	0.69	0.19	0.49
24 months	91.5	80.0	3.46	0.89	0.001	85.8	76.4	2.00	0.52	0.05
26 months	90.9	79.1	3.53	0.91	0.001	85.2	75.7	2.01	0.53	0.05
28 months	89.8	78.8	3.14	0.83	0.003	83.4	76.9	1.31	0.35	0.20

Table 3. DQ and IQ of FCG by entry age group.

Age at placement	42 months (BSID-II)				54 months (WPPSI-R)			
	N	Mean	SD	SE	*N*	Mean	SD	SE
0–18 months	14	94.4	11.9	3.2	14	84.8	16.0	4.3
18–24 months	16	89.0	11.3	2.8	15	86.7	14.8	3.8
24–30 months	22	80.1	13.3	2.8	22	78.1	19.5	4.2
30+ months	9	79.7	17.1	5.7	8	71.5	23.8	8.4

baseline (before randomization), 30 months, and 42 months with the Bayley Scales of Infant Development (BSID-II) (*20*) and at 54 months with the Wechsler Preschool Primary Scale of Intelligence (WPPSI-R) (*21*). Both tests were administered by trained and reliable Romanian psychologists. Upon entry into the study, our IG scored below our sample of community children (NIG) on developmental quotient (DQ). The IG also fared worse than the NIG on a variety of other developmental indices (*22*).

The BSID-II measure mental and motor development in infants from 1 to 42 months of age. The test measures a child's level of development in three domains: cognitive, motor, and behavioral. Scores on the mental development index (MDI, a scaled score) of the BSID-II can range from <50 to 150. Children who obtained raw scores that placed their scaled scores below 50 were assigned a numeric MDI score of 49. For our analyses, raw scores were assigned an extrapolated age-equivalent score to allow values <50 when needed (*23*). Thus, DQs were computed for each child [(extrapolated age-equivalent score/chronological age) × 100], allowing inclusion of the entire sample in analyses.

The WPPSI-R consists of 14 subtests that assess intellectual functioning in verbal and performance domains. The verbal section includes such tests as vocabulary, general information, and arithmetic; and the performance section includes such tests as picture completion, copying geometric designs, and using blocks to reproduce designs. Subtest and composite scores represent intellectual functioning in verbal and performance cognitive domains, as well as a child's general intellectual ability (full-scale IQ).

The BSID-II assess a wide range of abilities, focusing on tasks with sensorimotor responses in infancy, whereas the WPPSI-R provides a more focused assessment of children's cognitive abilities by using primarily language-based items. Although test-retest on BSID-II is good, prediction from BSID-II to school IQ is not as strong as prediction from WPPSI-R to later IQ. As a result, one might expect differences in children's performance on the BSID-II versus the WPPSI-R simply because of differences in the nature of the test instruments.

At the outset of our study, we implemented procedures to ensure its ethical integrity. A detailed description of these procedures is included in (*18*), but they are outlined here. First, our study was initiated at the invitation of the then–secretary of state for child protection in Romania and was approved by the local commissions on child protection in Bucharest, the Romanian ministry of health, and, in 2002, by an ad hoc ethics committee comprising appointees from several government and Bucharest University academic departments. It was therefore done with the participation and approval of local authorities. Second, the institutional review boards (IRBs) of the home institutions of the three principal investigators (the University of Minnesota, Tulane University, and the University of Maryland) approved the project. Third, we implemented a policy of noninterference with placement of children in both groups into alternative family care environments, leaving those decisions to Romanian child protection authorities (according to Romanian law). The only exception to the noninterference rule was that we ensured that no child placed in foster care as part of the randomization process would ever be returned to an institution (*18*, *24*–*26*). Fourth, after our preliminary results began to suggest positive benefits of foster care, we held a press conference to announce the results of our investigation. Key ministries in the Romanian government were invited to attend and sent representatives to this meeting. The then–U.S. ambassador to Romania (who was briefed in advance about our findings) gave the opening remarks at the conference. Fifth, although the usefulness of clinical equipoise is controversial among bioethicists (*18*), a reasonable interpretation of clinical equipoise supports the research design in this project. Clinical equipoise is the notion that there must be uncertainty in the expert community about the relative merits of experimental and control interventions such that no subject should be randomized to an intervention known to be inferior to the standard of care (*27*). Because of the uncertainty in the results of prior research, it had not been established unequivocally that foster care was superior to institutionalized care across all domains of functioning, especially with respect to how young children initially placed in institutional care function when placed in foster care as compared with children who remain in the institutional setting. Moreover, at the start of our study there was uncertainty about the relative merits of institutional and foster care in the Romanian child welfare community, with a historical bias in favor of institutional care. Additionally, given that the study was invited by Romanian authorities and conducted there, with the aim of guiding child welfare policy in Romania, it made sense to assess the study in view of the local standard of care, which was institutional care. The study also presented no more than minimal risk to the subjects; specifically, children assigned to the IG continued to receive the same care as if the study had not been conducted, and the measures we used have all been used for many years in developmental science research. Lastly, we were aware from the outset of the policy implications of our work, and as the study progressed we made our results available to government officials and child protection professionals. Indeed, several years after our study began, the Romanian government passed a law that prohibits institutionalizing children less than 2 years old, unless the child is severely handicapped.

Over the course of the study, there were instances of change in actual living arrangements and, in some cases, subject attrition (fig. S1). For example, of the 68 children who composed the IG, only 20 remained in institutions at the 54-month assessment. Seventeen children were lost to attrition. Of these, 9 were adopted or returned to their biological families, and their families decided not to continue participating in the study. Other children who remained in the study changed status: 2 children were adopted, 18 were placed in government foster care (which was not available at the onset of the study), 9 were reintegrated into their biological families, and 2 were placed in families with extended family members. Although some children changed their group assignment, an intent-to-treat approach was followed (*28*, *29*), whereby all analyses we report are based on children's original group assignment. Thus, our findings represent a conservative estimate of the response to intervention.

The first step of our data analysis focused on the randomized trial. Because, at the onset of the study, a number of children ($N = 15$) were not randomized until after they turned 30 months of age and others (12 children at 29 months and 7 children at 28 months) only shortly before then, we chose to focus our analyses on the later assessments. The NIG is included for reference only and is not included in the statistical analysis (*30*) (tables S1 and S2). Cross-sectional t tests at each time point yielded significant differences between IG and FCG at 42 months (BSID-II), $t(116) = 3.39$ and $P = 0.001$, and at 54 months (WPPSI-R), $t(108) = 2.48$ and $P = 0.015$. The effect size (the difference between means in multiples of standard deviations) was 0.62 at 42 months and 0.47 at 54 months. The primary finding of the randomized trial was that the foster care intervention led to improved cognitive outcomes as assessed by DQ and IQ (Table 1).

We next inquired into possible correlates of this finding within the FCG. We looked at three dichotomous factors: birth weight (above or less than 2500 g), gender, and age at entry to foster care (before or after 24 months of age). Neither birth weight nor gender was significantly associated with DQ or IQ at either 42 or 54 months. To examine the effect of entry age, we used t tests to compare DQ and IQ scores by dichotomized age at entry to foster care (younger than cutoff/older than cutoff) separately for placement cutoffs of 20, 22, 24, 26, and 28 months of age (*31*). Significant differences in 42-month DQ between early and late foster care placement groups existed for all age cutoffs, whereas for 54-month IQ the deflection point appeared to occur at 24 and 26 months (Table 2 and tables S3 and S4). In other words, the assessment at 42 months yielded significant differences in DQ regardless of age of placement, whereas the WPPSI-R data at 54 months suggested that children placed before 2 years of age had the best response to intervention.

In addition, we computed a regression of DQ at 42 months and IQ at 54 months on DQ at entry age. We used slope estimates to show the expected loss of 42- and 54-month DQ and IQ points for each additional month of institutionalization. Results revealed that the cost of remaining in the institution was 0.85 DQ points per month at 42 months ($P < 0.001$) and 0.59 IQ points at 54 months ($P < 0.09$).

Children's scores differed slightly on the BSID-II versus the WPPSI-R exam (Table 2). We attribute this to the different psychometric properties of these instruments as mentioned earlier. As a secondary analysis, we separated the FCG into two groups that experienced similar durations of intervention but that had entered foster care at different ages. One group consisted of those children who entered foster care before 18 months of age (n = 14, mean placement age = 12.0 months), and the other group consisted of children entering after 18 months (n = 47, mean placement age = 26.6 months). We then chose the measurement occasion that most nearly equated these groups on length of intervention, specifically the 30-month DQ assessment for the earlier entry group and the 42-month assessment for the later entry group. At these assessment points, the mean lengths of time in foster care were 18.2 and 16.1 months respectively, and the mean DQs were 89.6 and 83.1, $t(59) = 1.55$, and $P = 0.13$. Although not statistically significant, we interpret the difference in group means as supporting our general conclusions about the importance of earlier placement age for improved cognitive outcomes.

The above analysis did not possess sensitivity to finer gradations in age of placement, and a tertiary analysis was performed. We divided the FCG into four groups: those placed between 0 and 18 months, those placed between 18 and 24 months, those placed between 24 and 30 months, and those placed after 30 months (Table 3). One-way analyses of variance (ANOVAs) yielded significant differences in DQ and IQ at 42 months ($P = 0.008$) but not at 54 months ($P = 0.20$). At 42 months, the two earlier entry groups (0 to 18 months and 18 to 24 months) are not significantly differ from one another, nor are the two later entry groups, but the two early placement groups (0 to 18 months and 18 to 24 months) are different from the two later placement groups (24 to 30 months and above 30 months). The 54-month data showed the anticipated ordering of means, although there are no significant differences among pairwise comparisons. Taken together, these findings suggest that age of entry into foster care (i.e., the timing of placement) was critical in changing children's cognitive abilities [see Supporting Online Material (SOM) text for additional analyses that address the issue of timing and duration of foster care effects on DQ and IQ at 42 and 54 months].

Because we assessed children before randomization, we are confident that differences that resulted from the foster care intervention reflect true intervention effects rather than differences in sample makeup. Moreover, randomization before intervention addressed concerns about previous studies of adopted children that have the potential of selection bias with regard to who is adopted. Additionally, by randomizing children before intervention we increased the likelihood that unknown prenatal risk factors would be randomly distributed across the intervention and control groups. Lastly, the inclusion of an in-country comparison sample confirmed that our cognitive assessments were valid, given that the DQ and IQ means for the never-institutionalized Romanian children were very similar to the means for typically developing children in populations for which the BSID-II and the WPPSI-R have been standardized.

Three main findings emerge from this study. First, as we have previously reported (*22*), children reared in institutions showed greatly diminished intellectual performance (borderline mental retardation) relative to children reared in their families of origin. Second, as a group, children randomly assigned to foster care experienced significant gains in cognitive function. Lastly, at first glance our findings suggest that there may be a sensitive period spanning the first 2 years of life within which the onset of foster care exerts a maximal effect on cognitive development. However, a closer reading of our analyses suggests a more parsimonious conclusion: That the younger a child is when placed in foster care, the better the outcome. Indeed, there was a continuing "cost" to children who remained in the institution over the course of our study. These results are compatible with the notion of a sensitive period, but discovering whether such a period truly exists or determining the borders that delineate it would likely require a larger sample size with a broader age range at intervention onset.

The results of this study have implications for child welfare because they suggest that placement in families is more advantageous for cognitive development in infants and young children than placement in institutional settings. For countries grappling with how best to care for abandoned, orphaned, and maltreated young children, these findings deserve consideration. The results also indicate that previously institutionalized children's cognitive development benefits most from foster care if placement occurs relatively early in a child's life.

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Supporting Online Material

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Materials and Methods
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Fig. S1
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References

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