

# Alterations in Neural Processing and Psychopathology in Children Raised in Institutions

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**Context:** Young children raised in institutional settings experience severe deprivation in social, emotional, and cognitive stimulation. Although this deprivation is likely to disrupt brain development in ways that increase the risk for psychopathology, neurodevelopmental mechanisms linking adverse early environments to psychopathology remain poorly understood.

**Objective:** To examine whether abnormalities in the neural processing of facial and emotional stimuli are related to the high rates of psychopathology observed among institutionally reared children.

**Design, Setting, and Participants:** Data were drawn from the Bucharest Early Intervention Project, a cohort of children raised in institutions in Romania and an age-matched sample of community control subjects. At entry to the study (mean age, 22 months), event-related potentials were used to measure neural processing in 2 tasks: familiar and unfamiliar faces ( $n=114$ ) and facial displays of emotion ( $n=74$ ).

**Main Outcome Measures:** Psychiatric symptoms were assessed using the Preschool Age Psychiatric Assessment among children aged 54 months.

**Results:** As previously reported, institutionally reared children had elevated symptoms of attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and disruptive behavior compared with control children, and peak amplitudes of the P100 and P700 in response to facial stimuli were blunted among institutionalized children compared with community children in both tasks. Current analyses reveal that children with reduced P100 and P700 amplitudes in response to facial stimuli exhibited higher levels of ADHD and anxiety symptoms. Peak amplitude of the P700 in response to facial stimuli significantly mediated the association between institutional rearing and ADHD symptoms at 54 months.

**Conclusion:** Exposure to institutional rearing disrupts the P700, conferring risk for the onset of psychopathology. The high levels of ADHD symptoms among children exposed to early life deprivation may be attributable, in part, to abnormal patterns of neurodevelopment generated by these adverse rearing environments.

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**E**ARLY LIFE EXPERIENCES ARE increasingly understood as important determinants of psychopathology with consequences that persist throughout development. Institutional rearing often represents an extreme form of early life adversity, characterized by severe psychosocial deprivation. The United Nations Children's Fund estimates that 8 million children worldwide reside in institutions.<sup>1</sup> The harmful effects of institutional rearing have been well documented across numerous developmental outcomes, including growth,<sup>2,3</sup> social and emotional functioning,<sup>4,5</sup> cognitive and language ability,<sup>6,7</sup> neural structure<sup>8</sup> and functioning,<sup>9</sup> and facial processing.<sup>10,11</sup> The prevalence of psychiatric problems among previously institutionalized children is particularly elevated,<sup>12-16</sup> and recent evidence suggests that these elevations in psychopathology are explained, at least in part, by alterations in specific aspects of neurodevelopment—including pervasive cortical hypoactivation—resulting from early life deprivation.<sup>3,17</sup> For example, atypical patterns of brain electrical activity related to cortical hypoactivation are associated with attention-deficit/hyperactivity disorder (ADHD)<sup>3</sup> and indiscriminate social behavior<sup>17</sup> among children with histories of institutionalization. We examined whether atypical processing of facial stimuli is another such neurodevelopmental mechanism linking institutional rearing to psychopathology.

The processing of faces and facial emotion provides essential information for effective and appropriate social interactions,<sup>18</sup> and this developmental domain has been shown to be sensitive to the early social environment. Children exposed to severe early life adversity, including abuse

and neglect, exhibit disruptions in processing facial emotion,<sup>18,19</sup> which has been documented in both behavioral<sup>20</sup> and electrophysiological<sup>10,11</sup> studies. Studies of institutionalized and abused children suggest that event-related potentials (ERPs), such as the P100, N170, P400, and P700 components, are sensitive to facial stimuli and are influenced by environmental experiences.<sup>18,19</sup> In a series of studies from the Bucharest Early Intervention Project (BEIP), institutionalized children exhibited reduced ERP amplitudes when viewing familiar and unfamiliar faces and emotional facial expressions compared with community-reared children.<sup>21,22</sup> Blunted ERP responses to faces among institutionalized children may be a consequence of insufficient social interaction, a common experience of institutional life.<sup>23</sup> Neuroimaging studies suggest that recognizing and perceiving emotions depend on the amygdala and its connections to and from occipitotemporal regions, the thalamus, the superior temporal gyrus, and the orbitofrontal cortex.<sup>24,25</sup> Children exposed to severe adversity show structural and functional abnormalities in these systems.<sup>24,26</sup>

Atypical processing of visual stimuli, and faces in particular, may reflect or lead to disrupted socioemotional functioning. Social impairment is common in children with psychiatric disorders,<sup>27,28</sup> and this impairment may be a precursor or a consequence of deficits in the processing of faces or facial emotion. Indeed, several studies have documented alterations in behavioral<sup>29-32</sup> and neural responses<sup>33-36</sup> to facial emotion among children with psychiatric disorders relative to unaffected children. For example, children with ADHD exhibit deficits in facial emotion recognition relative to typically developing children.<sup>29,30</sup> Abnormal ERP responses to emotional stimuli have also been observed among children with autism spectrum disorders.<sup>33,36</sup> The specific neural substrates that underlie these associations are not yet clear. Limbic circuitry, and particularly the amygdala, may play a role given its importance for social perception and recognition of facial expressions<sup>37</sup> and evidence that it is related to the pathophysiology of ADHD<sup>38,39</sup> and autism.<sup>40</sup> Because disruptions in the neural processing of facial stimuli have been documented in children exposed to adverse rearing environments and in children with psychiatric disorders, alterations in facial processing may be a neurodevelopmental factor linking adverse environments to the later onset of psychopathology. Although processing of facial stimuli is a plausible mechanism linking early life adversity to psychiatric disorders, we are unaware of previous research examining this issue.

We addressed this gap in the literature using data from the BEIP, a longitudinal study of children reared in institutions in Romania and a matched sample of community-reared children. Prior research in this sample has documented elevated rates of psychopathology<sup>14</sup> and atypical neural responses to facial stimuli<sup>10,11</sup> among institutionally reared children relative to those raised in the community. We examined whether abnormalities in neural processing of faces, assessed using ERPs during recognition and emotion tasks, were associated with psychopathology and whether these visual processing abnormalities were a mechanism linking institutionalization to psychopathology. We anticipated that re-

duced ERP amplitudes in both face recognition and emotion recognition tasks would be associated with elevated psychiatric symptoms.

## MATERIALS

### SAMPLE

The BEIP was initiated as a randomized controlled trial of foster care for children who were raised in institutions from early infancy.<sup>41</sup> Children were recruited from all 6 institutions for young children in Bucharest, Romania, and a total of 187 children were screened for eligibility with physical examinations. Of these 187 children, 51 were excluded owing to medical reasons, including genetic syndromes (ie, Down syndrome), microcephaly, and fetal alcohol syndrome. The institutionalized sample comprised 136 children (institutionalized group [IG]) aged 6 to 30 months at entry to the study, and a sample of 72 age-matched comparison children from the community (never-institutionalized group [NIG]) was recruited from local pediatric clinics (N=208). Exclusion criteria for institutionalized children were also applied to the selection of comparison children. Institutionalized children had lived in an institution for at least half of their life, and more than half had resided in an institution for their entire life. At baseline, comprehensive assessments of health, cognitive ability, and brain development were completed. Half of the children in the institutionalized group were randomized to be placed in high-quality foster care that was developed and monitored by the BEIP team (n=68) and the other half remained in institutional care (n=68).<sup>14</sup> Details of randomization procedures are described elsewhere.<sup>41</sup> No differences in sex, age, birth weight, or percentage of life spent in an institution were observed between the intervention and control groups. By age 54 months, 25 children were lost to follow-up, largely as the result of adoption or reintegration with biological parents.<sup>11,14</sup>

The BEIP was developed with support from the Secretary of State for Child Protection in Romania. Numerous procedures were established to ensure ethical integrity,<sup>42-44</sup> and study methods were approved by the Romanian Ministry of Health, the local commissions on child protection in Bucharest, an ethical committee with appointees from Bucharest University and several government departments, and the institutional review boards at the institutions of the 3 primary investigators.

### FACIAL AND EMOTION PROCESSING TASKS

Prior to randomization, participants engaged in 2 tasks during which ERPs were recorded. The first was a recognition task that presented children with color images of familiar and unfamiliar comparably aged faces displaying neutral expressions. Pictures of the familiar faces were of the respondent's mother (NIG) or the preferred institutional caregiver (IG), as determined by staff consensus. Unfamiliar faces were of a woman with whom the child had no contact (eg, face of a different mother/caregiver). Familiar and unfamiliar faces each were pre-

sented in 35 separate trials in random order. The second was an emotional processing task that presented children with standardized images of a female expressing anger, sadness, fear, and happiness drawn from the MacBrain Face Stimulus Set.<sup>45</sup> These emotions were chosen because they are salient and meaningful to young children.<sup>46</sup> Each emotion was presented in 25 separate trials in random order. All children had visual acuity that permitted discrimination of the stimuli (ie, exceeded the task requirements).

Children were excluded from analyses owing to technical errors, having fewer than 10 artifact-free trials per stimulus condition, excessive eye movements or body artifacts, blinking while the picture was on the screen for more than 25% of the trials, or fussiness resulting in the inability to complete the task. A total of 60 children who participated in the recognition task and 100 of the children who participated in the emotion task were excluded for these reasons. Event-related potential data are available for 114 children for the recognition task (78 in the IG [37 females] and 36 in the NIG [18 females]), and ERP data are available for 74 children for the emotion task (54 in the IG [25 females] and 20 in the NIG [8 females]).

### ELECTROPHYSIOLOGICAL RECORDING

Continuous electroencephalogram (EEG) was recorded at 12 scalp sites (F3, F4, Fz, C3, C4, P3, P4, Pz, O1, O2, T7, and T8), in addition to the right and left mastoids, with the reference site at the vertex (Cz) and anterior midline (AFz). Electroencephalography was recorded using a Lycra stretchable cap with tin electrodes sewn into it. Abrasive gel was applied to electrode and mastoid sites. Impedance was measured at each electrode and was deemed acceptable at the level of 10 k $\Omega$  or less. All channels were digitized at 512 Hz onto a computer hard drive using a 12-bit A/D converter ( $\pm 2.5$ ) and Snap-Master acquisition software (HEM Data Corporation). The vertical electroculogram was recorded using electrodes above and below the left eye to record blinks and other eye movements. Using custom bioelectric amplifiers (SA Instrumentation Company), EEG and electroculogram signals were amplified by factors of 5000 and 2500, respectively. Amplifier filter settings were 0.1 Hz (high pass) to 100 Hz (low pass) for all channels.

Subsequent processing of the EEG signal was performed using ERP Analysis Systems (James Long Company). Blinks in the electroculogram were regressed out of the EEG using standard procedures.<sup>47</sup> Trials with an EEG signal that exceeded  $\pm 200$   $\mu$ V were excluded. Individual averages of ERP peak amplitude, relative to a 100-millisecond baseline, were computed for each stimulus type. In the recognition task, the amplitudes of ERP responses to familiar caregiver and unfamiliar faces were computed; in the emotion task, amplitudes were computed for the 4 emotions. We evaluated 5 ERP components shown previously to be involved in facial processing and attention<sup>19</sup>: 4 occipital components (measured at O1 and O2), including the P100 (90-200 milliseconds), N170 (150-300 milliseconds), P400 (250-500 milliseconds), P700 (675-850 milliseconds), and 1 fronto-

central component (Nc; 350-650 milliseconds, measured at F3, F4, and Fz).

### PROCEDURE

Each child was tested while sitting on the parent or caregiver's lap facing a computer monitor (approximately 40 cm away). The monitor was surrounded by black panels that blocked the child's view of the room. Above the monitor, a small hole in the screen allowed an observer to watch the child's behavior. For both tasks, trials consisted of a 100-millisecond baseline, followed by a 500-millisecond presentation of the stimulus and 1200 milliseconds of a blank blue screen. The intertrial interval varied randomly from 500 to 1000 milliseconds. The observer watched the infant from the hole in the screen and deleted trials in which the infant looked away. If necessary, the observer tapped on the screen or shook a rattle to attract the child's attention. The sessions ended once the child observed the maximum number of trials or was too fussy or uninterested to continue. The average durations of the recognition and emotion tasks were 3 and 4 minutes, respectively.

### PSYCHIATRIC ASSESSMENT

At 54 months, signs of ADHD, anxiety disorders, major depression, oppositional defiant disorder/conduct disorder were assessed using the Preschool Age Psychiatric Assessment (PAPA), a structured diagnostic interview of caregivers.<sup>48,49</sup> The PAPA collects information about the timing of onset, frequency, and duration of psychiatric symptoms from a child's caregiver. The PAPA is the most widely used psychiatric assessment for young children, and it is as reliable as diagnostic interviews for older children.<sup>48</sup> For the BEIP, the PAPA was translated into Romanian and then translated back into English to ensure that the original meaning was retained. Trained BEIP staff administered the PAPA to biological (NIG) or foster care mothers (for IG children who were placed in foster homes), and institutional caregivers for IG children who remained in institutions. An institutional caregiver who knew the child well or who was identified as the favorite caregiver by staff consensus was selected to complete the interview.

### DATA ANALYSIS

Standard tests of statistical mediation were used to evaluate neural processing of facial stimuli as a mechanism linking institutional rearing to psychopathology.<sup>50,51</sup> All analyses adjusted for birth weight, head circumference, and age at ERP measurement. First, we report previously established findings that demonstrate differences in psychiatric symptoms as a function of institutionalization using between-group analysis of variance. Second, we present previously reported differences in ERPs during the 2 tasks as a function of institutional rearing. For occipital components, 2 (hemisphere: right or left)  $\times$  2 (group: institutionalized vs control children)  $\times$  2 (condition: caregiver or stranger) and 2  $\times$  2  $\times$  4 (condition: anger, happy, fear, and sad) repeated-measure analyses of variance were

**Table 1. Psychiatric Symptoms Among Children Reared in Institutions and Community Control Children<sup>a</sup>**

	Mean (SE)		Group Difference	
	Institution	Community	F	P Value
ADHD	5.0 (0.5)	1.1 (0.9)	13.6 <sup>b</sup>	.0004
Anxiety	3.2 (0.2)	1.9 (0.4)	8.7 <sup>b</sup>	.004
Depression	1.1 (0.1)	0.3 (0.2)	13.1 <sup>b</sup>	.0004
ODD/CD	2.3 (0.3)	1.0 (0.5)	5.3 <sup>b</sup>	.02

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ODD/CD, oppositional defiant disorder/conduct disorder.

<sup>a</sup>Analyses control for birth weight, head circumference, and age.

<sup>b</sup>Significant at the  $P < .05$  level using a 2-sided test.

conducted. Similar analyses were performed for the frontocentral component (Nc). However, we used data from left, right, and central electrodes. The associations between ERPs during the facial and emotion processing tasks at baseline and psychopathology at 54 months were examined using linear regression. Finally, we evaluated the degree of attenuation in the association between institutionalization and psychiatric symptoms in models that included ERP responses during recognition and emotion tasks. The significance of the mediator was evaluated using a boot-strapping method that calculated bias-corrected confidence intervals for the indirect effect.<sup>52</sup> Confidence intervals that do not include zero indicate a significant indirect effect of the exposure on the outcome through the mediator.<sup>52</sup> When multiple ERP measures were related to a single psychiatric outcome, we computed a multiple mediation model that included all relevant ERP components.<sup>52</sup> Statistical significance was evaluated at  $P < .05$  using 2-sided tests.

## RESULTS

### INSTITUTIONALIZATION AND PSYCHOPATHOLOGY

As previously reported,<sup>3,14</sup> children reared in institutions had elevated symptoms of ADHD, anxiety, depression, and oppositional defiant disorder/conduct disorder relative to community control children ( $P < .05$ ) (**Table 1**).

### INSTITUTIONALIZATION AND NEURAL PROCESSING OF FACIAL STIMULI

As previously reported, for both recognition and emotional tasks, children exposed to institutionalization had significantly smaller peak amplitudes compared with community control children for 2 of the 5 ERP components considered (**Table 2** and **Figure 1** and **Figure 2**). Specifically, in the recognition task, there was a main effect of group for P100 ( $F_{1,93} = 5.07$ ;  $P = .03$ ) and P700 ( $F_{1,92} = 11.48$ ;  $P = .001$ ); and, similarly in the emotion task, there was a main effect of group for P100 ( $F_{1,57} = 4.98$ ;  $P = .03$ ) and P700 ( $F_{1,57} = 7.61$ ;  $P = .01$ ). For these components, we did not observe a significant effect of hemi-

**Table 2. Peak Amplitude ERP Values Among Children Reared in Institutions and Community Control Children<sup>a</sup>**

	Mean (SE)		Group Difference <sup>b</sup>	
	Institution	Community	F	P Value
<b>Recognition Task</b>				
P100				
Caregiver	12.6 (1.4)	17.2 (2.1)	5.07 <sup>b</sup>	.03
Stranger	11.7 (1.4)	19.1 (2.2)		
N170				
Caregiver	-7.2 (1.1)	-9.8 (1.7)	0.18	.67
Stranger	-8.8 (1.3)	-7.7 (2.0)		
P400				
Caregiver	15.0 (1.0)	15.8 (1.5)	1.36	.25
Stranger	15.0 (0.9)	18.6 (1.5)		
P700				
Caregiver	11.7 (0.7)	16.9 (1.1)	11.48 <sup>b</sup>	.001
Stranger	12.4 (0.8)	16.9 (1.2)		
Nc				
Caregiver	-13.4 (0.8)	-14.0 (1.2)	0.02	.88
Stranger	-14.5 (0.9)	-13.3 (1.4)		
<b>Emotion Task</b>				
P100				
Angry	11.3 (1.2)	17.3 (2.0)	4.98 <sup>b</sup>	.03
Happy	13.2 (1.4)	15.9 (2.3)		
Fearful	11.6 (1.1)	15.5 (1.8)		
Sad	12.0 (1.2)	17.7 (1.9)		
N170				
Angry	-6.8 (1.0)	-9.1 (1.6)	1.34	.25
Happy	-8.7 (1.1)	-8.7 (1.9)		
Fearful	-7.2 (1.1)	-9.9 (1.8)		
Sad	-7.7 (1.1)	-10.7 (1.8)		
P400				
Angry	15.5 (0.8)	18.6 (1.4)	0.64	.43
Happy	15.6 (1.1)	16.4 (1.8)		
Fearful	15.0 (1.0)	15.4 (1.6)		
Sad	16.3 (0.9)	16.7 (1.5)		
P700				
Angry	10.8 (0.8)	15.0 (1.3)	7.61 <sup>b</sup>	.008
Happy	11.5 (0.9)	14.8 (1.4)		
Fearful	11.3 (0.7)	14.8 (1.2)		
Sad	12.8 (0.7)	15.0 (1.2)		
Nc				
Angry	-14.4 (0.8)	-15.3 (1.4)	0.42	.52
Happy	-13.6 (1.0)	-12.8 (1.6)		
Fearful	-14.4 (0.9)	-15.8 (1.5)		
Sad	-13.9 (0.7)	-14.8 (1.2)		

Abbreviation: ERP, event-related potential.

<sup>a</sup>Peak amplitudes in microvolts; all analyses control for birth weight, head circumference, and age.

<sup>b</sup>Test of between-subject effects in repeated measures omnibus analyses of variance; significant at the  $P < .05$  level using a 2-sided test.

isphere, task condition, interactions between hemisphere and group, or interactions between task condition and group on either task. In contrast, we did not observe a main effect of group for peak amplitudes of N170, P400, and Nc during either task.

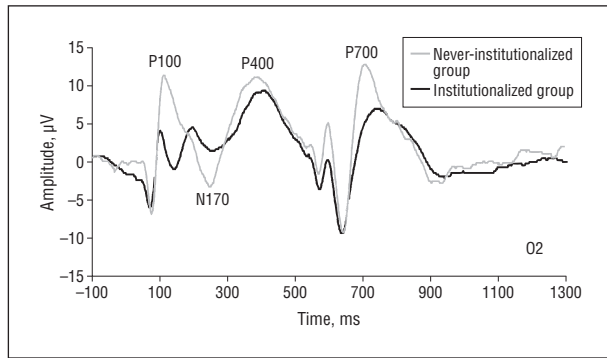
The P100 and P700 were thus the only ERP components that met the criteria for mediators of the institutionalization-psychopathology associations. Accordingly, we evaluated the associations of the P100 and P700 with psychiatric outcomes. We used mean peak amplitudes collapsed across conditions in subsequent analyses because no effect of hemisphere, task condition, interactions between hemisphere and group, or interactions



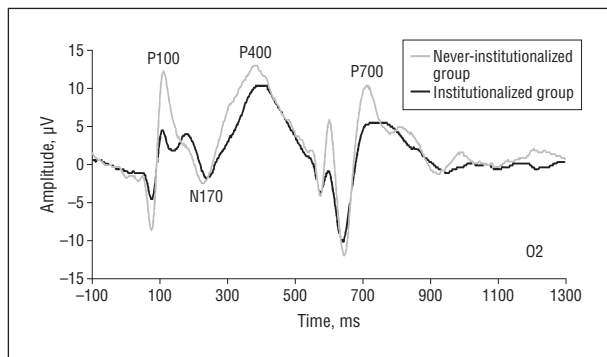
## MEDIATION MODELS

To examine whether atypical facial processing contributes to elevated rates of psychiatric symptoms among children reared in institutions, we evaluated mediation models for outcomes and mediators that met the first 3 criteria for mediation. **Table 4** presents the total effect of institutionalization on psychopathology and the indirect effect through P700 in response to facial stimuli. We first examined the mediating role of ERPs assessed during the recognition task. The total effect of institutionalization on ADHD symptoms was attenuated when P700 amplitude was added to the models, and a significant indirect effect of institutionalization on psychopathology through P700 was observed (95% CI, 0.19 to 2.88). We next evaluated the mediating role of P700 assessed during the emotion task on the association between institutionalization and anxiety symptoms. P700 during the emotion task was not a significant mediator of anxiety symptoms (95% CI, -0.06 to 1.72).

In sensitivity analyses, we explored whether time spent in home prior to institutionalization influenced mental health outcomes and ERP responses. There was no evidence that it was necessary to adjust for the proportion of life spent in an institution prior to baseline assessment in these models.



**Figure 1.** Grand averaged event-related potential waveforms of institutionalized and never-institutionalized children at the baseline assessment over the right occipital electrode collapsed across familiar and unfamiliar faces.



**Figure 2.** Grand averaged event-related potential waveforms of institutionalized and never-institutionalized children at the baseline assessment over the right occipital electrode collapsed across happy, sad, angry, and fearful emotions.

between task condition and group were observed for P100 or P700 components on either task.

### ERPs AND PSYCHOPATHOLOGY

Parameter estimates for the associations of ERPs at baseline and psychiatric symptoms at 54 months are presented in **Table 3**. In the recognition task, lower P700 peak amplitude in response to caregiver faces was associated with elevated symptoms of ADHD ( $\beta = -0.25$ ;  $P = .001$ ). In the emotion task, baseline models show that lower P100 peak amplitude was associated with ADHD ( $\beta = -0.21$ ;  $P = .04$ ) and anxiety ( $\beta = -0.11$ ;  $P = .02$ ) symptoms. And lower P700 peak amplitude was associated with symptoms of anxiety ( $\beta = -0.16$ ;  $P = .04$ ).

Prior to carrying out the mediation analyses, we constructed interaction terms to examine whether the associations between ERPs and psychiatric symptoms were consistent for institutionally reared children compared with children from the community. There were no significant interactions for P700 (Table 3). However, there was a strong pattern of statistical interaction between P100 and history of institutionalization, such that lower P100 amplitude was associated with psychiatric symptoms only among institutionally reared children. On this basis, only P700 was evaluated as a potential mediator between institutionalization and psychiatric symptoms.

### COMMENT

The objective of this study was to evaluate a potential neurodevelopmental mechanism underlying the association between institutional rearing and psychopathology. Neural processing of familiar and unfamiliar faces and of displays of emotion was evaluated using ERPs. The peak amplitudes of P100 and P700 in response to facial stimuli were diminished among institutionalized children compared with community control children in both tasks, and P700 in the caregiver/stranger task was associated with symptoms of ADHD independent of institutionalization history or placement into foster care. Lower P700 peak amplitudes in response to facial stimuli among institutionally reared children partially explained elevations in ADHD symptoms at 54 months. This aspect of neural processing of facial stimuli did not explain the relations between institutionalization and symptoms of oppositional defiant disorder/conduct disorder, depression, or anxiety. These findings contribute to a growing literature suggesting the presence of specific neurodevelopmental pathways that explain the heightened risk for psychopathology among institutionally reared children.<sup>3</sup>

The P100 is involved in the early stages of visual sensory processing, and the amplitude of this component reflects directed attentional resources to a stimulus.<sup>19,53</sup> The reduced P100 amplitude among institutionally reared children suggests reduced allocation of attention to facial stimuli among institutionally reared compared with community-reared children. Developmental studies suggest that face-sensitive ERP components are shaped by life experiences<sup>18,19</sup>; therefore, a blunted P100 in response to faces among the institutionalized children may be a con-

sequence of insufficient social interaction, a common experience of institutional life.<sup>23</sup> However, a blunted P100 amplitude in response to facial stimuli was only associated with psychiatric symptoms among institutionally reared children. This pattern suggests that blunted neural processing has different functional significance for children raised in institutional settings than those raised in the community, potentially because the blunted P100 reflects a more generalized pattern of neural hypoactivation among the institutionally reared children, which has been previously documented as a neurodevelopmental factor linking institutionalization to psychopathology in the BEIP sample.<sup>3</sup>

Compared with the P100, little is known about the functional significance of the P700 in early childhood or in relation to psychopathology in childhood or adulthood. In one study, Nelson and Nugent<sup>54</sup> examined the P700 among children ages 4 to 6 years in a task requiring recognition of happy and angry faces. The P700 distinguished between target and nontarget events (with lower amplitude for nontarget stimuli), which suggests that it may have a role in the allocation of attention and memory resources. Based on ERP patterns and scalp topography in comparable studies, researchers have hypothesized that the P700 in children may be analogous to the P300 component in adults,<sup>54</sup> with the difference in latency resulting from physiological, anatomic, and cognitive differences between children and adults (ie, resulting in faster processing of information among adults). In the case that P700 in children is comparable to P300 in adults, our findings may be consistent with research showing a relationship between reduced P300 in a variety of performance tasks and psychopathology, including ADHD and other externalizing symptoms in youth<sup>55-58</sup> and adults.<sup>59</sup> At present, we are unaware of prior evidence showing that a reduced P700 (or P300) mediates the relationship between adverse early experiences and psychopathology.

Our results are broadly consistent with prior research documenting deleterious effects of adverse early experiences, such as maltreatment and institutionalization, on neurodevelopment.<sup>18,60</sup> In this study, we cannot establish whether blunted P100 and P700 are specific to facial stimuli. It is plausible that children who are raised in deprived environments that lack stimulation may later become less responsive or attentive to both facial and non-facial stimuli. The blunted P100 and P700 ERP responses in our sample may reflect lower automatic and controlled attention to visual information, which may serve to recruit attentional and cognitive control for emotion regulation and behavioral inhibition. At present, the underlying neural substrates that may explain these findings are unknown. It is plausible that the amygdala may be indirectly involved, in light of evidence that (1) the amygdala is particularly sensitive to social adversity in early life,<sup>24,26</sup> (2) the amygdala is involved in the perception of faces,<sup>61</sup> and (3) abnormal amygdala structure and function is associated with psychopathology, including ADHD.<sup>35,39</sup> However, it is possible that disruptions in brain regions involved in more basic sensory processing of visual information, such as the thalamus and visual cortex, are also contributing to these findings.

**Table 3. Associations Between Peak Amplitude ERPs During Recognition and Emotion Tasks at Baseline and Symptoms of Psychopathology at 54 Months<sup>a</sup>**

	Recognition Task		Emotion Task	
	$\beta$	P Value	$\beta$	P Value
P100				
ADHD	-0.07 <sup>b</sup>	.23	-0.21 <sup>b,c</sup>	.04
Anxiety	-0.04 <sup>b</sup>	.11	-0.11 <sup>b,c</sup>	.02
Depression	-0.01 <sup>b</sup>	.27	-0.02 <sup>b</sup>	.27
ODD/CD	-0.06	.08	-0.08	.21
P700				
ADHD	-0.25 <sup>c</sup>	.01	-0.24	.16
Anxiety	-0.07	.17	-0.16 <sup>c</sup>	.04
Depression	-0.04	.08	-0.04	.35
ODD/CD	-0.06	.34	-0.05	.67

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ERP, event-related potential; ODD/CD, oppositional defiant disorder/conduct disorder.

<sup>a</sup>Adjusted for birth weight, head circumference, and age at ERP measurement.

<sup>b</sup>Significant interaction detected between ERP and history of institutionalization.

<sup>c</sup>Significant at the  $P < .05$  level using a 2-sided test.

**Table 4. Mediation of the Effect of Institutionalization on Symptoms of Psychopathology Through P700; Presented for ERPs and Outcomes That Met Criteria for Potential Mediation<sup>a</sup>**

Symptom Scores	Total Effect of Institutionalization		Indirect Effect of Institutionalization on Outcome Through Mediator
	$\beta$	P Value	$\beta$ (95% CI)
Recognition task			
ADHD symptoms	3.85	.0004	1.16 (0.19 to 2.88) <sup>b</sup>
Emotion task			
Anxiety symptoms	1.25	.004	0.53 (-0.02 to 1.72)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ERP, event-related potential.

<sup>a</sup>All models adjusted for birth weight, head circumference, and age at ERP measurement.

<sup>b</sup>Significant at the  $P < .05$  level using a 2-sided test.

Our findings contribute to a small but growing literature suggesting a role for differences in neurodevelopment as a mechanism linking adverse early experiences to the onset of psychopathology in children and adolescents. For example, in a study of female adolescents, greater left hemisphere EEG coherence significantly mediated the association between childhood maltreatment and psychiatric impairment.<sup>62</sup> A previous study in the BEIP found that reductions in alpha-relative power and elevations in theta-relative power, assessed using EEG, mediated the association between institutionalization and symptoms of ADHD.<sup>3</sup> Our findings build on this initial report by showing that neural hypoactivation in the occipital region to facial stimuli contributes to elevations in ADHD symptoms among institutionally reared children. Taken together, these studies are beginning to clarify the pathways through which early experiences become

biologically embedded to increase risk for psychopathology. Identifying these links is critical for advancing knowledge about the neural processes involved in the development of mental disorders among institutionalized youth. A more robust neurobiologic model of early life deprivation may help researchers identify aspects of neural processing that could be targeted by interventions for children exposed to adverse conditions to ameliorate the negative impact of adverse experiences on neural function and psychopathology.

Although our study focused on children exposed to a particularly extreme adverse rearing environment, the findings have relevance for understanding the neural mechanisms that link less severe forms of early life deprivation to psychopathology.<sup>60</sup> Child poverty and neglect are associated with elevated rates of childhood externalizing problems,<sup>63,64</sup> and similar neurodevelopmental mechanisms may underlie the associations between these exposures and externalizing psychopathology. Indeed, children from families with low maternal education exhibited blunted ERP amplitudes in a selective auditory attention task compared with children from families with higher levels of maternal education.<sup>65</sup> Further clarifying the effects of these other types of early life adversity on neural processing is an important goal for future research. Moreover, because the institutionalized children in the BEIP were exposed to pervasively disadvantaged conditions involving deprivation in social, emotional, language, and sensory stimulation, it is not possible for us to pinpoint the specific features of environmental deprivation that contributed to the abnormal processing patterns observed in this sample. This is another important objective for future research, given the relevance for targeting prevention efforts to children in high-risk environments.

The results of this study should be interpreted in light of several limitations. First, the BEIP only assessed ERPs during the presentation of facial stimuli; as a consequence, the results cannot differentiate whether deficits in neural functioning are face specific or represent more general visual-processing anomalies. Additional research that contrasts ERPs to face and nonface stimuli is needed to understand whether mediation is specific to facial perception. Second, the study focused on children reared in Romanian institutions characterized by significant deprivation. Our findings may not generalize to children who experience less severe forms of deprivation, and thus warrant replication in other populations. Third, it is possible that group differences in psychiatric symptoms and ERPs may have resulted from factors other than the rearing environment in early childhood, such as prenatal exposure to toxins,<sup>66</sup> malnutrition,<sup>67</sup> or genetic factors.<sup>68</sup> There is no evidence that Romanian families who place their children in institutional care experience more harmful prenatal exposures relative to families who do not. Importantly, the cultural and political context in Romania when the study was initiated was one in which institutionalization of children was common owing to chronic poverty and economic stagnation as well as a legacy of punitive laws regarding contraception and government policies that encouraged families to place children in institutional care.<sup>41</sup> Thus, these selection factors

were less likely to have influenced our results than they might in other samples of institutionalized children. Moreover, we controlled for potential prenatal factors by controlling for birth weight and head circumference in all analyses.

Fourth, the BEIP did not assess mental health status at baseline because of the children's ages; therefore, the extent to which abnormal ERPs are a cause vs consequence of psychiatric symptoms requires further investigation. However, given the young age of children at the ERP assessment, the hypothesized association of abnormal neural processing leading to later psychopathology is most plausible. Fifth, variation in the duration, extent, and timing of exposure to preferred caregiver vs mother is a limitation in using the caregiver as the familiar facial stimuli and reporting on the PAPA; however, caregivers are the adults who most resemble parents for institutionalized children, so this was the best available option. Great care was taken to select a caregiver who knew each child well. Finally, the relatively small size of our sample limited our statistical power to detect significant associations. For this reason, we examined continuous psychiatric symptom scores as outcomes rather than categorical diagnoses. Several future research questions arise from this study. Research is needed to examine the mechanisms by which abnormal ERPs to faces relate to ADHD symptoms. At present, it is unknown whether this mechanism functions at a behavioral level or if this association is largely a function of perturbations at the circuit level (in limbic circuitry or other regions) that are not evident in behavioral measures. In addition, more research is needed to understand the functional significance of P700 in children.

Abnormal neural processing of visual stimuli (in this study, faces) partially explained elevations in ADHD symptoms among children reared in institutional settings in Bucharest, Romania, relative to children raised in the community. Our results highlight the urgency of improving environmental conditions and the caregiving context for abandoned and orphaned children to prevent a cascade of deleterious effects on psychosocial and neural development that ultimately culminate in psychopathology. Greater understanding of the adverse effects of early adversity on brain development has the potential to inform interventions aimed at altering the social and biological pathways that link detrimental environments to the later onset of psychopathology.

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