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ADHD Symptoms in Post-Institutionalized Children are Partially Mediated by Altered Frontal EEG Asymmetry

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Abstract

Individual differences in the propensity for left versus right frontal electroencephalogram (EEG) asymmetry may underlie differences in approach/withdrawal tendencies and mental health deficits. Growing evidence suggests that early life adversity may shape brain development and contribute to the emergence of mental health problems. The present study examined frontal EEG asymmetry (FEA) following the transition to family care in children adopted internationally from institutional care settings between 15–36 months of age ($N=82$; 46 female, 36 male). Two comparison groups were included: an international adoption control consisting of children adopted from foster care with little to no institutional deprivation ($N=45$; 17 female, 28 male) and a post-adoption condition control consisting of children reared in birth families of the same education and income as the adoptive families ($N=48$; 23 female, 25 male). Consistent with evidence of greater approach and impulsivity-related behavior problems in post-institutionalized (PI) children, PI status was associated with greater *left* FEA than found in the other two groups. In addition, left FEA served as a mediator between institutionalization and age 5 ADHD symptoms for girls. Age at adoption and other preadoption factors were examined with results suggesting that earlier adoption into a supportive family resulted in a more typical pattern of brain functioning. Findings support the idea that the capacity of brain activity to evidence typical functioning following perturbation may differ in relation to the timing of intervention and suggest that the earlier the intervention of adoption, the better.

Keywords

Frontal Electroencephalogram Asymmetry; Early Adversity; Adoption; Attention Problems

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Ethical Approval: All procedures performed in this study involving human subjects were approved by the university's institutional review board and are in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all parents included in this study.

Children reared in early institutional care are at increased risk for a myriad of mental health problems. The most consistent are problems of self-regulation in the form of attention-deficit/hyperactivity symptoms and other executive function abnormalities, including indiscriminate friendliness and problems in regulating affect (Rutter, Kreppner, & O'Connor, 2001). Despite expectations that children adopted from institutions would display dysregulation in the form of marked increases in clinical levels of internalizing and externalizing problems, this has not been readily observed in childhood (Gunnar & van Dulmen, 2007; Juffer & Van Ijzendoorn, 2005), although it may emerge in adolescence (Kreppner et al., 2010). Unlike internalizing and externalizing disorders, dysregulation in the form of symptoms of disinhibited social engagement disorder (DSED; Lawler, Hostinar, Mliner, & Gunnar, 2014; Zeanah & Smyke, 2015) and attention-deficit/hyperactivity disorder (ADHD) are readily observed during childhood in post-institutionalized (PI) children (Pollak et al., 2010; Roy, Rutter, & Pickles, 2004; Rutter et al., 2001). These problems are so prevalent among PI children that some have suggested these excessive approach symptoms and lack of inhibition represent a core feature of institutional deprivation (Kreppner, O'Connor, & Rutter, 2001; Kumsta et al., 2010).

In line with current conceptualizations of psychopathology (e.g., Research Domain Criteria), childhood dysregulation problems are now recognized as conferring vulnerability to a range of psychopathology (Beauchaine & Thayer, 2015; Cole, Hall, & Hajal, 2013) including internalizing, externalizing, and ADHD symptoms and significantly increase risk for maladaptive outcomes in adulthood (Moffitt et al., 2011). Importantly, research suggests that the neural substrates of these regulatory capacities may be established in early childhood (Beauchaine, 2012). Taken together, these findings underscore the importance of identifying neural mechanisms that lead to regulatory vulnerabilities in the context of early adversity, as well as assessing their potential plasticity to inform intervention and prevention strategies.

Individual variation in frontal left and right alpha electroencephalogram (EEG) asymmetry is related to the capacity to regulate approach and withdrawal emotional reactive tendencies, respectively (Fox, 1991, 1994; Sutton & Davidson, 1997). Significant associations between children's baseline frontal EEG asymmetry (FEA) and children's regulatory behaviors provide support for its role in the development of regulation during childhood (Kim & Bell, 2006). Recent evidence indicates that FEA in young children predicts autonomic reactivity to emotion-eliciting stimuli and through this route right FEA is associated with internalizing problems and left FEA with externalizing problems (Gatzke-Kopp, Jetha, & Segalowitz, 2012). Although a number of studies have obtained associations between FEA and both internalizing and externalizing problems, particularly when stable measures of FEA are obtained (Smith & Bell, 2010), a recent meta-analysis indicates that overall the associations might be modest (Peltola et al., 2014). Recent examination of FEA in the context of trauma history points toward its potential role as a transdiagnostic marker of pathological adjustment rather than a correlate of one specific type of pathology (Meyer et al., 2015). In line with this view, exposure to adverse rearing conditions early in life is thought to influence the development of FEA. Greater relative right FEA appears to be a fairly consistent marker of early life adversity related to the presence of familial stressors, particularly maternal depression (see Peltola et al., 2014 for a meta-analysis of studies

including samples ranging from newborns to adolescents), insensitive maternal caregiving (Hane & Fox, 2006) and maltreatment (Curtis & Cicchetti, 2007; Miskovic et al., 2009).

Increasing evidence suggests that adverse rearing in the form of institutional deprivation impacts the developing brain (Sheridan, Drury, McLaughlin, & Almas, 2010). Impaired development of prefrontal regions of the brain is particularly associated with early deprivation (Hodel et al., 2015). While the majority of literature on early risk and atypical FEA patterns (i.e., heightened left or right frontal EEG asymmetry relative to a comparison group) has focused on early familial stressors (see Peltola et al, 2014), one known study did examine institutional care (McLaughlin, Fox, Zeanah, & Nelson, 2011). That study revealed a complex developmental story. Both institutionalized/post-institutionalized children and the comparison community children showed a shift from greater left to greater right FEA from infancy through the preschool period, followed by a shift back towards greater left FEA from preschool to 8 years of age. Children who were ever institutionalized were developmentally lagged such that whether they were more or less right or left frontal than the community children depended on the age the comparison was made. These findings, point toward possible age and developmental effects thus raising the potential importance of age at FEA assessment in accounting for previous inconsistencies regarding associations between institutional care and left versus right asymmetry. Greater right FEA was associated with more internalizing problems in the children, but this was not specific to the institutional care group.

Not only early neglect in the form of institutional care, but also the age of removal from such care is important. Some studies have shown few to no behavioral effects for children removed by 6 months of age (Behen & Chugani, 2015; Rutter & Sonuga-Barke, 2010), while other studies note diminishing capacity for recovery for children placed in families after 12 months and particularly after 24 months. This latter age appeared to denote the end of a sensitive period for recovery in the prior FEA study of institutionally-reared children (McLaughlin et al., 2011; Vanderwert et al 2010). We therefore examined FEA patterns for children adopted before and after 24 months in the present study.

Interestingly, recent growing evidence suggests that both risk-FEA and FEA-pathology relations may be moderated by sex with associations stronger in girls than boys (Gartstein, Bell, & Calkins, 2014; Peltola et al., 2014). Similarly, the link between FEA patterns and concurrent self-reported negative emotionality has been found to be stronger in adult females relative to males (Stewart, Bismark, Towers, Coan, & Allen, 2010). Given this evidence, we predicted FEA-outcome relations may be stronger in girls than boys.

The current longitudinal study addressed five questions: 1) Is early institutional care associated with differences in FEA 2 years post-adoption and, if so, are these associations most prominent for children experiencing greater preadoptive adversity (e.g., adopted at later ages)?, 2) Do FEA patterns predict later behavior problem symptoms (e.g., internalizing, externalizing, ADHD, and social engagement disorder) when children are approximately 5 years of age? and, 3) if so, do they mediate the association between early institutional care and later problems? Finally, 4) are the associations between FEA and behavior problems stronger for girls than boys? In addition, we also examined whether these effects were

specific to frontal electrode sites by contrasting the key results with asymmetry measured at parietal sites.

Relative to comparison groups, PI children were expected to exhibit greater frontal EEG asymmetry. It was expected that relations may be most pronounced among children adopted later (e.g., after the age of 24 months). Based on previous literature, it was expected that PI children would display elevated behavior problem symptoms and that FEA would mediate risk-pathology relations. Further it was expected that relations may be stronger in girls.

Method

Participants

Participants were 175 children taking part in a larger longitudinal study following the transition to family care after early life adversity. Participants included three groups: 82 post-institutionalized children (PI; 46 Female), 45 children adopted internationally from foster care (FC; 17 Female), and 48 same-aged non-adopted children (NA; 23 Female). PI children were 16–36 months old at adoption and were recruited into the study within the first year of adoption. PI children were recruited from a local international adoption clinic and through the aid of adoption agencies in the metro area. Approximately 70% of families agreed to participate. FC children were recruited from the International Adoption Project Registry, a registry consisting of approximately 50% of all families adopting internationally in the catchment area of our university and approximately 80% agreed to participate. FC children had been adopted by approximately 1 year of age, consistent with the earlier placement of children from countries using foster care for wards of the state. NA children were contacted through a department-maintained participant registry of families interested in research. NA families had similar education and income levels as families who adopt internationally. PI children spent the majority of their pre-adoptive lives in institutional care ($M=76\%$; duration $M=18.34$ months, $SD=8.00$) and FC child spent the majority of their pre-adoptive lives in foster care settings ($M=88\%$; duration $M=7.87$ months, $SD=1.78$). Demographic data for each of the groups are displayed in Table 1. See the online supplemental materials for region of origin differences in study variables and descriptive information on children's medication and health services use.

Eleven children were excluded for suspected prenatal alcohol exposure (9 PI, 2 FC); children were screened using the FAS Facial Photographic Analysis software (Astley & Clarren, 2000). Three children were excluded for congenital disorders (2 PI, 1 FC) and 3 NA children were excluded for atypical developmental experiences (1 autism, 1 maltreatment, 1 childhood cancer). Participants with partial data were included (across all three groups: $N=154$ had EEG data, $N=171$ had psychopathology data; out of a possible 127 internationally adopted youth, $N=116$ had DSED data). The majority of children had complete data (no missing assessments: 63 PI, 41 FC, 40 NA; 1 assessment missing: 15 PI 3 FC, 8 NA; 2 assessments missing: 4 PI, 1 FC). Nineteen children (11 PI, 4 FC, 4 NA) had no data at any of the assessments, resulting in the final reported sample of 175 children.

Procedure

Data for the present analysis included two assessment points: EEG data were collected at a session occurring approximately 24 months after the PI children's arrival into the family setting (PI time since arrival $M=24.16$, $SD=.57$) and child problem symptoms (internalizing, externalizing, ADHD, and social engagement symptoms) were collected at 5–5.5 years of age ($M_{age}=62.18$ months, $SD=2.15$). Parents provided informed consent and all study procedures and measures were approved by the University's institutional review board.

EEG data collection and FEA analyses—EEG was recorded using a 128-channel HydroCel Geodesic Sensor Net and sampled at 500 Hz, using EGI software (Net Station 4.4; Electrical Geodesic, Inc., Eugene, OR). Once the impedance values for all EEG channels were reduced to below 100 k Ω , data acquisition began. During recording, all channels were referenced to Cz and after acquisition, data were re-referenced to an average reference. Parents were present but interacted minimally during the collection. EEG was recorded during presentation of black (blank) monitor screens. Black screens were presented six times, for 30 seconds each, with experimenter prompt slides in between that acted as brief breaks for the child. Each of the six sections of EEG were collected alternating lights on and off to mimic the adult EEG paradigm in which adults open and close their eyes for fixed blocks and is in line with previously described child procedures (e.g., McLaughlin et al., 2011, Vanderwert et al., 2010, Zeanah et al., 2003). Trial order was fixed: Lights ON, OFF, ON, OFF, ON, OFF. Children were instructed to gaze at one of six toys placed in front of the screen, intended to provide a focal point to minimize head and eye movements. One toy was used for a lights ON and OFF segment; a total of three toys were used for each child. In line with procedures employed in studies of resting EEG in preschoolers, data were filtered offline using an FIR bandpass filter with a low pass frequency of 40 Hz and a high pass frequency of .3 Hz (e.g., Shankman et al., 2011). Data were segmented into lights on and lights off epochs and baseline corrected across the entire segment. Bad channels were identified and replaced in Net Station. Data were then exported to EEGLAB (Delorme & Makeig, 2004) for artifact scoring. Portions of data with artifact were deleted (M seconds of remaining artifact free data=103.27 sec, $SD=32.95$, range=24.48–170.61 sec). EEG artifact scorers were blind to group and completed 10 reliability cases (ICCs > .80). Periodic reliability was maintained between processors with 10% overlap maintained throughout processing.

Segmented data were then read into MATLAB R2012b (The MathWorks, Inc.) and a Fast Fourier Transformation (FFT) script was used to translate the EEG signal into .5 Hz frequency bins. The FFT used a 1 second window with 50% overlap and resulted in power spectral density estimates for each Hz bin, db/Hz. The number of seconds of artifact-free data was used to weight the data across the three lights on and lights off epochs and the weighted data were combined for calculation of power for total lights on and total lights off segments. Total lights on and lights off power were then each separately summed across alpha 6–9HZ frequency bands, predefined consistent with previous literature examining EEG in children (e.g., Marshall, Fox, & the BEIP Core Group, 2004; Tarullo, Garvin, & Gunnar, 2011). Using EGI Hydro-cell 128 nomenclature, frontal regions of interest were computed as the average of channels around F3 (24) and F4 (124) as focal points (left

channels: 24, 19, 20, 23, 27, 28; right channels: 124, 3, 4, 117, 118, 123). Scores were natural log-transformed to normalize data. EEG asymmetry was calculated by subtracting the power in the left frontal region from that in the right frontal region of the transformed data [$\ln(\text{right frontal region}) - \ln(\text{left frontal region})$] (McLaughlin et al., 2011). The resulting value of alpha power is inversely related to cortical activation such that scores above zero reflect greater activation in the left compared to right frontal region (i.e., greater left FEA) whereas scores below zero reflect greater activation in right compared to left frontal region (i.e., greater right FEA). Likewise, parietal regions of interest were computed to provide a contrast and distinguish between hemispheric versus regional effects. Parietal regions of interest were computed as the average of the channels around P3 (52) and P4 (92) as focal points (left channels: 52, 47, 51, 53, 59, 60; right channels: 92, 85, 86, 91, 97, 98).

Measures

Child Symptoms—Ratings of internalizing, externalizing, and ADHD symptoms were assessed using the MacArthur Health and Behavior Questionnaire (HBQ; Parent version for Middle Childhood; Boyce et al., 2002; Essex et al., 2002). The primary caregiver (92% mothers) completed the HBQ (3-point Likert scale) at the age 5–5.5 year assessment to reflect child behavior in the last 6 months. Internalizing was comprised of depression (7 items), overanxious (12 items), and separation anxiety (10 items) subscales. Externalizing was comprised of oppositional defiant (9 items), conduct problems (12 items), overt hostility (4 items), and relational aggression (6 items) subscales. ADHD consisted of inattention (6 items) and impulsivity (9 items) subscales. Reliability in the present sample was: internalizing $\alpha=.81$, externalizing $\alpha=.88$, ADHD $\alpha=.90$.

Disinhibited social engagement symptoms—Parents (89% mothers) of adopted children completed a semi-structured interview assessing symptoms of attachment disorders (DSED, formerly reactive attachment disorder or RAD disinhibited type; additionally a RAD inhibited scale was included). The measure was adapted from established measures of disturbances in attachment (O'Connor, Bredenkamp, & Rutter, 1999; Smyke, Dumitrescu, & Zeanah, 2002). Items were rated on a 3-point scale reflecting the degree to which each symptom was present. Consistent with previous work, few PI children displayed any RAD-inhibited symptoms (Zeanah, Smyke, Koga, & Carlson, 2005). Given evidence of greater social approach in PI children and in line with classification and criteria changes in DSM-5 (Regier, Kuhl, & Kupfer, 2013), we focused solely on the DSED symptoms. The 4-item DSED scale reflected children's lack of reticence and the willingness to approach unfamiliar adults, tendency to wander, and overly familiar verbal and physical behaviors with strangers. Internal consistency for DSED in the present sample was $\alpha=.72$. Inter-rater reliability was calculated on 24% of tapes across interviewers (all ICCs $.72$).

Preadoptive adversity—Children's *age at adoption* was used as a predictor in both the PI and FC groups and was highly correlated with duration of institutional care, $r(123)=.83$, $p=.00$. In the PI group, the quality of preadoptive social and physical institutional care was assessed using a semi-structured interview in which the child's primary caregiver described what they observed in the institution. The interviewer rated both the physical and social care quality of the institution each on a 5-point scale (1=very poor, 3=adequate, 5=very good).

The *physical care quality* rating reflected the availability of toys, cleanliness of the institution, and appropriate clothing for the children. The *social care quality* rating reflected the caregiver-to-child ratio, caregiver affection toward children, and the degree of individualized care. Reliability was established through independent ratings on 10 interview scenarios (κ s $>.80$). Exemplar descriptions for each care rating and additional reliability information are provided in the online supplemental materials.

Data analytic plan

Group membership (PI, FC, NA) was used as an index of early life adversity. Preliminary analyses were conducted prior to main analyses to determine relevant covariates. Main analyses addressed the five previously outlined aims. ANCOVA and regression analyses were used to examine relations between group, FEA and parietal asymmetry, and child psychopathology symptoms. Mediation was assessed among variables with significant relations identified in previous analyses and were conducted in the structural equation modeling framework. Within the PI group only, individual differences in preadoptive adversity were examined as a follow-up to the group differences. Moderation by child sex was examined among all five aims to assess whether relations between study variables differed among boys and girls. Moderation by child sex was examined by inclusion of sex by predictor interactions in ANCOVA and regression and multi-group analyses were conducted to examine moderation in the context of mediation.

Results

Prior to testing the main hypotheses, we examined correlations as well as group and sex differences among all study variables (see Tables 2 and 3). As expected, externalizing, ADHD, and DSED symptoms were significantly correlated. FEA and parietal asymmetry were not significantly correlated. FC children were slightly older at assessments (means between 1 and 5 months depending on assessment). Boys had higher rates of internalizing and ADHD symptoms. Covariates in subsequent analyses were included based on significant correlations and ANOVA comparisons identified in these preliminary analyses.

EEG asymmetry patterns

Due to significant group differences, both age at the EEG assessment and length of artifact-free EEG period (seconds of lights on and lights off) were included as covariates. ANCOVAs revealed significant differences in left relative to right FEA, $F(2,147)=4.26$, $p=.02$, $\eta^2_p=.06$. Fisher's LSD post hoc comparisons indicate that PI children, $M=0.07$, $SE=0.03$, displayed greater left relative to right FEA compared to FC children, $M=-0.06$, $SE=0.04$, $p=.01$, and NA children, $M=-0.02$, $SE=0.04$, $p=.04$. There were no group differences in parietal asymmetry, $F(2,147)=1.00$, $p=.37$, $\eta^2_p=.01$; PI $M=0.04$, $SE=0.04$, FC $M=0.10$, $SE=0.06$; NA $M=-0.01$, $SE=0.05$. Additional analyses were performed examining child sex as a moderator of the group-FEA association and did not find evidence for a significant sex X group interaction in predicting FEA, $F(2,144)=0.82$, $p=.45$, $\eta^2_p=.01$, or parietal asymmetry, $F(2,144)=0.90$, $p=.41$, $\eta^2_p=.01$. Figure 1 depicts group- and sex-specific means for FEA. Given the lack of group differences in parietal asymmetry, analyses focus on FEA.

Child Psychopathology Symptoms

Including child age as a covariate, univariate ANCOVAs revealed significant differences in ADHD, $F(2,166)=4.99$, $p=.01$, $\eta^2_p=.06$, and DSED symptoms, $F(1,104)=5.13$, $p=.03$, $\eta^2_p=.05$. Fisher's LSD indicated that PI children, $M=0.82$, $SE=0.04$, had heightened ADHD symptoms relative to NA children, $M=0.60$, $SE=0.06$, $p=.00$, but not FC children, $M=0.74$, $SE=0.06$, $p=.31$. PI children also had heightened DSED symptoms, $M=0.53$, $SE=0.06$, relative to FC children, $M=0.28$, $SE=0.08$, $p=.03$ [Note: DSED not assessed in NA children]. There were no group difference in internalizing, $F(2,167)=0.75$, $p=.47$, $\eta^2_p=.01$, or externalizing problems, $F(2,164)=2.03$, $p=.13$, $\eta^2_p=.02$. Subsequent analyses examined child sex as a moderator. There were no significant group X sex interactions predicting any of the outcomes including internalizing, $F(2,164)=0.66$, $p=.52$, $\eta^2_p=.01$, externalizing, $F(2,161)=2.47$, $p=.09$, $\eta^2_p=.03$, ADHD, $F(2,163)=0.01$, $p=.99$, $\eta^2_p=.00$, and DSED symptoms, $F(1,102)=0.44$, $p=.51$, $\eta^2_p=.00$.

Associations between FEA patterns and child outcomes

Due to relations with some psychopathology symptoms, length of artifact-free EEG period (seconds of lights on and lights off) were included as covariates. Univariate linear regression analyses indicated there were no significant associations between FEA and age 5 internalizing, $\beta=.10$, $p=.25$, $R^2=.04$, externalizing, $\beta=.12$, $p=.16$, $R^2=.02$, ADHD, $\beta=.13$, $p=.13$, $R^2=.03$, or DSED symptoms, $\beta=.09$, $p=.37$, $R^2=.05$. Subsequent regression analyses examined child sex as a moderator. There was a significant effect of child sex by FEA on children's ADHD symptoms, $\beta=-.26$, $p=.02$; $R^2=.11$. Simple slope tests revealed that the effect of FEA on ADHD symptoms was significant for girls, $t=2.66$, $p=.01$, but not boys, $t=-.93$, $p=.35$ (see Figure 2). There was no effect of child sex by FEA interactions on internalizing, $\beta=.12$, $p=.27$, externalizing, $\beta=-.09$, $p=.43$, or DSED symptoms, $\beta=-.20$, $p=.14$.

The mediating role of greater left FEA

Following the significant relations identified above, formal tests of mediation were conducted to determine whether greater left FEA was a mediator between early adversity and ADHD symptoms. Moderated mediation was also conducted to examine whether child sex moderated the associations between early adversity, FEA, and ADHD utilizing multi-group analyses in the SEM framework. To assess the impact of early life adversity, two comparisons among groups were examined. First, as a test of any early life adversity, an adopted (PI/FC) versus NA contrast was tested. Second, to examine the specific impact of institutionalization, a PI versus FC contrast was included. A chi-square difference test was used to compare nested models with parameters free to vary or constrained to be equal among boys and girls. Bootstrapping (1000 draws) was conducted as a test of mediation. Length of artifact-free EEG period (lights on, lights off) were included as covariates of FEA. Child age was examined as a covariate of FEA and child outcomes; however, age was unrelated to variables in the model and was dropped as a covariate.

The constrained model fit the data significantly worse, $\chi^2(15)=24.22$, $p=.06$, than the model with regression parameters, means, and variances free to vary across child sex, $\chi^2(6)=2.96$, $p=.81$; $df=9$, $\chi^2_{diff}=21.27$, $p<.05$, providing support for child sex as a moderator of the

mediation model (see Figure 3). The model provided good fit to the data, CFI=1.00, RMSEA= .00. There was a direct effect of adoption (PI/FC vs. NA) on heightened age 5 ADHD symptoms for both girls, $\beta=.21$, $p=.02$, and boys, $\beta=.21$, $p=.04$. Additionally, institutionalization on ADHD was mediated by left FEA for girls, indirect effect: $\beta=.11$, $p<.05$, 95% CI [.001, .21], but not boys, indirect effect: $\beta=-.02$, $p=.52$, 95% CI [-.06, .03]. In girls, institutionalization (PI vs. FC) was associated with greater left FEA, $\beta=.33$, $p=.00$, and left FEA was associated with greater parent-reported ADHD symptoms at age 5, $\beta=.32$, $p=.01$ (see Figure 3 for group-specific parameter estimates). The proportion of the maximum indirect effect (Preacher & Kelley, 2011) was calculated and indicated a medium effect size for this indirect effect in girls, $K^2=.11$.

Age at Adoption and Quality of Institutional Care

As a follow-up to the group analyses, univariate linear regression analyses were conducted within the PI sample to examine the impact of individual differences in timing and quality of preadoptive care. Analyses controlled for length of artifact-free EEG (seconds lights on and lights off). Main effects and moderation by child sex were examined for both a continuous age at adoption variable and a dichotomized at 24 months variable. There was a statistical trend between a continuous measure of age at adoption and FEA, $\beta=.22$, $p=.06$, $R^2=.10$. However, the effect of age at adoption on FEA was significant when controlling for child sex, $\beta=.42$, $p=.01$. Subsequent linear regression analyses examined child sex X age at adoption predicting FEA and was not significant, $\beta=-.27$, $p=.11$. As a follow-up, age at adoption dichotomized at 24 months was also examined, and was not associated with FEA, $\beta=.17$, $p=.15$, $R^2=.08$. However, there was a significant sex X age at adoption interaction using the dichotomized variable (at 24 months), $\beta=-.41$, $p=.04$, $R^2=.13$. Simple slope tests revealed that the effect of age at adoption (dichotomized) on FEA was significant for girls, $t=2.38$, $p=.02$, but not boys, $t=-0.56$, $p=.58$ (see Figure 4). Girls who were adopted after the age of 24 months displayed pronounced left FEA, whereas girls who were adopted prior to 24 months did not. Lastly, there were no significant associations for main effects, $\beta=.04$, $p=.78$, $R^2=.06$; $\beta=-.11$, $p=.41$, $R^2=.08$, or sex X care quality interactions, $\beta=-.24$, $p=.26$; $\beta=-.01$, $p=.96$, for social or physical care quality predicting FEA (respectively). To be thorough we also examined age at adoption within the FC children and there were no significant main effects, $\beta=.10$, $p=.55$, $R^2=.11$, or age at adoption X child sex interactions, $\beta=.04$, $p=.89$.

Discussion

The results provided evidence that two years after removal from institutional care as toddlers (ages 16 to 36 months), children exhibited greater left frontal EEG patterns relative to both children reared from birth in their families of origin and those adopted internationally from foster care settings. The impact of early adversity was unique to FEA and was not observed in the parietal measure. In line with previous studies, the present study revealed significant effects of age at adoption on FEA patterns suggesting that earlier adoption yields favorable adoption intervention effects. When considering threshold effects, adoption after 24 months showed a more pronounced effect on FEA; however, these effects were only noted among girls. While it is possible that timing of removal impacted PI boys differentially, the study

design did not allow assessment of such effects prior to 16 months, the earliest age of PI adoption in this sample.

These early institutional deprivation associations with greater left FEA differed markedly from the results of studies examining the impact of maternal depression and domestic maltreatment where FEA findings converge on greater right rather than left FEA (e.g., Peltola et al., 2014). It is not clear why early deprivation of care as found in institutional settings might differ from the correlates of other forms of early adversity. Of course, as noted by Peltola and colleagues (2014) the majority of the other studies have examined maternal depression. Studies of depression were the first to identify greater right FEA as a signature of the disorder (Davidson, 1991). Thus it is possible that the child's FEA mirrors the mother's due to both frequent interaction and matching of mood states between the two and/or genetic similarity. However, even within the research on maternal depression discrepancies are noted. Forbes and colleagues (2006) have found that greater left FEA was associated with greater psychopathology in offspring of parents with childhood-onset depression. Despite this support for greater left FEA, the results of a meta-analysis on FEA and child adversity (e.g., Peltola et al., 2014), which included the Forbes et al. (2006) study, yielded more consistent support for greater right FEA.

Further consideration of age at assessment may be important for understanding the role early adversity on FEA. As noted, the other study of institutionalized children did not report greater right FEA in either the institutionalized or post-institutionalized children (McLaughlin et al., 2011). Instead they noted that all children showed a shift from greater left to greater right asymmetry from infancy into the toddler years and then a shift towards less right and more left asymmetry as they were followed to age 8. The PI children placed in families after 24 months lagged in this pattern. Thus whether they would be noted to be more left or right in their FEA than the never institutionalized children depended on the age of assessment. This is an important caution to interpretation of the present findings. Specifically, although we found the PI children to exhibit a greater left FEA than the other children this should be qualified by noting that this was at an average of roughly four years of age. If followed to later ages, EEG asymmetry may shift as might the pattern of differences between groups.

Consistent with previous findings using parent-report measures of psychopathology, we did not note any significant group differences in age 5 internalizing or externalizing symptoms; however, we did find that PI children exhibited greater ADHD and DSED symptoms (Gunnar & van Dulmen, 2007; Rutter et al., 2001). There was no evidence across children that FEA was correlated with internalizing, externalizing, or DSED symptoms. Greater left FEA did, however, mediate the link between early institutional care and ADHD symptoms and, as predicted, this association was moderated by child sex such that it was noted among girls but not boys.

Indeed, several sex differences emerged. Relative to girls, boys displayed elevated ADHD and internalizing symptoms. Collapsing across all groups, boys appeared to be at risk for elevated ADHD regardless of FEA (see Figure 2) whereas girls appeared to be at risk only in the context of greater left FEA. Within the PI group both boys and girls displayed

equivalently heightened left FEA, yet support for FEA as a neurobehavioral mechanism in contributing to ADHD was only found in girls. It is unclear why the pattern of frontal EEG asymmetry might be associated with psychological processes more in females than males. Future research may shed light on the mechanisms underlying ADHD in males, and whether institutional care alters these mechanisms. Previous literature indicates that autonomic reactivity moderates the association between resting asymmetry and psychopathology suggesting that leftward asymmetry is neither inherently risky nor protective, but interacts with specific individual and contextual risk factors to shape outcomes (Gatzke-Kopp et al., 2012). Additionally, recent studies have related EEG patterns to the serotonin genotypes in females but not males (Volf, Belousova, Knyazev, & Kulikov, 2015), thus it is possible that EEG activity recorded over the frontal regions marks different neurobiological and neurogenetic processes in females and males. Additional research has demonstrated that the impact of institutionalization is sometimes moderated by sex. Findings from the Bucharest Early Intervention Project noted that telomere length was associated with percentage of institutional care in infancy for girls but throughout childhood for boys (Drury et al., 2012) while such care had great impact on psychopathology in childhood for boys than for girls (Tibu, Humphreys, Fox, Nelson, & Zeanah, 2014). These findings argue that we need to consider sex-differences in neurobehavioral development long before puberty and not solely in terms of whether behaviors or neural activity exhibits significant differences in levels between girls and boys.

It was surprising to find associations with ADHD symptoms rather than internalizing problems. As noted, the evidence for FEA associations with problem behaviors is typically stronger for internalizing problems (Peltola et al., 2014). Nonetheless, an association with orienting and regulatory capacity was noted for girls in a prior study of 10-month-olds (Gartstein et al., 2014). The ADHD symptoms noted among PI children often seem to reflect a more general problem in executive functioning and self-regulation (Hostinar et al., 2012). To the extent that greater left FEA is associated with poor regulatory capacities in the face of approach motivations, then this would be consistent with impulsivity and regulatory difficulties reflected in ADHD symptoms. Although most prior studies with children have not examined ADHD in relation to greater left FEA, Marshall and colleagues (2004) did, however, find reductions in alpha relative power and increases in theta relative power among PI children. They found that this pattern of brain activity significantly mediated the association between institutionalization and ADHD symptoms at age 54 months. Furthermore, recent studies of adults with ADHD (Keune et al., 2011) and children of parents with ADHD (Hale et al., 2010) have shown an association with greater left FEA (often discussed in this work as greater right frontal power). Thus evidence that greater left FEA was associated with ADHD symptoms for girls is consistent with the limited literature on ADHD-FEA associations.

In line with previous studies, the current study revealed significant correlations between ADHD and DSED symptoms among adopted youth (see Table 2). While researchers have raised the possibility that these two phenotypic presentations share an underlying neurobiological cause (e.g., Kreppner et al., 2001), the present data suggest that FEA represents a unique mechanism specific to ADHD and not DSED. It is unclear why FEA was not found to be related to DSED in the present sample. Previous research notes

associations between FEA and attachment (Gander & Buchheim, 2015), suggesting that the link between DSED and FEA may change as a function of attachment. However, the relation between DSED and attachment remains unclear. Future studies may benefit from considering attachment to further shed light on potential associations.

Despite several interesting findings, there are limitations. First, as noted, we measured EEG asymmetry at only one point in development. As shown in the study by McLaughlin and colleagues (2011), the pattern of development of FEA and thus the association between FEA and group differences may vary as a function of early deprivation. Longitudinal charting of FEA development over time would allow for a better understating of developmental effects which may be coming in to play in the present findings. A meta-analysis that examined effects of psychosocial risk factors unrelated to institutional care on children's FEA included samples varying in ages from newborns to adolescents (Peltola et al., 2014). Findings revealed that age did not moderate the link between general psychosocial risk and EEG asymmetry, but did moderate effects of maternal depression and child EEG, with larger effect sizes emerging in younger samples. Nevertheless, even after accounting for age effects, right EEG asymmetry still appeared to be a consistent marker of the presence of familial stressors in children. This does not appear to be the case in the context of early deprivation in the form of institutional care and requires further research.

Second, for obvious reasons we could not randomly assign the children to adversity conditions. Thus the differences we noted may be due to numerous uncontrolled factors that differed between the PI, FC, and NA groups. Third, the FC group was included as an adoption control who had little or no institutional experience; they were not similar to the PI group in age at adoption as countries using foster care for wards of the state tend to have policies that allow children to get to permanent placements earlier in life (Gunnar, Bruce, & Grotevant, 2000). Fourth, as in much of the literature on children's behavioral problems, we are reliant on parent-report with all the limitations that accompany their use as measures of maladjustment. Finally, our study did not include every PI child adopted during this period into our area. However, because we believe we contacted all of the children adopted from institutions during our timeframe, a 70% acceptance rate provides a reasonably representative sample.

Results of the present study are consistent with the argument that very early experiences during infancy impact the development of brain structure and function. Furthermore, the results indicate that these neural modulations mediate the impact of early adversity on the later emergence of behavioral problems known to have potentially long lasting detrimental effects. Importantly, our results suggest the importance of timing when considering the impact of early caregiving environments on the infant and young child's developing brain. Our results indicate that earlier adoption yields favorable outcomes, thus suggesting an early time window of neural plasticity, during which brain activity may be most susceptible to recovery. During the first two years of life basic brain circuitry is coming on line and being established for the first time, for a variety of socio-emotional, cognitive, and self-regulatory capacities. It is well known that the impact of perturbations, including stress and deprivation, depends on the developmental state of the circuits that are being impacted (Hensch, 2005; Kolb & Gibbs, 2001). Likewise, the capacity of brain circuits and functions to restore

themselves following perturbation should differ as a function of whether the brain had the “right early experience” and the timing of the intervention (Nelson, 2000a, 2000b). The fact that age at adoption bore a linear relationship with the likelihood of atypically strong left FEA supports the idea that earlier adoption into a supportive family resulted in a more typical pattern of brain functioning. In this study there was inconsistent evidence that 24 months defined a critical window for intervention, rather the results suggested that the earlier the intervention of adoption, the better. This has clear clinical and preventive intervention implications for children without permanent parents who need to be placed in care by the state.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

FEA differences among early adversity groups and child sex.

Note. Figure depicts group- and sex-specific means in FEA for post-institutionalized (PI), post foster care (FC), and non-adopted (NA) children. There is a significant group main effect for FEA.

Figure 2.

Sex X FEA interaction predicting ADHD symptom severity

Note. Figure depicts ± 1 SD in FEA asymmetry. Girls and boys are collapsed across all groups.

Figure 3.

Left FEA as a mediator between Early Adversity and ADHD Symptoms at Age 5 Moderated by Sex.

Note. Figure depicts standardized regression coefficients for girls (left) and boys (right). Bolded lines indicate statistically significant pathways. $*p < .05$, $**p < .01$. Covariates not included in figure. A significant indirect effect was only found among girls. PI=post institutionalized, FC=post foster care, NA=non-adopted.

Figure 4.

Age at adoption (dichotomized at 24 months) X sex interaction predicting left FEA among post institutionalized (PI) children only.

Table 1

Participant Demographics by Group.

	PI	FC	NA
Total <i>N</i>	82	45	48
Child Sex (<i>N</i> Female)	46	17	23
EEG Age in months <i>M</i> (<i>SD</i>)	49.08 (5.40)	55.88 (5.07)	50.76 (5.59)
Child Symptom Age in months <i>M</i> (<i>SD</i>)	61.55 (1.69)	63.63 (1.89)	61.91 (1.89)
Child Race (<i>N</i>)			
African/Black	29	0	0
American Indian/Alaska Native	4	9	0
Asian	33	33	1
White	11	0	43
Multiracial	2	0	4
Unknown	3	3	0
Child Ethnicity (<i>N</i>)			
Hispanic/Latino	6	12	2
Region of Origin (<i>N</i>)			
Africa	24	0	0
Latin America/Caribbean	12	12	0
Russia/Eastern Europe	21	0	0
Southeast Asia	25	33	0
United States	0	0	48
Primary Caregiver (<i>N</i> Female)	76	40	47
Marital Status (<i>N</i> Married)	71	43	46
Primary Caregiver Education (Median)	Bachelor's Degree	Bachelor's Degree	Bachelor's Degree
Secondary Caregiver Education (Median)	Bachelor's Degree	Bachelor's Degree	Bachelor's Degree
Median Household Income in thousands	\$100-\$125	\$75-\$100	\$75-\$100
<i>Pre-Adoptive Care</i>			
Age at Adoption in months <i>M</i> (<i>SD</i>)	24.90 (5.29)	9.64 (1.41)	---
Adopted at 24 months or greater (<i>N</i>)	40	0	---
Institutional Social Care Quality <i>M</i> (<i>SD</i>)	3.20 (1.46)	---	---
Institutional Physical Care Quality <i>M</i> (<i>SD</i>)	3.02 (1.24)	---	---

Note. There were no differences in household income by group, $\chi^2(16)=15.90$, $p=.46$. PI=post institutionalized, FC=post foster care, NA=non-adopted.

Table 2

Correlation Table

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
<i>All participants</i>																
1. Left FEA	---															
2. Parietal EEG Asymmetry	.13	---														
3. Age 5 Internalizing Symptoms	.08	-.08	---													
4. Age 5 Externalizing Symptoms	.13	-.07	.49***	---												
5. Age 5 ADHD Symptoms	.13	.07	.32***	.51***	---											
6. Age at T1 (EEG)	-.04	-.03	-.01	.00	-.02	---										
7. Age at T2 (Outcomes)	-.07	.06	.08	-.02	.02	.70***	---									
8. T1-T2 Length of Time	.03	.02	.02	.01	.03	1.00***	-.70***	---								
9. Duration Lights On	-.01	.04	-.17*	-.07	-.10	.13	.09	-.13	---							
10. Duration Lights Off	-.12	.00	-.14	-.09	-.11	.07	-.01	-.07	.76***	---						
11. Child Sex	.09	.07	.17*	.06	.15*	.13	.15	-.13	-.03	-.07	---					
<i>Internationally-Adopted Children Only (PI & FC)</i>																
12. Age at Adoption	.28**	-.10	-.02	.04	.06	-.12	-.26**	.11	-.06	.05	-.14	---				
13. DSED Symptoms	.06	-.15	.12	.41***	.48***	-.14	-.01	.13	.14	.21*	-.06	.16	---			
14. Age at DSED Interview	-.10	.16	.08	.13	.13	.59***	.87***	-.58***	.01	-.01	.13	-.31***	.00	---		
<i>Post-Institutionalized Children Only (PI)</i>																
15. Institution Social Care Quality	.01	.04	-.07	-.10	-.20	.02	-.27*	-.02	-.12	.01	-.16	.02	-.19	-.04	---	
16. Institution Physical Care Quality	-.15	.10	.05	.15	-.01	.05	-.16	-.05	-.04	.09	-.03	.05	-.04	-.04	.52***	---

Note. * $p < .05$,** $p < .01$,*** $p < .001$.

Table 3

Group and Sex Differences among Study Variables

Group Comparisons		PI		FC		NA		Pairwise Comparisons (<i>p</i> < .05)		
		<i>M</i> (<i>SD</i>)		<i>M</i> (<i>SD</i>)		<i>M</i> (<i>SD</i>)		<i>df</i>	<i>F</i>	η^2
All Participants										
Left FEA		0.06 (0.22)		−0.05 (0.25)		−0.02 (0.22)		2, 151	3.38*	.04
Parietal EEG Asymmetry		0.05 (0.31)		0.09 (0.32)		0.00 (0.37)		2, 151	0.77	.01
Age 5 Internalizing Symptoms		0.28 (0.17)		0.30 (0.18)		0.25 (0.20)		2, 168	0.99	.01
Age 5 Externalizing Symptoms		0.31 (0.22)		0.30 (0.19)		0.23 (0.18)		2, 165	2.01	.02
Age 5 ADHD Symptoms		0.82 (0.44)		0.75 (0.33)		0.60 (0.32)		2, 167	4.97**	.06
Age at EEG		49.08 (5.40)		55.88 (5.07)		50.76 (5.59)		2, 170	23.56***	.22
Age at Outcome Assessment		61.55 (1.69)		63.63 (2.50)		61.91 (1.89)		2, 169	16.29***	.16
T1-T2 Length of Time		11.13 (5.28)		4.50 (5.04)		9.27 (5.76)		2, 169	22.38***	.21
Duration Lights On		50.87 (17.83)		53.55 (16.77)		59.50 (17.91)		2, 150	3.11*	.04
Duration Lights Off		48.88 (16.65)		47.47 (16.59)		52.39 (19.17)		2, 150	0.89	.01
Internationally-Adopted Children Only (PI & FC)										
Age at Adoption		24.14 (5.35)		8.93 (1.66)		---		1, 125	359.99***	.74
DSED Symptoms		0.51 (0.58)		0.31 (0.34)		---		1, 114	4.21*	.04
Age at DSED Interview		5.13 (0.17)		5.31 (0.21)		---		1, 116	24.10***	.17
Sex Comparisons										
		Female		Male						
		<i>M</i> (<i>SD</i>)		<i>M</i> (<i>SD</i>)				<i>df</i>	<i>F</i>	η^2
All Participants										
Left FEA		−0.01 (0.26)		0.03 (0.20)				1, 152	1.17	.01
Parietal EEG Asymmetry		0.03 (0.35)		0.07 (0.31)				1, 152	0.60	.00
Age 5 Internalizing Symptoms		0.25 (0.15)		0.31 (0.21)				1, 169	4.76*	.03
Age 5 Externalizing Symptoms		0.27 (0.22)		0.29 (0.19)				1, 166	0.55	.00
Age 5 ADHD Symptoms		0.68 (0.38)		0.79 (0.39)				1, 168	3.92*	.02
Age at EEG Assessment		50.50 (5.77)		52.07 (6.20)				1, 171	2.96	.02

Group Comparisons	PI M (SD)	FC M (SD)	NA M (SD)	df	F	η^2	Pairwise Comparisons ($p < .05$)
Age at Outcome Assessment	61.86 (1.81)	62.49 (2.40)		1, 170	3.70	.02	
T1-T2 Length of Time	9.72 (5.66)	8.14 (6.21)		1, 173	3.10	.02	
Duration Lights On	54.45 (18.30)	53.27 (17.44)		1, 151	0.17	.00	
Duration Lights Off	50.72 (16.83)	48.16 (17.79)		1, 151	0.84	.01	
<i>Internationally-Adopted Children Only (PI & FC)</i>							
Age at Adoption	19.94 (7.75)	17.59 (9.14)		1, 125	2.18	.02	
DSED Symptoms	0.47 (0.56)	0.40 (0.47)		1, 114	0.46	.00	
Age at DSED Interview	5.17 (0.16)	5.22 (0.23)		1, 116	3.47	.03	
<i>Post-Institutionalized Children Only (PI)</i>							
Institution Social Care Quality	3.44 (1.28)	2.97 (1.59)		1, 62	1.65	.03	
Institution Physical Care Quality	3.05 (1.19)	2.98 (1.30)		1, 63	0.04	.00	

Note. * $p < .05$,

** $p < .01$,

*** $p < .001$.

Post hoc pairwise comparisons ($p < .05$) are reported using Fisher's LSD. PI=post institutionalized, FC=post foster care, NA=non-adopted; F=female, M=male.