# **PERSPECTIVES**

# Psychiatric Outcomes in Young Children with a History of Institutionalization

Karen Bos, MD, MPH, Charles H. Zeanah, MD, Nathan A. Fox, PhD, Stacy S. Drury, MD, PhD, Katie A. McLaughlin, PhD, and Charles A. Nelson, PhD

Children raised in institutions, considered an extreme example of social deprivation, are one group through which we can better understand the impact of neglect on child health and development. The Bucharest Early Intervention Project (BEIP) is the first randomized, controlled trial of foster care as an intervention for institutionalized children. In this review we describe the mental health outcomes from the BEIP. Specifically, we report findings on attachment styles, attachment disorders, emotional reactivity, and psychiatric symptomatology for children in the BEIP. We describe the impact of the foster care intervention on these outcomes and also describe how outcomes differ by gender and by length of time spent in the institution. In addition, we explore the influence of genetic variation on individual outcomes and recovery from early severe social deprivation, as well as the role of differences in brain development in mediating later psychiatric morbidity. The results from the BEIP confirm and extend the previous findings on the negative sequelae of early institutional care on mental health. The results also underscore the benefit of early family placement for children living in institutions. (HARV REV PSYCHIATRY 2011;19:15-24.)

Keywords: child neglect, emotional and social development, foster care, institutionalized children

Children who experience early deprivation and neglect have a significantly increased risk of a range of emotional and behavioral disorders. 1-3 Over 500,000 children in the

From Harvard Medical School (Drs. Bos and Nelson); Laboratories of Cognitive Neuroscience, Children's Hospital Boston, Boston, MA (Drs. Bos and Nelson); Tulane University School of Medicine (Drs. Zeanah and Drury); University of Maryland, College Park (Dr. Fox); Harvard School of Public Health (Dr. McLaughlin).

Original manuscript received 21 November 2009; revised manuscript received 15 June 2010, accepted for publication subject to revision 30 August 2010; final manuscript received 11 November 2010.

Correspondence: Charles A. Nelson, PhD, Children's Hospital Boston-Laboratories of Cognitive Neuroscience, 1 Autumn St., 6th fl., Boston, MA 02115. Email: charles.nelson@childrens.harvard.edu

© 2011 President and Fellows of Harvard College

DOI: 10.3109/10673229.2011.549773

United States alone are victims of neglect each year (by estimate of the Child Welfare League of America) and therefore at risk for a range of negative outcomes across social, emotional, cognitive, and behavioral domains.

Children raised in institutions—which is considered an extreme example of social deprivation—are one group through which we can better understand the impact of neglect on child health and development. Institutional care, while less common in the United States, remains common worldwide, with one recent report estimating that up to eight million children currently live in orphanages (2009 estimate by Save the Children UK). Despite the variability among institutions, factors that are generally common to institutional life include isolation, regimentation, an unfavorable child/caregiver ratio, lack of psychological investment by caregivers, and limited stimulation.4

We have known for over 50 years that children raised in institutions are at great risk for developmental delays and disorders, including mental health disorders.<sup>5</sup> Young children with a history of institutional care often show poor attention, hyperactivity, difficulty with emotion regulation, elevated levels of anxiety, increased rates of attachment



disorders, and indiscriminate friendliness. 5-10 They are also at increased risk for a syndrome described by Rutter and colleagues<sup>11</sup> as quasi-autism, a pattern of features similar to autism but marked by more flexibility in communication than would normally be expected with autism, more substantial social approach, and increased incidence of indiscriminately friendly behavior.

In addition to increased rates of specific psychopathology in children with a history of institutional care, recent neuroimaging and endocrine findings indicate that they have distinct neurological differences—which are helping us better define the global detrimental impact on these children. For example, one study using MRI identified diminished white matter connectivity in certain areas of the brain involved in higher cognitive and emotional function (such as the amygdala and frontal lobe) in adopted children with a history of institutional care. 12 Another study examined the effects of early institutional care on oxytocin and vasopressin, hormones associated with affiliative and positive social behavior. Institutionalized children were shown to have lower overall levels of vasopressin and, after interactions with their caregivers, lower levels of oxytocin than never institutionalized comparison children. <sup>13</sup> The authors of this latter study recently extended their investigation to include cortisol and found that, compared to never institutionalized children, post-institutionalized children showed higher levels of cortisol when interacting with their mothers than with unfamiliar adults, and that a history of more severe early neglect was associated with the highest basal cortisol levels. These differences in cortisol indicate greater dysregulation of the hypothalamic-pituitaryadrenal (HPA) axis in children with a history of institutional care.<sup>14</sup>

Despite the growing literature concerned with the longterm consequences of institutionalization, most previous studies faced significant methodological limitations when examining children with a history of institutional care compared to those without such history. Three such limitations stand out as being especially problematic. First, children in all previous studies were not randomly selected for removal from institutional care. The result is a potential issue of selection bias, with the consequence that the studies may not accurately reflect the true degree of impairment that institutionalized children face. Second, choosing an appropriate comparison group is often difficult since children placed into institutions may differ in significant ways from children raised in typical families. Third, previous studies of institutionalized children have been limited by the lack of information about these children's preadoption status. Often little is known about the conditions in which post-institutionalized children were raised and about the children's psychological and physical status at the time of removal and adoption.

#### STUDY DESIGN

To address previous difficulties in the study of institutionalized children and to determine in a definitive manner the effects of early social deprivation, we launched an ambitious scientific and humanitarian undertaking, the Bucharest Early Intervention Project (BEIP).4 The study is the first randomized, controlled trial of foster care as an intervention for institutionalized children. The BEIP started in 2000 and is currently ongoing.

Before discussing the details of the intervention, it is important to recognize a number of ethical issues we grappled with prior to launching the study. The participants were a vulnerable population of children, and we engaged in careful planning to ensure that the study was ethically sound. We were able to randomly assign children to foster care or continued institutional care because when we began the study, there was little or no in-country foster care, and Romania had banned most international adoption. Thus, children randomized to the institutional group were receiving care as usual. A second ethical requirement that we established was that no child whom we placed in foster care would ever be returned to institutional care. We were able to meet this guarantee through close collaboration with the Romanian government and also a nongovernmental organization, Fundatia SERA [Solidarité Enfants Roumains Abandonés] Romania. Third, we agreed not to interfere with any placement decisions made by the Romanian child protection officials that might involve removal from the institution of children randomized to remain there. In fact, many of these children were reunited with their families or, later in the project, placed in newly developed government foster care. Of the 68 children originally assigned to care as usual, only 20 remain in an institution as of this writing.

We initially screened 187 children younger than 31 months of age who were living in any of the six institutions for young children in Bucharest, Romania. A total of 51 children were excluded for medical reasons, including obvious chromosome, genetic, or neurological abnormalities or fetal alcohol syndrome. The remaining 136 children were enrolled in the study. Comprehensive assessments were performed on these children at the time of enrollment, and their caregiving environments in the institutions were described. Following the baseline assessments, half of the children in the study were randomly assigned to foster care created specifically for the study (referred to in this article as the foster care group), and half to continued institutional care (referred to as the care-as-usual group). The foster parents were recruited and screened prior to placement and received extensive training, monitoring, and support from study staff that continued after placement. 15 The average age at foster care placement was 22 months (range, 6–31 months).



After randomization, children were seen for follow-up assessments at 30, 42, and 54 months of age. The development of children in foster care was compared to the development of children randomized to remain in the institutions and to a group of never institutionalized, typically developing children (community controls). We assessed a broad range of developmental domains, including physical growth, cognitive function, social-emotional development, attachment, problem behaviors and psychiatric symptomatology, language development, caregiving environment, genetics, and brain development (Table 1). In this article we will review some of the previous findings of the BEIP, with a focus on mental health outcomes.

Regarding methods, all observational procedures were videotaped in Bucharest and then coded in the United States or in Romania by coders who were unaware of group status and often unaware of the design of the study. All coders attained reliability in observational and interview measures.

# **RESULTS: FINDINGS IN INSTITUTIONALIZED CHILDREN**

All our findings to date have been analyzed by adopting an intent-to-treat design, which preserves randomization by evaluating results based on original group membership rather than current placement. This approach is the most statistically stringent, and thus our results, across domains, are likely conservative estimates of the effects of the intervention.

#### Attachment

Attachment was assessed using the Strange Situation Procedure. 16 This paradigm includes a series of eight brief episodes between a child, his or her regular caregiver, and a stranger. These episodes are designed to assess individual differences in the child's use of the caregiver as a secure base. Two aspects of the child's behavior are coded: (1) the amount of exploration (e.g., playing with new toys) that the child engages in throughout the episodes, and (2) the amount to which the child seeks proximity to the caregiver in response to distress induced by separation. In our sample, institutionalized children were assessed with their single "favorite" caregivers as determined by staff consensus. If a favorite caregiver could not be identified, a child was assessed with a caregiver who worked frequently with the child and knew the child well. Children living in the community were assessed with their mothers. From the child's behavior, attachment styles were classified as one of four types: secure, avoidant, resistant, or disorganized. These categories can be further reduced to secure versus insecure attachment, the latter encompassing avoidant, resistant,

and disorganized styles, or organized (secure, avoidant, and resistant) versus disorganized. In general, both secure and organized attachments are considered protective for psychopathology, whereas insecure and disorganized attachments styles suggest greater cause for concern. 17,18

At the baseline assessment, only 19% of institutionalized, but 74% of never institutionalized, children were securely attached. Further, only 22% of the institutionalized children had an organized attachment to their favorite caregivers, as compared to 78% of (never institutionalized) children living with their biological parents. In addition, 13% of institutionalized children had so little attachment behavior that it could not even be classified as disorganized and was designated unclassifiable. Finally, whereas 100% of community children were rated as having fully formed attachments, only 3% of institutionalized children were so rated. All of these differences were large and statistically significant. 19

#### **Attachment Disorders**

The Disturbances of Attachment Interview was used to evaluate signs of clinical disturbances of attachment. Responses of caregivers to the interview were coded to derive continuous scores of emotionally withdrawn/inhibited and indiscriminately social/disinhibited reactive attachment disorder (RAD). Emotionally withdrawn RAD is typically characterized by the absence of organized attachment behaviors, impaired social engagement and reciprocity, and problems with emotion regulation. Indiscriminately social/disinhibited RAD is generally described by a lack of expected hesitance about engaging with unfamiliar adults, a failure to check back with a caregiver in unfamiliar settings, and the willingness to approach, interact with, and even go off with complete strangers. Items are scored on a scale of zero (none or never) to two (considerable or frequently).

At baseline, children in the institutionalized group demonstrated significantly higher levels of emotionally withdrawn/inhibited RAD than children in the community comparison sample. Institutionalized children also scored significantly higher than the community sample on indiscriminately social/disinhibited RAD. The differences in signs of both types of RAD were large and statistically significant.19

#### **Emotional Reactivity**

Children in our sample were also administered two tasks from a standardized battery called the Lab-TAB. These two tasks, called Puppets and Peek-a-Boo, were designed specifically to elicit positive affect in young children. For the Puppets task, the child was seated on his or her caregiver's lap and presented with two puppets that talked to each other



Table 1: Measures Administered to 8 Years

Measures	Construct evaluated	Baseline assessment	30-month assessment	42-month assessment	54-month assessment	8-year assessment <sup>a</sup>
	Attı	achment				
Disturbances of Attachment Interview	Attachment disturbances & disorders	X	X	X	X	X
Stranger at the Door	Indiscriminate behavior				X	X
Strange Situation Procedure	Attachment style	X	X	X		
		behavioral				
EEG (asymmetry, coherence, and power)	Brain function	X	X	X		X
Dot probe task	Engagement and disengagement of attention					X
Facial emotion discrimination (ERP, VPC)	Emotion discrimination	X	X	X		X (ERP only)
Familiar-unfamiliar face recognition (ERP, VPC)	Face recognition	X	X	X		
Mismatch negativity (EEG)	Auditory attention	X	X	X		
Posner cued-attention task	Orientation to sensory stimuli					X
Magnetic resonance imaging	Brain structure					X
	Caregivin	g environmer	nt			
Observational Record of Caregiving Environment	Quality and frequency of caregiver behaviors	X	X	X		
	Co	gnition				
Bayley Scales of Infant Development	Mental, motor, and behavioral development	X	X	X		
Wechsler Preschool Primary Scale of Intelligence	Verbal and performance IQ				X	
Wechsler Intelligence Scales for Children	IQ					X
	Emotional reac	tivity/temper	ament			
LAB-TAB Puppets Episode	Attention and positive/negative affect	X	X	X		
LAB-TAB Peek-A-Boo Task	Attention and positive/negative affect	X	X	X		
		enetics				
Buccal swabs	Saliva				X	X
	Hypothalamic-p	ituitary-adre	nal axis			
Salivary cortisol	Integrity & responsiveness of HPA axis				X	
	La	nguage				
Receptive-Expressive Emergent Language Test	Receptive & expressive language		X	X		
Reynell Developmental Language Scales	Verbal comprehension & expressive language		X	X		
Language sample from free play	Spontaneous expressive		X	X		
	language		(participant subset)	(participant subset)		
Nonword repetition	Vocabulary predictor					X
Sentence repetition	Grammar					X
Rapid naming	Vocabulary predictor					X
	Mot	or skills				
Bruininks-Osteretsky Test of Motor Proficiency	Gross and fine motor skills					X
					(Continued	d on next page)



Table 1: Measures Administered to 8 Years (Continued)

Measures	Construct evaluated	Baseline assessment	30-month assessment	42-month assessment	54-month assessment	8-year assessment <sup>a</sup>
	Phy	sical growth				
Head circumference		X	X	X	X	X
Height		X	X	X	X	X
Weight		X	X	X	X	X
	Probl	em behaviors				
Infant Toddler Social Emotional Assessment	Symptoms of behavior & emotion problems	X	X	X		
	Psychi	atric problems				
Preschool Age Psychiatric Assessment	Psychiatric symptoms and disorders				X	X
	Social commun	ication and int	eraction			
Early Social Communication Skills	Nonverbal communication	X	X	X		
Crowell Play Procedure	Caregiver-child interaction	X	X	X		
	Placem	ent disruptions	5			
	Changes in placement status	_	X	X	X	X

ERP, event-related potential; VPC, visual paired-comparison task.

and to the child, and attempted to tickle the child. In the Peek-a-Boo task, the child was seated on the lap of a research assistant and watched as the child's caregiver played peek-aboo through a wooden screen with open and closed windows. The tasks were videotaped and subsequently coded for the child's facial expressions, vocal behaviors, and attention to the task presentations.

At baseline, children who were in the institutionalized group displayed significantly less positive affect and significantly more negative affect during these tasks compared to typically developing Romanian children living with their biological parents.<sup>20</sup>

#### **RESULTS: FOSTER CARE INTERVENTION**

Let us turn our attention to the efficacy of our foster care intervention. Like the group randomized to continued institutional care, the foster care group was assessed initially and again at 30, 42, and 54 months.

#### Attachment

At 42 months, the Strange Situation Procedure was repeated, and episodes were coded using a modified coding scheme that is used with preschool children. This system distinguished five attachment patterns—secure, avoidant, dependent, disorganized/controlling, and insecure/other that were combined to contrast secure versus insecure (all others) attachment and typical (secure, avoidant, dependent) versus atypical (disorganized/controlling, insecure/other) attachment. Again, secure attachment is expected to function as a protective factor, and atypical as a risk factor, for psychopathology.

The foster care intervention favorably affected security and organization of attachment. At 42 months, 65% of children in the never institutionalized group and 49% of children placed in foster care demonstrated secure attachment. Statistically, this percentage for the foster care group was significantly larger than the 18% of children in the care-asusual group who were securely attached. The distribution of the particular attachment patterns across the three groups of children differed significantly. For example, when analyzed with the dichotomy of typical versus atypical attachment, substantially more children in the foster care group had typical attachment patterns (77%) than children in the care-as-usual group (54%), a difference that was statistically significant.15

# **Attachment Disorders**

Following randomization to the foster care group, children had large and statistically significant reductions in signs of emotionally withdrawn/inhibited RAD. Specifically, children in the foster care group had no elevation in signs of emotionally withdrawn/inhibited RAD compared to children in the community (never institutionalized) sample at 30, 42, and 54 months of age. In contrast, both the children in foster care and the community children had statistically significantly fewer signs of emotionally withdrawn/inhibited RAD



<sup>&</sup>lt;sup>a</sup>Results from data collected at the 8-year assessment are not yet available.

than children in the care-as-usual group. The reductions in signs of indiscriminately social/disinhibited RAD for children placed in foster care were less dramatic. Only at 42 months were children in the foster care group statistically significantly lower than the care-as-usual group.

Because these results concerning attachment disorders were based exclusively on structured interviews with caregivers, we decided that it would be potentially helpful to add an observational measure of attachment behavior when the children were 54 months of age. The additional measure, the Stranger at the Door Procedure, assesses for the indiscriminate/disinhibited pattern of RAD, in which the child lacks the expected reticence about engaging with unfamiliar adults. The procedure was added after some of the 54-month assessment had been completed, with the consequence that only 99 of the 136 children had codable data from this assessment. In this Stranger at the Door Procedure, we arranged to have the children and their primary caregivers greet a research assistant who was unknown to them at the door when he arrived for a home visit assessment. The stranger invited the child to accompany him out of the house (or institution) by saying, "Come with me. I have something to show you." The parent/caregiver was instructed not to give instructions to the child about what to do. We coded whether the child "left" with the unfamiliar research assistant or not. Behavior of the children in this procedure was different in the three groups, with the majority of children in the care-as-usual group accompanying the stranger, compared to almost none of the community children, with the foster care group in between these extremes.<sup>21</sup>

#### **Emotional Reactivity**

At 30 and 42 months of age, the two previously discussed tasks from the Lab-TAB were again administered to examine the effects of the foster care intervention on measures of positive and negative affect. Results revealed that at both 30 and 42 months, children taken out of the institution and placed into foster care displayed statistically significantly greater positive affect in response to the tasks compared to children randomized to remain in institutional care. There were no differences in negative affect between the groups. Children placed into the foster care intervention also displayed greater attention to the tasks than children randomized to remain in the institution.<sup>22</sup>

#### **Psychiatric Symptomatology**

Psychiatric symptoms were assessed at 54 months of age using the Preschool Age Psychiatric Assessment (PAPA),<sup>23</sup> a semistructured psychiatric interview of parents/caregivers that assesses the full range of psychiatric symptoms and

disorders in children aged two to five years. The PAPA also assesses school/day-care functioning, family structure and functioning, parenting behaviors, and demographic variables, including socioeconomic status. Results indicate that a substantial number of children in our sample had psychiatric disorders. For example, 53% of children who had ever been placed in institutions (both the foster care and careas-usual groups) had a diagnosable psychiatric disorder at 54 months. In contrast, only 22% of never institutionalized children met criteria for a disorder. Using a logistic regression model, this difference in disorders between institutionalized and never institutionalized children was significant. Children in both the care-as-usual and foster care groups had higher levels of internalizing symptoms and disorders (anxiety disorders and depressive disorders) and externalizing symptoms and disorders (attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder, and conduct disorder), and were also more impaired, than the never institutionalized group. Indeed, children in the care-as-usual group were nearly three times more likely to be diagnosed with anxiety disorders than children in the never institutionalized group.24

We also explored the impact of foster care placement on rates of emotional and behavioral disorders. As hypothesized, children in the foster care group exhibited significantly fewer internalizing disorders, such as anxiety, than children in the care-as-usual group. However, the same effect was not seen with externalizing disorders. There was no statistically different rate of externalizing disorders, such as ADHD, oppositional defiant disorder, and conduct disorder, between the care-as-usual and foster care groups.<sup>24</sup>

# **DISCUSSION**

# **Timing Effects**

Due to the nature of this study design, we were able to examine the impact of the timing of the intervention on outcomes, thus examining whether children placed into foster care earlier had different outcomes than those children placed later. While outcomes in some domains, such as IQ,25 suggest clear effects of timing, evidence of timing effects on psychiatric outcomes was more limited. Children placed in foster care before 24 months of age demonstrated more secure attachments at 42 months than children placed in foster care after 24 months. Also, the earlier children were placed in foster care, the more organized their attachments. 15 Timing had no impact, however, on other psychiatric outcomes.<sup>24</sup>

There are several hypotheses for why externalizing symptoms/disorders were not affected by the foster care intervention. It may be that prenatal experiences of the



children, such as malnutrition or drug exposure, led to substantially increased risk of externalizing disorders. Alternatively, it may be that the intervention, with an average age at placement of 22 months, was started too late, and thus the neural architecture that underlies externalizing disorders might have already been established and passed through its sensitive period.

#### Gender Differences

One of the most striking findings regarding psychiatric outcomes in this study was the gender difference. Female gender was protective for virtually all types of psychopathology among children with a history of institutional rearing. This finding was in contrast to the never institutionalized group, which showed males more vulnerable to externalizing symptoms but no gender differences in internalizing symptoms. For children with a history of institutional care, the majority of internalizing-symptom reduction was seen in female children, with limited recovery in the male children placed in foster care. Males in foster care were as likely as males in the care-as-usual group to exhibit internalizing symptoms.<sup>24</sup> The seeming protective effect in females may be the result of biological differences, cultural practices with regard to how male and female children are treated, or females' better capacity to benefit from the enhanced caregiving available in the foster care setting.

#### Gene-Environment Interaction

Though the results presented above indicate the potential for enhanced foster care to minimize or even reverse the negative effects of early institutional care on psychological outcomes, this study and others have noted that recovery is not uniform across all children.26 One area of recent interest is the interaction between genetics and the environment in mental health outcomes. For example, there is increasing evidence that variations in gene sequences interact with early life stress to affect the development of depression.<sup>27-29</sup> However, few studies have investigated the possible gene-environment interaction for children in the setting of early social deprivation. Two recent studies from the English and Romanian Adoptee Project have demonstrated that the effects of severe early institutional deprivation can be moderated by genetic variation. In the first study a particular haplotype of the dopamine transporter (DAT), which contained the 10 allele of the variable number tandem repeat (DAT VNTR) previously associated with ADHD in non-institutionalized children, moderated the relationship between symptoms of ADHD and institutional care in later childhood and in adolescents.<sup>30</sup> In the

second study the short allele of the serotonin transporter gene length polymorphism (5HTTLPR) moderated the relationship between severe psychosocial deprivation in early life and the development of emotional problems in adolescence.31

The BEIP study design allows further delineation of environmental impact through gene-environment studies. In particular, following the randomization to foster care, one can investigate the impact not only of early exposure, but also of a changed environment. Buccal swab DNA was collected from children enrolled in the BEIP and genotyped for the catechol-O-methyltransferase (COMT) val 158 met functional polymorphism that has been implicated previously in mood disorders. 32-34 COMT is the main regulator of dopamine and other catecholamines in the prefrontal cortex; the met variant has a fourfold decreased enzyme activity, resulting in slower degradation of dopamine in the prefrontal cortex; and studies show a co-dominant effect of these alleles such that heterozygotes have an intermediate phenotype of enzyme level, and thus levels of dopamine, in the prefrontal cortex.<sup>35,36</sup> Due to the known relation between catecholamines levels and mood disorders, COMT enzyme level variations and genetic variations have been extensively investigated in relation to the pathophysiology of mood disorders. One study previously found a relation between the val allele and early-onset mood disorders.<sup>37</sup> In the BEIP we examined the relationship between the COMT allele status and depressive symptoms as measured on the PAPA at 54 months of age in 98 of the 111 children for which PAPA data was collected. There were no differences on the PAPA between the 98 children for whom a genotype was obtained and the 13 children who either refused DNA collection or for whom genotype data was not obtained secondary to DNA quality. Results indicate that the mean level of depressive symptoms was lower among participants with the met allele compared to those with two copies of the val allele (p < 0.05). After controlling for group and gender, children with the met/met or met/val genotype had significantly lower rates of depressive symptoms compared to children with the val/val genotype, suggesting an intermediate impact for heterozygotes. Furthermore, findings differed significantly within groups. In the care-as-usual group, we identified a significant protective effect of the met allele on depressive symptoms: compared to children with val/val genotypes, the risk for depressive symptoms was lower by an estimated 108% for children homozygous for the met/met allele, and by an estimated 60% for heterozygous (met/val) children. The protective effect of the COMT genotype was thus specific to the children with the greatest exposure to institutional care, since this relationship was not seen within the foster care group.<sup>38</sup>

These findings are similar to those in the two English and Romanian Adoptee Project studies discussed earlier,



where the impact of genotype appeared stronger in those children adopted after six months of age. Collectively, these studies demonstrate that genetic variation can moderate the outcome of institutional care, but point to the possibility that the duration and timing of social deprivation may further modify genetic influences.

## Brain Development and Psychiatric Morbidity

Though the association between institutional care and poor mental health outcomes is well established, to our knowledge no study to date has indentified a precise neurodevelopmental mechanism through which early severe deprivation affects later psychiatric morbidity.

Electroencephalogram (EEG) was performed on all children prior to randomization to the foster care intervention (at ages 6 to 30 months). Significant reductions in alpha relative power and increases in theta relative power were seen among institutionalized children in frontal, temporal, and occipital regions.<sup>39</sup> Although several explanations for this pattern of brain findings are possible, it has been posited (in ADHD) that the pattern of elevated low-frequency activity and reduced high-frequency activity reflects a developmental delay in cortical maturation.  $^{40-42}$  In typically developing children, this pattern of EEG power is evident in earlier developmental stages; as children mature from infancy through middle childhood, their EEGs are characterized by increasing power at higher-frequency components. 43 Longitudinal findings documenting a substantial delay in cortical maturation among children with ADHD, as compared to children without the disorder, appear to support the developmental-delay theory.<sup>44</sup> In the BEIP, this pattern of brain activity predicted symptoms of hyperactivity and impulsivity at age 54 months (assessed on the PAPA), and delay in cortical maturation significantly mediated the association between institutionalization and ADHD symptoms. 45 This neurodevelopmental mechanism was specific to the development of the ADHD symptoms of hyperactivity and impulsivity, and was unrelated to other types of psychopathology, including anxiety, depression, and disruptive behavior disorders.

These results indicate that the difference in prevalence of hyperactivity and impulsivity between children with a history of early institutional care, compared to their never institutionalized peers, may be explained, at least in part, by differences in brain development between these groups. This result suggests that cortical maturation is sensitive to early environmental context, and provides novel evidence of a neurodevelopmental pathway linking institutionalization to psychopathology.

#### **CONCLUSIONS**

The results from the BEIP confirm and extend the previous findings on the negative sequelae of early institutional care on mental health. As the first randomized, controlled trial of foster care as an intervention for children living in institutions, the results from this study also underscore the benefit of early family placement and enhanced caregiving for children living in institutions. Specifically, altering early experience by removing young children from institutions and by placing them in foster care resulted in improved attachment patterns, reduced signs of emotionally withdrawn/inhibited RAD, improved measures of positive affect, and reduced prevalence of internalizing disorders. Additional factors, which we are now exploring, are the influence of genetic variation on individual outcomes and recovery from early severe social deprivation, and the role of differences in brain development in mediating later psychiatric morbidity.

There are several limitations that should be noted. First, as previously mentioned, the mean age of placement into foster care for participants in this study was nearly two years, and thus the study is unable to address the potential consequences of earlier placement into foster care on the developmental trajectory in these domains. Second, the data collected so far in this study provide information on outcomes only at the age of 54 months. Future research needs to investigate whether the results found here persist into adolescence and adulthood. Third, both the Romanian institutions and the high-quality foster care system set up for this study may not be representative of the care in other settings, with the consequence that these results may not be generalizable to all children with a history of early psychosocial deprivation or institutionalization.

What are the long-term implications of this body of work from both a policy and developmental perspective? First, this project may already have had an impact in Romania, which several years ago passed a law forbidding the institutionalization of children under two years of age unless the child is severely handicapped. Second, this project has implications for the nearly 100 million orphaned or abandoned children around the world (UNICEF estimate), for whom a common societal response is to place them in institutions. As it is increasingly clear that institutional care has a significant negative impact on these children, our results highlight the importance of carefully evaluating this practice and of removing children from institutions as early in life as possible. Third, our results have implications for the thousands of children in the United States who are managed within the child protection system. Specifically, the earlier that children in child protective services can be placed in enhanced and stable caregiving environments, the better the potential



outcomes will be. Finally, these studies have implications for the understanding of sensitive periods in human brain development since the timing of the foster care intervention differentially affects recovery, with the particular difference depending upon the domain being examined. Understanding these sensitive periods may, in turn, lead to a better understanding of how the structure of experience weaves its way into the structure of the brain-leading to renewed efforts by policymakers to ensure that all our children get off to a good start in life.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

#### REFERENCES

- 1. Egeland B, Sroufe LA, Erickson M. The developmental consequence of different patterns of maltreatment. Child Abuse Negl 1983:7:459-69
- 2. Cicchetti D, Barnett D. Attachment organization in maltreated preschoolers. Dev Psychopathol 1991;4:397-411.
- 3. Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry 2007;64:49–56.
- 4. Zeanah CH, Nelson CA, Fox NA, et al. Designing research to study the effects of institutionalization on brain and behavioral development: the Bucharest Early Intervention Project. Dev Psychopathol 2003;15:885-907.
- 5. MacLean K. The impact of institutionalization on child development. Dev Psychopathol 2003;15:853-84.
- 6. Colvert E, Rutter M, Beckett C, et al. Emotional difficulties in early adolescence following severe early deprivation: findings from the English and Romanian adoptees study. Dev Psychopathol 2008;20:547-67.
- 7. Tizard B, Rees J. The effect of early institutional rearing on the behaviour problems and affectional relationships of four year old children. J Child Psychol Psychiatry 1975;16:61-73.
- 8. Chisholm K, Carter MC, Ames EW, Morison SJ. Attachment security and indiscriminately friendly behaviour in children adopted from Romanian orphanages. Dev Psychopathol 1995:7:283-94
- 9. Hodges J, Tizard B. Social and family relationships of ex-institutional adolescents. J Child Psychol Psychiatry 1989:30:77-97
- 10. Ellis BH, Fisher PA, Zaharie S. Predictors of disruptive behavior, developmental delays, anxiety, and affective symptomatology among institutionally reared Romanian children. J Am Acad Child Adolesc Psychiatry 2004;43:1283-92.
- 11. Rutter M, Kreppner J, Croft C, et al. Early adolescent outcomes of institutionally deprived and non-deprived adoptees. III. Quasi-autism. J Child Psychol Psychiatry 2007;48:1200–7.
- 12. Eluvathingal TJ, Chugani HT, Behen ME, et al. Abnormal brain connectivity in children after early severe socioemo-

- tional deprivation: a diffusion tensor imaging study. Pediatrics 2006:117:2093-100.
- 13. Wismer Fries AB, Ziegler TE, Kurian JR, Jacoris S, Pollak SD. Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. Proc Natl Acad Sci U S A 2005;102:17237-40.
- 14. Fries AB, Shirtcliff EA, Pollak SD. Neuroendocrine dysregulation following early social deprivation in children. Dev Psychobiol 2008;50:588-99.
- 15. Smyke AT, Zeanah CH, Fox NA, Nelson CA, Guthrie D. Placement in foster care enhances quality of attachment among young institutionalized children. Child Dev 2010;81:212-23.
- 16. Ainsworth MDS, Blehar MC, Waters E, Wall S. Patterns of attachment. Hillsdale, NJ: Erlbaum, 1978.
- 17. Green J, Goldwyn R. Annotation: attachment disorganization and psychopathology: new findings in attachment research and their potential implications for developmental psychopathology in childhood. J Child Psychol Psychiatry 2002;43: 835-46
- 18. Lyons-Ruth K, Bureau JF, Riley CD, Atlas-Corbett AF. Socially indiscriminate behavior in the Strange Situation: convergent and discriminant validity in relation to caregiving risk, later behavior problems, and attachment insecurity. Dev Psychopathol 2009;21:355-72.
- 19. Zeanah CH, Smyke AT, Koga SF, Carlson E; Bucharest Early Intervention Project Core Group. Attachment in institutionalized and community children in Romania. Child Dev 2005:76:1015-28
- 20. Smyke AT, Koga SF, Johnson DE, et al. The caregiving context in institution-reared and family-reared infants and toddlers. J Child Psychol Psychiatry 2007;48:210-8.
- 21. Smyke, AT, Zeanah CH, Egger HL. Timing effects on attachment and psychiatric morbidity: the Bucharest Early Intervention Project. Paper presented at a symposium at the Society for Research in Child Development, Denver, CO, April 2009.
- 22. Ghera MM, Marshall PJ, Fox NA, et al. The effects of foster care intervention on socially deprived institutionalized children's attention and positive affect: results from the BEIP study. J Child Psychol Psychiatry 2009;50:246-53.
- 23. Egger HL, Erkanli A, Keeler G, Potts E, Walter BK, Angold A. Test-retest reliability of the Preschool Age Psychiatric Assessment (PAPA). J Am Acad Child Adolesc Psychiatry 2006;45:538-49.
- 24. Zeanah CH, Egger HL, Smyke AT, et al. Institutional rearing and psychiatric disorders in Romanian preschool children. Am J Psychiatry 2009;166:777-85.
- 25. Nelson CA 3rd, Zeanah CH, Fox NA, Marshall PJ, Smyke AT, Guthrie D. Cognitive recovery in socially deprived young children: the Bucharest Early Intervention Project. Science 2007;318:1937-40.
- 26. Rutter ML, Kreppner JM, O'Connor TG; English and Romanian Adoptees study team. Specificity and heterogeneity in children's responses to profound institutional privation. Br J Psychiatry 2001;179:97-103.
- 27. Caspi A, Sugden K, Moffitt T, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.



- 28. Ritchie K, Jaussent I, Stewart R, et al. Association of adverse childhood environment with late-life depression. J Clin Psychiatry 2009;79:1281-8.
- 29. Xie P, Kranzler HR, Poling J, et al. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry 2009;11:1201-9.
- 30. Stevens SE, Kumsta R, Kreppner JM, Brookes KJ, Rutter M, Sonuga-Barke EJ. Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: developmental continuities in gene-environment interplay. Am J Med Genet B Neuropsychiatr Genet 2009;150B: 753 - 61
- 31. Kumsta R, Stevens S, Brookes K, et al. 5HTT genotype moderates the influence of early institutional deprivation on emotional problems in adolescence: evidence from the English and Romanian Adoptee (ERA) study. J Child Psychol Psychiatry 2010;51:755-62.
- 32. Burdick KE, Funke B, Goldberg JF, et al. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. Bipolar Disord 2007;9:370-6.
- 33. Funke B, Malhotra AK, Finn CT, et al. COMT genetic variation confers risk for psychotic and affective disorders: a case control study. Behav Brain Funct 2005;1:19.
- 34. Shifman S, Bronstein M, Sternfeld M, et al. COMT: a common susceptibility gene in bipolar disorder and schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2004;128B: 61 - 4
- 35. Lachman H, Papolos D, Satio T, Yu YM, Szumlanski C, Weinshilboum R. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 1996;6:243-50.
- 36. Lotta T, Vidgren J, Tilgmann C, et al. Kinetics of a soluble and membrane-bound catechol-O-methyltransferase: a revised

- mechanism and description of the thermolabile variant of the enzyme. Biochemistry 1995;34:4204-10.
- 37. Massat I, Souery D, Del-Favero J, et al. Association between COMT (Val158Met) functional polymorphism and early onset in patients with major depressive disorder in a European multicenter genetic association study. Mol Psychiatry 2005; 10:598-605
- 38. Drury SD, Theall KP, Smyke AT, et al. Modification of depression by COMT val158 met polymorphism in children exposed to early severe psychosocial deprivation. Child Abuse Negl 2010;34:387-95.
- 39. Marshall PJ, Fox NA; BEIP Core Group. A comparison of the electroencephalogram between institutionalized and community children in Romania. J Cogn Neurosci 2004;16:1327-38.
- Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 2003;114:171-83
- 41. Matsuura M, Okubo Y, Toru M, et al. A cross-national EEG study of children with emotional and behavioural problems: a WHO collaborative study in the western Pacific Region. Biol Psychiatry 1993;34:52-8.
- 42. Kinsbourne M. Minimal brain dysfunction as a neurodevelopmental lag. Ann N Y Acad Sci 1973;205:268-73.
- 43. Marshall PJ, Bar-Haim Y, Fox NA. Development of the EEG from 5 months to 4 years of age. Clin Neurophysiol 2002;113:1199-208
- 44. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/ hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A 2007;104:19649-54.
- 45. McLaughlin KA, Fox NA, Zeanah CH, Sheridan MA, Marshall P, Nelson CA. Delayed maturation in brain electrical activity partially explains the association between early environmental deprivation and symptoms of attention-deficit/hyperactivity disorder. Biol Psychiatry 2010;68:329-36.

