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Fostering Early Brain Development

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JAMA PEDIATRICS

Effect of Early Institutionalization and Foster Care on Long-term White Matter Development: A Randomized Clinical Trial

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IMPORTANCE Severe neglect in early life is associated with compromises in brain development and associated behavioral functioning. Although early intervention has been shown to support more normative trajectories of brain development, specific improvements in the white matter pathways that underlie emotional and cognitive development are unknown.

OBJECTIVE To examine associations among neglect in early life, early intervention, and the microstructural integrity of white matter pathways in middle childhood.

DESIGN, SETTING, AND PARTICIPANTS The Bucharest Early Intervention Project is a randomized clinical trial of high-quality foster care as an intervention for institutionally reared children in Bucharest, Romania, from 2000 through the present. During infancy, children were randomly selected to remain in an institution or to be placed in foster care. Those who remained in institutions experienced neglect, including social, emotional, linguistic, and cognitive impoverishment. Developmental trajectories of these children were compared with a group of sociodemographically matched children reared in biological families at baseline and several points throughout development. At approximately 8 years of age, 69 of the original 136 children underwent structural magnetic resonance imaging scans.

MAIN OUTCOMES AND MEASURES Four estimates of white matter integrity (fractional anisotropy [FA] and mean [MD], radial [RD], and axial [AD] diffusivity) for 48 white matter tracts throughout the brain were obtained through diffusion tensor imaging.

RESULTS Significant associations emerged between neglect in early life and microstructural integrity of the body of the corpus callosum (FA, $\beta = 0.01$ [$P = .01$]; RD, $\beta = -0.02$ [$P = .005$]; MD, $\beta = -0.01$ [$P = .02$]) and tracts involved in limbic circuitry (fornix crus [AD, $\beta = 0.02$ ($P = .046$)] and cingulum [RD, $\beta = -0.01$ ($P = .02$); MD, $\beta = -0.01$ ($P = .049$)]), frontostriatal circuitry (anterior [AD, $\beta = -0.01$ ($P = .02$)] and superior [AD, $\beta = -0.02$ ($P = .02$); MD, $\beta = -0.01$ ($P = .03$)] corona radiata and external capsule [right FA, $\beta = 0.01$ ($P = .03$); left FA, $\beta = 0.01$ ($P = .03$); RD, $\beta = -0.01$ ($P = .01$); MD, $\beta = -0.01$ ($P = .03$)]), and sensory processing (medial lemniscus [AD, $\beta = -0.02$ ($P = .045$); MD, $\beta = -0.01$ ($P = .04$)] and retrolenticular internal capsule [FA, $\beta = -0.01$ ($P = .002$); RD, $\beta = 0.01$ ($P = .003$); MD, $\beta = 0.01$ ($P = .04$)]). Follow-up analyses revealed that early intervention promoted more normative white matter development among previously neglected children who entered foster care.

CONCLUSIONS AND RELEVANCE Results suggest that removal from conditions of neglect in early life and entry into a high-quality family environment can support more normative trajectories of white matter growth. Our findings have implications for public health and policy efforts designed to promote normative brain development among vulnerable children.

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It is estimated that 6.3 million children worldwide died in 2013 before attaining 5 years of age, from mostly preventable diseases.¹ Within North America, nearly 1.2 million US children are homeless, more than 1 in 3 children of color younger than 5 years live in poverty, and 1 in 9 lack access to adequate food.² Further, as many as 153 million children worldwide, ranging from infants to teenagers, have lost one or both of their parents, and 7 million are in institutional care.³ As recently as 1989, in the final year of the Ceausescu regime, about 170 000 Romanian children were being raised in state-run institutions, the result of an ill-conceived, "pro-natalist" social program designed to augment a national workforce through mandated conceptions and births.⁴

In 2007, Nelson and colleagues⁵ observed that the "unnatural experiment" unfolding in Romania might offer an unprecedented opportunity to compare the neurodevelopmental outcomes of chil-

dren raised in orphanages with those of children raised in foster families, within the context of a true random-assignment study. The result was the Bucharest Early Intervention Project (BEIP), a randomized trial of placement in high-quality foster care as an intervention for institutional rearing involving 136 abandoned Romanian children. Previous reports from this study have documented diminished intellectual capacities in institutionalized children, significant gains in IQ and developmental quotient (DQ) among those placed in foster care, and an increasing gap between institutional and foster care groups with advancing age at placement.⁵ In a recent report in *JAMA Pediatrics*, Bick et al⁶ examined structural magnetic resonance images for children aged 8 years in a majority subset of the original study sample (69/136 children). White matter integrity was estimated using fractional anisotropy and diffusion tensor imaging, and significant

microstructural differences were detected in multiple brain regions between children who had been placed in foster care (n = 23; mean age, 9.8 years) and those remaining in institutions (n = 26; mean age, 9.7 years). Specifically, such differences were found in the corpus callosum, limbic and frontostriatal circuitry, and sensory processing areas. Previously abandoned, institutionalized children who received early foster care placements showed more normative white matter development in follow-up analyses.

These findings are deserving of attention for at least 3 reasons. First, the reported differences in brain images were in white matter, ie, the glial cells and myelinated neuronal axons that facilitate and accelerate signal transmission within cortical circuitry and between cortex and lower brain centers. Although increases in gray matter volume plateau in adolescence, changes in regional myelination continue throughout the life span, with white matter volume reflecting the relative balance between production and degeneration. Aberrations in both white matter structure and function are found in many neurodevelopmental disorders,⁷ suggesting that the white matter differences newly identified between children in institutions and children in BEIP foster care may constitute a microanatomical substrate for the previously reported differences in IQ and DQ.

Second, the more normative white matter characteristics found among children given early foster care placements were in brain regions of critical importance for early cognitive and emotional development. The corpus callosum integrates sensory, motor, and cognitive signaling between the 2 hemispheric sides of the cerebral cortex; frontostriatal circuits subserve the acquisition and maintenance of executive functions and emotion regulation; and sensory processing areas enable the multisensory integration of environmental signals. Third, the BEIP findings offer yet another example of how nurturant, dependable parental care is foundational for raising children to become intact, fully functional human beings. Previous studies have suggested the existence of conserved, possibly epigenetically mediated parental influences on the normative, adaptive neurodevelopment of offspring.⁸ Given such evidence, could any less damaging or consequential effects be expected for the development of children who were conceived under duress; born into conditions of poverty, neglect, and need; and abandoned in infancy to the care of understaffed Romanian orphanages?

Two other features of the BEIP warrant special comment. First, even though random assignment trials involving human children of-

ten and appropriately evoke important ethical dilemmas, these studies are generally handled through the requisite approval of local institutional review boards. In contrast, BEIP investigators, aware of the very real ethical issues raised by the randomization of institutionalized, preverbal children to a "care as usual" group, addressed these issues publicly and transparently, from the inception of the project. Taking into account issues of exploitation, risk/benefit ratios, resource imbalances, and possible violations of cultural sensitivities, BEIP scientists openly examined the planned study design, in both North America and Romania, in light of established, international frameworks for the conduct of ethical human research. At the project's outset in 2001, officials within and outside the Romanian government had serious uncertainties about whether institutional or foster care was the preferable, more protective response to child abandonment. Because interpretation of the alternative—an adoption study design—would be confounded by almost inevitable selection bias and the impossibility of causal inference, the only means of addressing official uncertainties and offering uniquely convincing evidence for the developmental advantages of in-family care was a randomized design. Investigators with the BEIP and their Romanian counterparts ultimately concluded that benefits would outweigh risks for all enrolled children and that only a randomized clinical trial would produce strong, credible evidence.

Second, as informative and conclusive as the project design became, it was unable to eliminate altogether the conflation of effects derived from deinstitutionalization and those resulting from placements in high-quality foster homes. Both happened to each of the intervention group children and were causally inseparable. With this single caveat, however, the Romanian study has provided scientifically valid research affirming the singular developmental importance of social environments in early life.

Given the evidence that health and well-being are substantially derived from the care, protection, and support offered to children in the early years of life, the BEIP findings issue challenges to the societal practices currently guiding treatment of the very young. Children constitute societies' most precious and irreplaceable resources, as well as the demographic subgroup most susceptible to social interventions and conditions. It is thus increasingly plausible to assert that the societies most attentive to the needs of their children will be the most successful, progressive, and strong.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Boyce reported that he co-leads a Canadian Institute for Advanced Research program on Child and Brain Development, of which Charles Nelson is a member, and that he coauthored a single article with Nelson (and others) in 1998.

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