
Delayed Maturation in Brain Electrical Activity Partially Explains the Association Between Early Environmental Deprivation and Symptoms of Attention-Deficit/Hyperactivity Disorder

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Background: Children raised in institutional settings are exposed to social and environmental circumstances that may deprive them of expected environmental inputs during sensitive periods of brain development that are necessary to foster healthy development. This deprivation is thought to underlie the abnormalities in neurodevelopment that have been found in previously institutionalized children. It is unknown whether deviations in neurodevelopment explain the high rates of developmental problems evident in previously institutionalized children, including psychiatric disorders.

Methods: We present data from a sample of children raised in institutions in Bucharest, Romania ($n = 117$) and an age- and sex-matched sample of community control subjects ($n = 49$). Electroencephalogram data were acquired following entry into the study at age 6 to 30 months, and a structured diagnostic interview of psychiatric disorders was completed at age 54 months.

Results: Children reared in institutions evidenced greater symptoms of attention-deficit/hyperactivity disorder, anxiety, depression, and disruptive behavior disorders than community controls. Electroencephalogram revealed significant reductions in alpha relative power and increases in theta relative power among children reared in institutions in frontal, temporal, and occipital regions, suggesting a delay in cortical maturation. This pattern of brain activity predicted symptoms of hyperactivity and impulsivity at age 54 months, and significantly mediated the association between institutionalization and attention-deficit/hyperactivity disorder symptoms. Electroencephalogram power was unrelated to depression, anxiety, or disruptive behaviors.

Conclusions: These findings document a potential neurodevelopmental mechanism underlying the association between institutionalization and psychiatric morbidity. Deprivation in social and environmental conditions may perturb early patterns of neurodevelopment and manifest as psychiatric problems later in life.

Key Words: Attention-deficit/hyperactivity disorder (ADHD), brain development, deprivation, electroencephalogram (EEG), institutionalization

In many parts of the world, children who are abandoned or orphaned are raised in bleak institutional settings. Such institutions can be characterized by marked psychosocial, linguistic, and sensory deprivation (1), and their effects on child development are profound. Elevated psychiatric morbidity among previously institutionalized children is particularly striking (2–5). Increases in symptoms of attention-deficit/hyperactivity disorder (ADHD) are so marked that some have suggested they represent a core feature of an institutional deprivation syndrome (4). Here we report findings indicating that atypical patterns of brain activity evident in children reared in institutional

settings are directly responsible for these elevations in ADHD symptoms, providing the first documentation of a neurodevelopmental mechanism linking environmental deprivation to mental health problems.

The United Nations Children Fund estimates that 8 million children worldwide currently reside in institutional settings, including 1.5 million children in Europe alone (6). Institutionalization is a growing problem in Africa where increasing numbers of children are orphaned because of the AIDS epidemic and armed conflict (7). At the same time, doors to international adoption are closing rapidly. The number of children adopted internationally in the United States has declined by approximately 44% since 2005 (8). These trends raise concerns about how societies will manage the substantial burden of health problems among previously institutionalized children. Children raised in institutions exhibit wide-ranging developmental abnormalities, including stunted growth (9), physical and mental health problems (5,9), cognitive and language deficits (9,10), and atypical social and emotional development (11,12). Many of these problems persist long after children are removed from institutional care (13).

Although the deleterious effects of institutionalization on developmental outcomes are clear, the mechanisms that underlie these associations remain poorly understood. Children raised in institutions confront social and environmental circumstances that deviate markedly from the expectable environments necessary for normal brain development. During sensitive periods of neurodevelopment, expected environmental inputs are neces-

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sary to guide neural differentiation and pruning. The environmental inputs necessary for proper development of the visual system and for language acquisition, for example, are well characterized (14). It is likely that many of the expected environmental conditions necessary for proper neurodevelopment are either absent or inadequate in institutional settings. Indeed, increasing evidence finds marked detrimental effects of institutional deprivation on brain development (15–17). It has therefore been suggested that the lasting effects of severe early deprivation on neurodevelopment are responsible for the wide range of physical and mental health problems that are associated with institutionalization (18). Although intuitive, evidence to support this claim has thus far been lacking.

We examined this hypothesis in this study. Specifically, we evaluated whether elevations in psychiatric problems among children reared in institutions were attributable to atypical patterns of brain development resulting from institutional deprivation. Data came from the Bucharest Early Intervention Project (BEIP), a longitudinal study that has followed a sample of children reared in institutional settings in Romania and a matched sample of children from the community. Relative to children living in the community, institutionalized children in the BEIP evidenced abnormalities in brain activity, possibly suggesting a delay in cortical maturation (15). A similar pattern of brain activity has also been found among children with ADHD (19–23). We investigated whether this pattern of brain activity, assessed at entry into the BEIP, was associated with the subsequent development of ADHD symptomatology and other psychiatric problems in early childhood. Finally, we determined whether atypical patterns of brain development represent a mechanism underlying the association between institutionalization and psychopathology.

Methods and Materials

Sample

The BEIP is a longitudinal study that has followed a sample of children who were raised from early infancy in institutions in Bucharest, Romania. The BEIP was designed as the first randomized controlled trial of foster care among abandoned children placed in institutions (24). A sample of 136 children (aged 6–30 months) was recruited from institutions in Bucharest. An age-matched sample of 72 children who had never been institutionalized was recruited for participation from pediatric clinics in Bucharest. Half of children in the institutionalized group were randomized to a foster care intervention developed by the BEIP team (24). Comprehensive assessments of each child's health, cognitive ability, and brain functioning were completed at initial entry into the study and at 30 and 42 months. Psychiatric disorders were assessed at 54 months.

Study participants were selected from each of the six institutions for young children in Bucharest. Physical examinations were completed on 187 children residing in these institutions. Of this group, 51 were excluded from participation for medical reasons ranging from genetic syndromes (e.g., Down syndrome), fetal alcohol syndrome, and microcephaly (24). The remaining 136 children had lived in an institution for at least half of their lives ($M = 89.0\%$; 51.5% had resided in an institution for their entire life). Following the baseline assessments, half of the children ($n = 69$) residing in institutions were randomized to a foster care intervention and half ($n = 67$) remained in institutional care. Randomization was performed by assigning each child a number from 1 to 136. Numbers were written on slips of

paper and placed into a hat. The first number drawn from the hat was assigned to remain in the institution, the next was assigned to foster care, and so on, until all children had been assigned. The two sets of twins in the study were written on the same piece of paper and were placed together. No differences were found between the intervention and control group in gender distribution, age, birth weight, or percentage of life spent in the institution. By the 54-month assessment, 14 children were lost to follow-up, primarily because of adoption or reintegration with their biological parents. The study design and methods have been described in detail previously (24).

The BEIP was initiated at the request of the Secretary of State for Child Protection in Romania. All study procedures were approved by the local commissions on child protection in Bucharest, the Romanian Ministry of Health, an ethics committee comprising appointees from several government and Bucharest University academic departments, and the institutional review boards of the home institutions of the three principal investigators. A more complete description of procedures employed to ensure ethical integrity has been published previously (25) and commented on by the scientific community (26,27).

Electroencephalogram Methods

Children completed resting electroencephalogram (EEG) assessment on entry into the study, before randomization. EEG was recorded using a Lycra stretchable cap that had tin electrodes sewn into it. EEG was recorded at 12 scalp sites (F3, F4, Fz, C3, C4, P3, P4, Pz, O1, O2, T7, and T8) and the right and left mastoids. EEG was collected with reference to the vertex (Cz), and an anterior midline site (AFz) served as the ground. The scalp underlying each electrode site was gently abraded, and electrolytic conducting gel was inserted into the space between the scalp and the electrode. Impedances were measured at each electrode site and were considered acceptable if they were at or below 10 Ω s. Channels were digitized at 512 Hz onto the hard drive of a personal computer using a 12-b A/D converter (± 2.5 V input range) and Snap-Master acquisition software (HEM Data, Southfield, Michigan). One channel of vertical electro-oculogram (EOG) was recorded using tin electrodes placed above and below the left eye to record blinks and other eye movement. The EEG and EOG signals were amplified by factors of 5000 and 2500, respectively, using custom bioelectric amplifiers from SA Instrumentation Company (San Diego, California). Amplifier filter settings for all channels were .1 Hz (high pass) and 100 Hz (low pass). Before the recording of EEG from each participant, a 50- μ V 10-Hz signal was input into each of the channels, and the amplified signal was recorded for calibration purposes.

During EEG collection, a standard experimental protocol used for infants and toddlers was used (28). An experimenter placed several brightly colored balls in a bingo wheel and spun the wheel for a total of nine trials, each lasting 10 sec. After each trial, the experimenter stopped spinning the wheel for 10 sec and changed the number of balls in the wheel to maintain the child's attention. The EEG signal was recorded for the entire 3-min period, but only data from epochs in which the wheel was being spun were subjected to further analysis.

Processing and analysis of the EEG signal was performed using the EEG Analysis System from James Long Company (Caroga Lake, New York). Epochs containing blinks or other eye movement were excluded from analysis, as were epochs in which the EEG signal exceeded ± 250 μ V. The EEG channels were rereferenced in software to an average mastoids reference. The artifact-scored, rereferenced EEG data were spectrally ana-

lyzed using a discrete Fourier transform (DFT) with a 1-sec Hanning window having 50% overlap between adjacent windows. Consistent with prior research specifying EEG frequency bands in this age range (28–30), spectral power in the following frequency bands was then computed: theta (3–5 Hz), alpha (6–9 Hz), and beta (10–18 Hz).

We computed absolute power (AP) in each frequency band by taking the natural logarithm of power in that band. Relative power (RP) in each frequency band was computed as the proportion of power at a given electrode site relative to total power at that same electrode site. EEG relative power thus represents the relative contribution of a particular frequency band to the total electrical activity at a specific scalp site. Relative power minimizes individual differences in absolute power resulting from variations in age at assessment as well as skull thickness and other anatomic factors (28,31,32). This analysis focuses on the left- and right-sided electrodes over the frontal (F3, F4), central (C3, C4), parietal (P3, P4), occipital (O1, O2), and temporal (T7, T8) scalp regions and does not include midline sites (Fz, Cz, Pz).

EEG data were collected from 166 children (117 institutionalized and 49 community control subjects) who were at least 9 months of age, because EEG frequency bands are poorly defined before 9 months (28). We did not collect EEG data from 3 institutionalized children and 14 community control subjects because of fussiness before or during placement of the EEG cap. The parents of two control children declined to have EEG recorded from their child. Of the children from whom we collected EEG data, three (two institutionalized, one control) were excluded from analyses because of excessive noise across channels.

Psychiatric Assessment

Symptoms of psychiatric disorders, including ADHD, anxiety disorders, major depression, and oppositional defiant disorder (ODD) were assessed using a structured diagnostic interview for young children, the Preschool Age Psychiatric Assessment (PAPA) (33,34). This instrument collects information from a caregiver about the presence, frequency, and duration of psychiatric symptoms and generates DSM-IV diagnoses (35). The PAPA has been demonstrated to have comparable reliability to structured diagnostic interviews used with adults and older children (33). The interview was translated into Romanian and back-translated into English, and retention of original meaning was assessed by bilingual study staff. The PAPA was administered by trained study interviewers. Biological or foster care mothers completed the assessment for noninstitutionalized children. An institutional caregiver provided information for children living in institutional settings. Caregivers who worked with the child regularly and knew the child well were selected to complete the interview. If the child had a favorite caregiver, agreed on by staff consensus, the favorite caregiver completed the assessment.

Statistical Analysis

We investigated whether patterns of brain development associated with institutionalization were responsible for the elevated rates of psychiatric symptoms among institutionalized children relative to community control subjects using standard tests of statistical mediation. To provide evidence for mediation, four criteria must be met (36,37). First, an association between the exposure and outcome of interest must be established. Here, we examined differences in symptoms of ADHD, anxiety, depression, and ODD at 54 months between children reared in institutions versus the community using univariate analyses of variance

(ANOVAs) with group (ever institutionalized vs. community) as a between-subjects factor. Because previous research suggests that different patterns of EEG activity are associated with the predominantly inattentive, predominantly hyperactive/impulsive, and combined subtypes of ADHD (19,38), we examined symptoms of inattention, hyperactivity, and impulsivity as separate outcomes.

Second, the exposure must be associated with the putative mediator. We examined group differences in brain development using univariate ANOVAs with group as a between-subjects factor. We examined EEG relative power, or the proportion of total electrical activity at a specific electrode that is contributed by each frequency band, in frontal, occipital, parietal, and temporal regions. Third, the mediator must be associated with the outcome. Here, we examined the associations of EEG relative power with psychopathology outcomes using linear regression. Birth weight and head circumference were included as covariates in all analyses, and statistical significance was evaluated using .05-level, two-sided tests.

The final critical test of mediation involves the degree of attenuation in the association between the exposure and outcome in a model that includes the mediator. If this association is attenuated significantly, a significant indirect effect of the exposure on the outcome through the mediator exists, establishing evidence for mediation (36,37). Here, we tested the significance of the mediator using a bootstrapping approach that provides bias-corrected confidence intervals and allows multiple mediators (i.e., EEG components) to be examined in one model (39). Confidence intervals that do not include zero indicate significant mediation.

Results

Institutionalization and Psychopathology

Elevations in psychiatric symptomatology were evident among institutionalized children relative to community control subjects at 54 months. Children who were institutionalized had a greater number of ADHD symptoms of inattention [$F(1,147) = 21.3, p < .001$], hyperactivity [$F(1,147) = 11.4, p < .001$], and impulsivity [$F(1,147) = 16.6, p < .001$], at 54 months than community control subjects (Table 1). Symptoms of anxiety [$F(1,147) = 10.3, p = .002$], depression [$F(1,147) = 15.0, p < .001$], and ODD [$F(1,147) = 9.1, p = .003$] were also more common among institutionalized children.

Although children who were randomized to the foster care intervention evidenced lower levels of anxiety and depressive symptoms than children in the care as usual group, the prevalence of symptoms of ADHD and ODD did not differ between institutionalized children as a function of foster care placement (3).

Institutionalization and Brain Development

As documented previously (15), we found significant associations between institutionalization and brain development. Increased theta relative power was observed among children who were institutionalized compared with community controls in frontal [$F(3,131) = 5.2, p = .024$], temporal [$F(3,131) = 6.0, p = .015$], and occipital regions [$F(3,131) = 6.7, p = .010$; Table 2]. Children reared in institutions also evidenced decreased alpha relative power in frontal [$F(3,131) = 4.6, p = .033$] and occipital regions [$F(3,131) = 9.4, p = .003$], relative to community controls. No group differences in beta relative power were observed.

Brain Development and Psychopathology

EEG relative power at baseline was associated with ADHD symptoms of hyperactivity and impulsivity at 54 months. Specifically, theta relative power in the temporal region ($\beta = .22, p =$

Table 1. Psychiatric Symptoms Among Children Reared in Institutions and Their Community Controls^a

	Institution		Community		Group Difference	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>F</i>	<i>p</i> Value
ADHD	5.5	.4	1.2	.7	22.4 ^b	.001
Inattention	2.6	.3	.4	.4	21.3 ^b	.001
Hyperactivity	1.8	.2	.6	.3	11.4 ^b	.001
Impulsivity	1.1	.1	.3	.2	16.6 ^b	.001
Anxiety	3.4	.2	2.2	.3	10.3 ^b	.002
Depression	1.3	.2	.3	.2	15.7 ^b	.001
ODD	1.7	.2	.7	.3	9.1 ^b	.003

ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder.

^aAnalyses control for birth weight and head circumference. Results were unchanged when age was included as a covariate.

^bSignificant at the .05 level, two-sided test.

.019), and alpha relative power in the frontal region ($\beta = -.18$, $p = .040$) was associated with hyperactivity. Theta relative power in frontal ($\beta = .25$, $p = .007$), temporal ($\beta = .26$, $p = .004$), and parietal regions ($\beta = .27$, $p = .006$) and alpha relative power in frontal ($\beta = -.22$, $p = .012$) and parietal regions ($\beta = -.21$, $p = .024$) was associated with impulsivity. Beta relative power was not associated with hyperactivity or impulsivity. EEG relative power across all frequency bands was unrelated to symptoms of inattention, anxiety, depression, and ODD, with the exception of an association between theta in the temporal region and inattention and between theta in frontal and parietal regions with anxiety (Table 3).

Mediation Models

To evaluate the hypothesis that atypical brain development mediates the effect of institutionalization on ADHD symptomatology, we examined separate multiple mediation models predicting hyperactivity and impulsivity. EEG relative power in cortical areas that were associated with both institutionalization and the relevant outcome were included in each model. We present the total effect of institutionalization on each of these outcomes as well as the indirect effect of institutionalization once EEG power is included in the multiple mediation model (39).

The total effect of institutionalization on hyperactivity ($\beta = 1.11$, $p = .006$) is attenuated when EEG power is added to the model ($\beta = .90$, $p = .030$; Figure 1), and the indirect effect of institutionalization on hyperactivity through EEG power is statistically significant (95% confidence interval [CI] .01–.56). The association between institutionalization and hyperactivity is reduced by 19.2% when EEG power is added to the model. The association between institutionalization and impulsivity ($\beta = .81$, $p = .0003$) is also attenuated when EEG power is added to the model ($\beta = .67$, $p = .003$), and the indirect effect is statistically significant (95% CI .02–.36). The association between institutionalization and impulsivity is reduced by 17.3% when EEG power is added to the model. These results indicate that the difference in prevalence of hyperactivity and impulsivity between children reared in institutions compared with those raised in the community is partially explained by differences in brain development between these groups.

Discussion

We provide evidence for a neurodevelopmental mechanism linking early institutional rearing with hyperactivity and impulsivity, two core features of ADHD. Specifically, we find that

Table 2. Electroencephalogram Relative Power Among Children Reared in Institutions and Their Community Control Subjects^a

	Institution		Community		Group Difference	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>F</i>	<i>p</i> Value
Theta						
Frontal	.576	.01	.541	.01	5.21 ^b	.024
Parietal	.563	.01	.552	.01	.62	.434
Occipital	.585	.01	.547	.01	6.72 ^b	.010
Temporal	.500	.01	.456	.02	6.04 ^b	.015
Alpha						
Frontal	.268	.01	.295	.01	4.61 ^b	.033
Parietal	.266	.01	.273	.01	.45	.504
Occipital	.246	.01	.277	.01	9.42 ^b	.003
Temporal	.225	.01	.239	.01	1.68	.196
Beta						
Frontal	.156	.01	.165	.01	.77	.380
Parietal	.171	.01	.176	.01	.17	.684
Occipital	.169	.01	.176	.01	.28	.601
Temporal	.274	.01	.305	.02	2.57	.111

^aAnalyses control for birth weight and head circumference. Results were unchanged when age was included as a covariate.

^bSignificant at the .05 level, two-sided test.

Table 3. Associations Between EEG Relative Power at Baseline and 54-Month Psychopathology^a

EEG Component	Inattention		Hyperactivity		Impulsivity		Depression		Anxiety		ODD	
	β	p Value	β	p Value	β	p Value	β	p Value	β	p Value		
Theta												
Frontal	.08	.384	.13	.191	.25 ^b	.007	.07	.449	.17 ^b	.050	.09	.335
Parietal	.08	.408	.12	.225	.27 ^b	.006	.06	.549	.20 ^b	.044	-.01	.899
Occipital	.13	.180	.06	.524	.18	.059	.05	.605	.14	.135	-.01	.890
Temporal	.18 ^b	.050	.22 ^b	.019	.26 ^b	.004	.07	.417	.17	.071	.11	.211
Alpha												
Frontal	-.13	.163	-.18 ^b	.040	-.22 ^b	.012	-.15	.094	-.16	.073	-.15	.096
Parietal	-.10	.270	-.15	.100	-.21 ^b	.024	-.16	.085	-.17	.071	-.05	.561
Occipital	-.12	.197	-.03	.714	-.15	.102	-.08	.383	-.06	.495	.04	.627
Temporal	-.09	.336	-.11	.208	-.14	.113	-.09	.311	-.08	.359	-.04	.644
Beta												
Frontal	.04	.683	.05	.585	-.09	.329	.09	.359	-.07	.453	.06	.548
Parietal	-.01	.973	-.01	.980	-.13	.162	.08	.403	-.08	.371	.07	.478
Occipital	-.05	.620	-.04	.663	-.08	.401	.01	.913	-.11	.245	-.02	.816
Temporal	-.12	.183	-.14	.124	-.17	.061	-.02	.821	-.11	.227	-.08	.352

EEG, electroencephalogram; ODD, oppositional defiant disorder.

^aAnalyses control for birth weight and head circumference. Results were unchanged when age was included as a covariate.

^bSignificant at the .05 level, two-sided test.

differences in brain activity among young children raised in Romanian institutions relative to community control subjects explain, in part, differences in the prevalence of symptoms of ADHD between these groups at 54 months. This neurodevelopmental mechanism is specific to the development of the ADHD symptoms of hyperactivity and impulsivity and is unrelated to other types of psychopathology. These findings provide, to our knowledge, the first empiric demonstration of an underlying neurodevelopmental pathway that explains the association between institutionalization and subsequent psychiatric problems. This finding sheds light on pathophysiologic pathways to ADHD and has implications for understanding the effect of early experience on neurodevelopment.

ADHD symptomatology has been associated with increased low-frequency (theta) and decreased mid-frequency (alpha) and high-frequency (beta) brain activity in a number of previous studies (19–23). Because the EEG has poor spatial resolution, it is unclear which specific brain structures are driving the pattern of findings described here. Although many possible explanations for this pattern exist, the consistently identified gray matter reductions in frontostriatal circuits among children with ADHD represent one potential explanation (40). Several studies have observed reductions in cortical gray matter volume among children with ADHD (41–43). For example, decreased volume in a variety of areas, most consistently in the prefrontal cortex and basal ganglia, have been documented among children with ADHD relative to control subjects (40,43). Recent evidence suggests that cortical thinning in children with ADHD may be more widespread across the cortex (42). These findings are consistent with our observation of elevated theta and reduced alpha power across several cortical regions. Alternatively, it has been posited that in ADHD, the pattern of brain activity observed in our study reflects a developmental delay in cortical maturation that results in greater relative theta activity (19,21,44). In typically developing children, this pattern of EEG power is evident in earlier developmental stages; as children mature from infancy through middle childhood, their EEG is characterized by increasing power at higher-frequency components (28). Longitudinal findings documenting a substantial delay in cortical maturation among children with ADHD compared with children without the disorder appear to support the developmental delay theory (41). We extend these findings by providing evidence suggesting that aspects of neural functioning measured by the EEG, potentially reflecting cortical maturation, are sensitive to social and environmental context and may be delayed or stunted in deprived environments, leading to psychopathology.

The pattern of elevated low-frequency EEG power and decreased mid- to high-frequency power indicative of a delay in cortical development uniquely predicted hyperactivity and impulsivity in this study and was largely unrelated to inattention, anxiety, depression, or ODD. This finding is consistent with prior research documenting different profiles of brain activity among

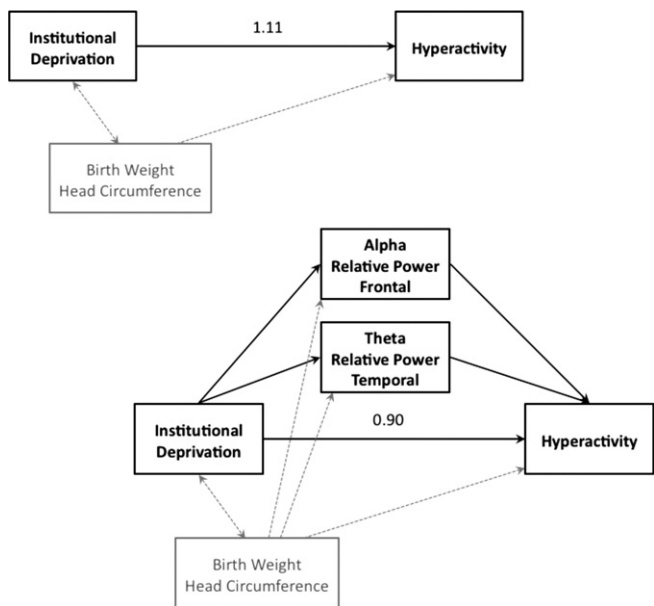


Figure 1. The total effect of institutionalization on hyperactivity and the final mediation model for hyperactivity. Paths represent unstandardized beta coefficients. All paths shown in solid lines are significant ($p < .05$).

children with primarily inattentive ADHD compared with impulsive/hyperactive ADHD (19,38). It should be noted, however, that alpha and theta relative power were marginally related to inattention. The lack of significant associations here may actually reflect problems with the measurement of inattention in early childhood. At 54 months, parents and guardians have observed the children in numerous situations that would differentiate them along the dimensions of activity level and impulsivity but considerably fewer situations that would differentiate them along the dimensions of sustained and focused attention. Because the latter dimensions become more obvious once children begin school, the associations between EEG power and inattention warrant reexamination when the children are older and parents or guardians have had more opportunities to observe inattentive behaviors. Importantly, the specificity of the identified neurodevelopmental pathway to ADHD symptomatology suggests that other mechanisms that have yet to be identified underlie the associations between institutional rearing and other psychiatric outcomes. However, because impulsivity and hyperactivity are associated with elevated risk for the subsequent development of other psychiatric problems such as oppositional defiant disorder and substance abuse (45,46), this neurodevelopmental pathway may indirectly underlie the association between institutionalization and these psychiatric outcomes at later points in development, a possibility that remains to be examined in future research.

It is possible that differences in EEG profiles and ADHD symptomatology between children reared in institutions versus the community resulted from factors other than institutional care. However, evidence from other samples of institutionalized children indicates similar associations of institutionalization with ADHD (2,4,5) and abnormal brain development (16,17). Moreover, the foster care intervention had some ameliorative effects on EEG profiles in the BEIP (47), suggesting that EEG differences resulted, at least in part, from institutionalization. Previous research suggests that children removed from institutional care before 6 months of age are at considerably lower risk for the development of ADHD than children placed later (2,4,5), indirectly suggesting the presence of a very early sensitive period for the development of neural circuits underlying ADHD. The lack of intervention effects for ADHD symptoms in the BEIP is therefore unsurprising, given that none of the children were placed before 6 months. Importantly, the beneficial effects of foster care on EEG profiles were observed only among children removed from institutional care at the earliest ages (47). Together, these lines of evidence suggest that EEG and ADHD group differences reflect true effects of institutionalization.

Identification of a neurodevelopmental pathway linking early experience to psychopathology has relevance for understanding the relations between other types of early-life deprivation and psychiatric disorders. Although institutional rearing represents an extreme environment, psychosocial deprivation and neglect are not uncommon among maltreated children (48–50). Moreover, a similar pattern of increased low-frequency and decreased mid- to high-frequency EEG activity, as well as higher rates of ADHD, has been reported among children raised in poverty (51–53). It is therefore possible that similar neurodevelopmental mechanisms underlie the associations of ADHD with neglect and child poverty. However, because institutional rearing deprives children of multiple domains of expected environmental experiences ranging from sensory stimulation to language exposure to the ability to form an attachment to a primary caregiver (12), it remains unclear which environmental factors are associated with

the atypical patterns of brain development found in institutionalized children. Identification of the specific aspects of environmental deprivation that predict neurodevelopmental abnormalities is imperative for targeting high-risk populations that would benefit from preventive intervention.

Findings must be interpreted in light of study limitations. First, although EEG power is an indicator of brain development that reflects observable changes as children develop (28), we did not measure brain development per se given that the EEG was examined only at one time point. Second, we acknowledge that group differences in ADHD symptoms may have resulted, at least in part, from factors other than postnatal rearing environments, such as prenatal malnutrition or exposures to toxins (54,55). We have no evidence to suggest that harmful prenatal exposures were more common in Romanian families who give their children over to institutional care, but this remains a possible alternative explanation for our findings. Although we cannot rule out genetic contributions to ADHD, most children in BEIP were placed in institutions at birth so that selective placement of children suspected of abnormalities is unlikely. Third, EEG assesses mass neural action, particularly in the cortex, such as the potentials of aligned pyramidal cells (56). EEG profiles therefore provide a global assessment of brain development but contain limited information regarding localized functioning due to poor spatial resolution. Finally, because of the relatively small sample size, we examined psychiatric symptoms as outcomes rather than categorical diagnoses. Importantly, however, symptoms were assessed using a reliable structured diagnostic interview, which is the gold standard psychiatric assessment for young children (33).

Atypical brain development related to institutionalization partially explains the association between institutional rearing and ADHD symptomatology. Deprivation in social and environmental conditions may become biologically embedded during early neurodevelopment and manifest as psychiatric problems later in life. Identification of neurodevelopmental mechanisms linking deprivation to psychopathology is critical for the development of interventions to reduce the mental health consequences of adverse early environments.

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