Early Psychosocial Neglect Adversely Impacts Developmental Trajectories of Brain Oscillations and Their Interactions

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Abstract

■ Rhythmicity is a fundamental property of neural activity at multiple spatiotemporal scales, and associated oscillations represent a critical mechanism for communication and transmission of information across brain regions. During development, these oscillations evolve dynamically as a function of neural maturation and may be modulated by early experiences, positive and/or negative. This study investigated the impact of psychosocial deprivation associated with institutional rearing in early life and the effects of subsequent foster care intervention on developmental trajectories of neural oscillations and their cross-frequency correlations. Longitudinally acquired nontask EEGs from three cohorts of children from the Bucharest Early Intervention Project were analyzed. These included abandoned children initially reared in institutions and subsequently randomized to be placed in foster care or receive care as usual (prolonged institutional rearing) and a group of never-institutionalized children. Oscillation trajectories were estimated from 42 to 96 months, that is, 1–3 years after all children in the intervention arm of the study had been placed in foster care. Significant differences between groups were estimated for the amplitude trajectories of cognitive-related gamma, beta, alpha, and theta oscillations. Similar differences were identified as a function of time spent in institutions, suggesting that increased time spent in psychosocial neglect may have profound and widespread effects on brain activity. Significant group differences in cross-frequency coupling were estimated longitudinally between gamma and lower frequencies as well as alpha and lower frequencies. Lower cross-gamma coupling was estimated at 96 months in the group of children that remained in institutions at that age compared to the other two groups, suggesting potentially impaired communication between local and long-distance brain networks in these children. In contrast, higher cross-alpha coupling was estimated in this group compared to the other two groups at 96 months, suggesting impaired suppression of alpha–theta and alpha–delta activity, which has been associated with neuropsychiatric disorders. Age at foster care placement had a significant positive modulatory effect on alpha and beta trajectories and their mutual coupling, although by 96 months these trajectories remained distinct from those of never-institutionalized children. Overall, these findings suggest that early psychosocial neglect may profoundly impact neural maturation, particularly the evolution of neural oscillations and their interactions across a broad frequency range. These differences may result in widespread deficits across multiple cognitive domains. ■

INTRODUCTION

Postnatal maturation of the human brain, including the topological reorganization and optimization of neural circuitry, is a relatively long and heterogeneous process that occurs over a period of almost two decades. Neural maturation is particularly rapid in the first few years of life, during which experiences—positive and negative—can have profound and long-term effects on fundamental aspects of brain activity and consequently cognitive function. Negative early experiences, such as social and emotional deprivation, have been shown to impact brain structure (Bick et al., 2015; McLaughlin et al., 2014; Bauer et al., 2009; Cohen et al., 2009; Eluvathingal et al., 2006; Chugani et al., 2001) and neural activity (McLaughlin, Fox, Zeanah, Sheridan, & Nelson, 2011; McLaughlin et al., 2010; Vanderwert, Marshall, Nelson, Zeanah, & Fox, 2010; Marshall, Reeb, Fox, Nelson, & Zeanah, 2008; Marshall, Fox, Bucharest Early Intervention Project Core Group, 2004). Specifically, diffusion tensor imaging has revealed significant differences in multiple white matter tracts between previously institutionalized children that have been placed in foster homes and children who have remained in institutions, including large tracts such as the corpus callosum and tracts that are part of limbic and frontostriatal circuits associated with emotion and executive function among several other processes (Bick et al., 2015). MRI has shown significantly less cortical thickness in prefrontal, temporal, and parietal brain regions of children placed in institutions at early ages (McLaughlin et al., 2014), smaller cerebellar volumes (Bauer, Hanson, Pierson, Davidson, & Pollak, 2009), and reduced gray and

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white matter volume (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). PET has revealed decreased metabolic activity in distributed brain regions of institutionalized children, including prefrontal and temporal structures and the brain stem (Chugani et al., 2001). Electrophysiological studies (scalp EEG) have shown that institutionalized children placed in foster homes before the age of 24 months have statistically higher power in the alpha band (8–12 Hz) as well as higher local network coherence in the first 4 years of life in comparison to children who remained in institutions (Marshall et al., 2008), and by 8 years statistically similar alpha power to children who have never been institutionalized (Vanderwert et al., 2010). Furthermore, distinct trajectories of frontal EEG asymmetry in the alpha band have been estimated in children placed in foster homes compared to those who remained in institutions (McLaughlin et al., 2011). Earlier studies have shown that psychosocial deprivation also impacts brain activity in other frequency bands, resulting in higher delta and theta power as well (Otero, Pliego-Rivero, & Ricardo, 2003; Roelfsema, Engel, Konig, & Singer, 1997; Otero, 1994).

Brain oscillations represent a fundamental characteristic of neural activity across spatial and temporal scales and are paramount to cognitive function. Depending on their characteristic frequencies, which fall in distinct bands in the range less than 1 Hz to greater than 100 Hz, they facilitate transient interactions between local and distant brain regions in response to cognitive demands (Buzsaki & Draguhn, 2004). Consequently, they play a critical role in cognitive processing (Ward, 2003). For example, theta oscillations have been associated with memory processes, particularly encoding and retrieval as well as decision-making (Lisman & Jensen, 2013; Canolty et al., 2006; Jacobs, Hwang, Curran, & Kahana, 2006; Buzsaki & Draguhn, 2004; Caplan, Madsen, Raghavachari, & Kahana, 2001; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999). Alpha oscillations have been associated with multiple cognitive domains including attention and perception (Buzsaki & Draguhn, 2004; Adrian & Matthews, 1934). Beta oscillations are correlated with motor behaviors and have also been shown to be generated after periods of sustained gamma activity (gamma–beta transition; Haenschel, Baldeweg, Croft, Whittington, & Gruzelier, 2000; Traub, Whittington, Buhl, Jefferys, & Faulkner, 1999; Salmelin & Hari, 1994). Gamma oscillations have been associated with perceptual binding, working memory loads, and attention among other processes (Canolty et al., 2006; Buzsaki & Draguhn, 2004; Ward, 2003; Csibra, David, Spratling, & Johnson, 2000). High-frequency oscillations (>80 Hz) in the human brain are less well understood but have been implicated in pathological processes such as epilepsy (Stamoulis, Schomer, & Chang, 2013; Stamoulis, Gruber, Schomer, & Chang, 2012).

Although brain oscillation amplitude (or power) and to a less extent frequency have been extensively investigated, transient interactions between distinct oscillations, referred to as cross-frequency coupling, have not been systematically characterized. Nevertheless, previous studies have shown that cross-frequency coupling is critical for efficient transmission of information between brain regions and neural computation (Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009; Jensen & Colgin, 2007; Canolty et al., 2006; Ward, 2003; Roelfsema et al., 1997). For example, gamma amplitude appears to be modulated by the theta phase in both animal and human recordings (Canolty et al., 2006), and the two oscillations are thought to form a neural code for an organized representation of the outside world, for example, the representation of spatial information in the hippocampus and hierarchical information transfer across brain regions (Lisman & Jensen, 2013). Lower-frequency coupling, such as between alpha and theta and alpha and delta oscillations have been associated with orientation and the evaluation of novel environments (Isler, Grieve, Czernochowski, Stark, & Friedman, 2008) and may also be correlated with emotion, motivation, and reward (Schutter & Knyazev, 2012).

The maturation of brain oscillations and their interactions during infancy is only partially understood. Some may be robust at birth, for example, the delta oscillation associated with sleep; others may develop later and at distinct rates, as a function of the acquisition of increasingly complex cognitive skills (Grossman, Johnson, Farroni, & Csibra, 2007; Kaufmann, Csibra, & Johnson, 2005; Csibra et al., 2000; Gasser, Verleger, Bacher, & Sroka, 1988). Despite limited data on their developmental trajectories, it is thought that brain oscillations in early life evolve dynamically as a result of profound changes in the neuroarchitecture of the brain due to neural maturation, including selective elimination of redundant connections and reorganization and strengthening of remaining connections (Tierney, Strait, O'Connell, & Kraus, 2013; Uhlhaas & Singer, 2011; Takano & Ogawa, 1998). Early experiences are believed to play a critical role in most aspects of neural maturation. Given the importance of the first few years of life for the formation of basic neural circuits in the brain, it is critical to understand how these oscillations and their interactions change with age and are impacted by experiences. To date, adverse effects of psychosocial deprivation on these oscillations have been quantified in primarily cross-sectional investigations (McLaughlin et al., 2010, 2011; Marshall et al., 2004, 2008). These studies have provided important information on the impact of early institutionalization on neural activity but have not quantified potentially aberrant changes in the developmental trajectories of brain oscillations or the development of cross-frequency correlations that may be associated with aberrant neural maturation. For example, these studies have not investigated potential modulations of cross-frequency coupling, an important mechanism of neural information processing that may help explain cognitive deficits previously identified in these children (Mazaheri et al., 2014; McLaughlin et al., 2014).

The current study aimed to quantify the effects of psychosocial neglect associated with institutionalization in early life on the developmental trajectories of neural oscillations and their cross-frequency coupling in three cohorts

of children from the Bucharest Early Intervention Project (BEIP): a group of institutionalized children who were randomized to a high-quality foster care placement (the intervention), a group who received care as usual, and a group of never-institutionalized children from the Bucharest community. Using longitudinal EEG data, the goal of the study was to investigate age-related differences in fundamental aspects of brain activity in these children and thus potentially differential neural maturation that may be a consequence of their history of adverse experiences and may also be affected by early intervention. The study focused on the trajectories of oscillation parameters (frequency, amplitude, and coupling) predominantly in the interval of 42–96 months. It compared the trajectories of children removed from institutions and placed in foster care to those who remained in institutions and to those children who were born and raised in typical Romanian families. It was hypothesized that in this time interval cortical oscillations and their interactions changed differentially in the three groups, with lowest amplitudes and cross-frequency coupling in the group that remained in institutions and highest corresponding parameters in the never-institutionalized group.

METHODS

Bucharest Early Intervention Project

Designed as a randomized controlled trial, the BEIP is an ongoing longitudinal study that aims to investigate short- and long-term effects of early psychosocial deprivation associated with institutionalization on the structure and function of the developing brain, as well as potentially positive effects of removal from an institution and placement in foster care (Zeanah et al., 2003, www.bucharestearlyinterventionproject.org/). Children placed in Romanian institutions in early life were randomized to either foster care placement (Foster Care Group [FCG]) or continued institutionalization (Care As Usual Group—CAUG). One hundred thirty-six children ages 6–30 months at study entry were randomized to each trial arm (n = 68 per arm). A third group of 72 never-institutionalized children (Never Institutionalized Group [NIG]) were also included as a comparison group of typically developing Romanian children. All participants underwent a pediatric exam at study entry; exclusion criteria included any neurological or genetic sign or syndrome and facial dysmorphology consistent with fetal alcohol syndrome. In addition, cognitive functioning, social communication and interaction, problem behaviors, and temperament were all assessed at all assessment time points using relevant scales. Institutional conditions, the experimental design, and the many ethical issues involved in the study are described in detail in Nelson, Fox, and Zeanah (2014) and Zeanah et al. (2003). The foster care intervention is described in Nelson et al. (2014) and Smyke, Zeanah, Fox, and Nelson (2009).

Study Participants

This study investigated the dynamics of brain oscillations and their interactions estimated from longitudinally acquired EEG. Therefore, only subgroups of the BEIP cohorts with measurements at a minimum of 2 time points were included. Specifically, 62 children in the CAUG (median age at study entry = 23.0 months, (25th, 75th) quartiles = (17.0, 26.0) months), 61 children in the FCG (median age at study entry = 23.0 months, (25th, 75th) quartiles = (17.0, 28.0) months), and 44 children in the NIG (median age at study entry = 16.5 months, (25th, 75th) quartiles = (12.0, 24.0) months) were studied. Participants were measured at study entry (baseline) as well as at 30–33, 42, and 96 months. Twelve children did not have EEG data at 30–32 months, 31 did not have EEG at 42 months, and 44 did not have EEG at 96 months. These data were assumed to be missing at random.

EEG Data

EEG signals were recorded from 12 scalp electrodes and bilateral mastoids (M1, M2, F3, F4, Fz, C3, C4, P3, P4, Pz, T7, T8, O1, O2) using an Electro-Cap (Electro-Cap International, Inc., Eaton, OH). The data were sampled at 512 samples/sec. The amplifier bandpass filter cutoff frequencies were 0.1 and 100 Hz, respectively. At baseline, 30–33 and 42 months assessments, nontask EEG were collected under two conditions: (1) a bingo wheel with brightly colored balls was spun for 3 min (nine trials, each 10 sec long with a 10-sec intertrial interval) to keep children engaged; (2) lights were turned off during EEG collection (~1–3 min long; Marshall et al., 2008). Although both sets of EEGs were analyzed, results presented in this study are primarily from the lights-off condition. At 96 months, nontask EEG were collected during a 6-min interval during which children sat quietly alternating eyes open and closed in 1-min intervals (Vanderwert et al., 2010). Only signals recorded under the eyes-closed condition were included in the analysis.

Additional Demographic Data

Additional variables pertinent to the study included gestational age; age at study entry and at the second time point (30–33 months); age at foster care placement (for children in the FCG); and percent of time spent at institutions at baseline, 42 months, and 96 months. A total of 84 female and 83 male participants were included in the study. Birth weight was in the range 0.9–4.5 kg (median = 3.0 kg, (25th, 75th) quartiles = (2.5, 3.3) kg). These data were not available for 15 children and were assumed to be missing at random. Head circumference was also measured at each assessment, with the second measurement taken at 30 months. Median circumference at baseline was 46.8 cm, ((25th, 75th) quartiles = (45.4, 47.9) cm), 48.0 cm at 30 months ((25th, 75th) quartiles = (47.0, 49.0) cm),

48.6 cm at 42 months ((25th, 75th) quartiles = (47.9, 49.5) cm), and 51.0 cm at 96 months ((25th, 75th) quartiles = (50.0, 52.0) cm). These data were missing in 17 children at baseline, 16 children at 30 months, 25 children at 42 months and 32 children at 96 months. Age at foster care placement for children in the FCG was in the range 6.8–33 months, median = 24.8 months, (25th, 75th) quartiles = (18.6, 28.7) months. At baseline, median percent of time spent at institutions was 98.6% in the CAUG and 95.9% in the FCG (corresponding (25th, 75th) quartiles = (81.6%, 100.0%) and (69.4%, 100.0%), respectively). At 42 months, median percent of time spent at institutions was 85.0% in the CAUG and 48.9% in the FCG ((25th, 75th) quartiles = (64.4%, 97.1%) and (35.0%, 61.8%), respectively). Finally, at 96 months, the corresponding percent of time was 53% in the CAUG and 23.4% in the FCG ((25th, 75th) quartiles = (36.2%, 79.8%) and (18.3%, 28.6%), respectively).

EEG Data Preprocessing

Power line noise at 50 Hz and its 100-Hz harmonic were eliminated using a stopband filterbank of third-order elliptical filters with a 1-Hz bandwidth, 0.5 dB ripple in the passband, and 20 dB in the stopband.

Artifacts associated with eye blinking were eliminated using a matched-filtering approach, where signal templates for eye blinks were used to detect intervals containing these artifacts and locally filter them (Stamoulis & Chang, 2009). Further denoising was achieved via signal decomposition and elimination of noise-related (random) components (Stamoulis & Betensky, 2011). Finally, extreme amplitude outliers, that is, above a threshold equal to the median plus three times the interquartile difference (Tukey, 1977), were also eliminated.

Signal Analysis

Estimation of Dominant EEG Oscillations

Narrowband EEG components with distinct characteristic frequencies were estimated in the time domain using a modification of the unsupervised empirical mode decomposition (EMD) method (Huang et al., 1998). This method is appropriate for nonstationary signals such as EEG and makes no a priori assumptions on the number, waveform, and spectral content of dominant signal components. The EMD approach was applied to each EEG signal. Noise- and/or artifact-related components were eliminated using the risk function proposed in Stamoulis and Betensky (2011). In addition, to ensure that estimated components corresponded to individual oscillations and were nonrandom, the autocorrelation of each component was also estimated (the autocorrelation of a random (temporally uncorrelated) signal is expected to have a narrow peak at zero time lag and very low correlation values at all other lags). Both the autocorrelation function and a zero-crossing method were used to estimate the characteristic frequency of identified nonrandom EEG components (Stamoulis et al., 2014). A sliding 1-sec window was used in this estimation process.

Estimation of Cross-frequency Coupling

Given that individual oscillations were estimated from each EEG signal and in each 1-sec sliding window in the time domain, the cross-correlation function was used to estimate coupling between EEG components with distinct characteristic frequencies within each analysis window. Peak cross-correlation was used to quantify coupling between oscillations separately for each electrode. Median (across analysis windows) frequencies, amplitudes, and coupling are reported in this study.

Statistical Analysis

Differences in oscillation parameters at each age assessment were estimated using ordinary linear regression models, with frequency, amplitude, or cross-frequency coupling as the dependent variable and group (categorized as CAUG = 0, FCG = 1, NIG = 2), birth weight, and sex (categorized as female = 0, male = 1) as independent variables. Note that at baseline, that is, before randomization, there are only two groups, institutionalized versus never institutionalized.

Linear mixed effects models were developed to investigate the temporal trajectories of oscillation parameters. For all children randomized to the intervention arm, foster care placement occurred before 42 months of age. Therefore, to assess intervention-related effects, we focused on trajectories of oscillation parameters between 42 and 96 months. Data from two time points were included in the mixed effects models, with oscillation frequency, amplitude, or coupling at 42 and 96 months as the dependent variables. The models included a subject-specific intercept and a subject-specific time slope to assess potential subject contributions of individual trajectories on the mean trajectory. Note that age (time) was treated as a continuous variable in the range 42–96 months. Other independent variables included the corresponding baseline oscillation parameter (frequency, amplitude, or cross-coupling depending on which parameter trajectory was modeled as the dependent variable), sex, birth weight, head circumference, group, age at foster care placement, and percent of time spent at institutions. Given the sample size, only relatively small models were developed, with combinations of one to three independent variables. A second set of multinomial mixed effects logistic regression models were also tested where group was treated as the dependent variable (instead of oscillation parameters) and oscillation measures as well as the above independent parameters/confounders were treated as the independent variables. The same results were obtained for both sets of models. All signal processing and statistical analysis

were done using the software Matlab (MathWorks, Inc., Natick MA).

RESULTS

Oscillation Frequency and Amplitude Trajectories

Frequency–amplitude plots for all estimated oscillations at each time point are shown in Figure 1. Oscillation parameters were averaged over time, and then the median over scalp electrodes was chosen as the relevant statistic for each subject. Raw data are shown in each panel, that is, not model-based estimates with adjustments for age at measurement, which is a relevant parameter for the first and second time points where age was variable, birth weight or head circumference. Therefore, group-specific differences in these plots could be confounded by any of these factors. Median values across participants and interquartile ranges (vertical bars for amplitude and horizontal bars for frequency) are shown. As previously noted, at 96 months, nontask EEGs under the eyes-closed condition were analyzed. For a relevant comparison, EEGs at ages less than 96 months are reported for the lights off condition instead of the bingo wheel. However, the corresponding frequency–amplitude plots for the bingo wheel condition are shown in Appendix A, Figure A1. Although oscillation amplitudes across the EEG spectrum decrease during neural maturation, lower amplitudes at 96 months compared to earlier ages in Figures 1 and A1 could also be associated with differences in the nontask recording condition. Summary statistics for estimated oscillation frequency and amplitude for each group are provided in Table 1.

Baseline

First, ordinary linear regression models were developed to assess the significance of group-specific differences in oscillation parameters at baseline and adjust for confounders. These models are summarized in the Appendix Table A1 (only oscillations where significant correlations were estimated are included). Statistically significant differences in baseline gamma and beta oscillation frequency were estimated between institutionalized and never-institutionalized groups ($p = .0003$ for gamma, Wald statistic = 13.47, $p = .02$, Wald statistic = 4.33 for beta). An adjustment for age at measurement was included, which was significant for all oscillations ($p < .015$), that is, independent of the significance of group differences. Similarly, an adjustment for head circumference was also significant for all oscillations ($p < .008$). Statistically significant differences between groups were also estimated for baseline gamma amplitude ($p = .038$, Wald statistic = 4.31).

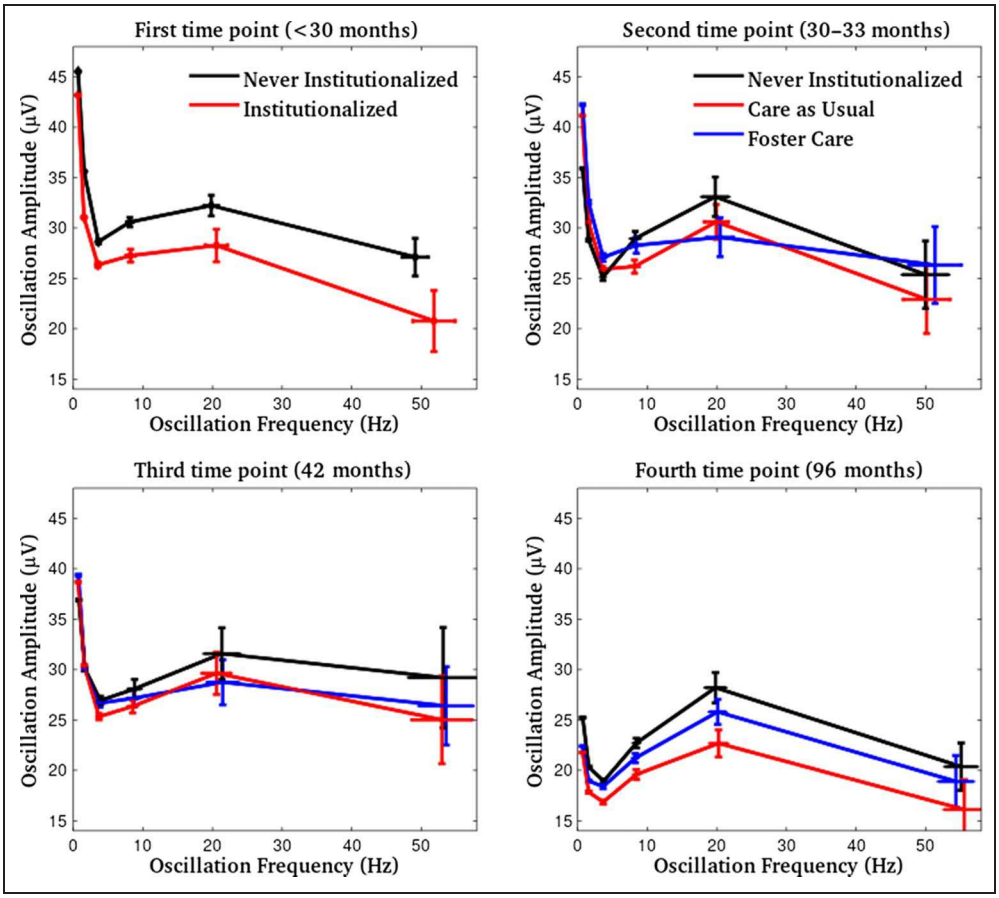

Figure 1. Frequency–amplitude plots of estimated oscillations at baseline (top left) and clockwise at ~30–33, 42, and 96 months, respectively. At the first three time points, resting EEGs under the lights-off recording condition are shown. Never-institutionalized children are shown in black, CAUG in red, and FCG in blue. Both frequency and amplitude interquartile ranges are superimposed (horizontal and vertical bars, respectively).

Table 1. Frequency and Amplitude Summary Statistics for the Six Estimated Oscillations, Separately for Each Group (NIG, FIG, and CAUG) at 96 Months

		NIG		*FCG*		*CAUG*	
Parameter	*Band Range*	*Median*	*(25th, 75th) Quartiles*	*Median*	*(25th, 75th) Quartiles*	*Median*	*(25th, 75th) Quartiles*
Frequency (Hz)	Gamma	55.12	(53.26, 56.37)	54.34	(52.25, 55.83)	55.54	(53.19, 57.20)
	Beta	19.81	(18.93, 21.08)	20.13	(19.31, 20.86)	20.25	(19.43, 21.16)
	Alpha	8.45	(8.05, 8.82)	8.28	(8.06, 8.63)	8.43	(8.15, 8.76)
	Theta	3.74	(3.60, 3.90)	3.66	(3.53, 3.83)	3.67	(3.56, 3.81)
	Delta	1.61	(1.55, 1.69)	1.58	(1.53, 1.65)	1.61	(1.53, 1.66)
Amplitude (μV)	Gamma	20.88	(18.75, 25.04)	19.37	(15.93, 24.00)	17.11	(15.12, 21.90)
	Beta	28.91	(25.94, 34.00)	26.45	(22.11, 29.28)	23.68	(21.49, 26.64)
	Alpha	23.28	(21.11, 26.13)	21.75	(19.81, 23.97)	20.59	(19.09, 22.5)
	Theta	19.41	(17.54, 21.05)	18.85	(17.16, 20.14)	17.86	(16.58, 19.44)
	Delta	20.83	(19.05, 23.45)	19.44	(17.56, 21.50)	18.84	(16.89, 21.00)

These results are also summarized in Table 2. Age at measurement had at nonsignificant effect for gamma ($p = .93$) but was significant for lower-frequency oscillations ($p < .01$). Similarly, head circumference had a nonsignificant effect on oscillation amplitude except for theta ($p = .04$) and delta ($p = .007$). No significant birth weight or sex effects between groups were estimated for any oscillation at baseline.

42–96 Months

We investigated differences in oscillation frequency trajectories and oscillation amplitude trajectories (from 42 to 96 months) between groups with adjustments for covariates that included foster care placement, sex, birth weight, head circumference (at 42 and 96 months), and corresponding oscillation parameters at baseline. Separate linear mixed effects models including time and group only or time, group, and age at foster care placement (or sex or birth weight), and a subject-specific intercept (effects of subject-specific slopes for time were nonsignificant) were developed. No statistically significant differences in frequency trajectories were estimated between groups or as a function of any other variables. In contrast, significant group differences in amplitude trajectories were found for the gamma ($p = .05$, Wald statistic = 3.96), beta ($p = .001$, Wald statistic = 11.02), and alpha ($p = .03$, Wald statistic = 4.84) trajectories, in addition to the time effect, which was significant across oscillations ($p < .0001$). These results are summarized in Table 2. When adjusted for birth weight, group differences in these oscillation trajectories remained significant, and in addition, the theta oscillation trajectory was also found to be statistically distinct in the three groups ($p = .03$, Wald statistic = 4.75; see Table 3). Head circumference had a nonsignificant effect on oscillation trajectory group differences ($p \geq .06$). Finally, when group was replaced with time spent in institutions (in months) at 42 and 96 months, respectively (for NIG this parameter was 0), similar results were obtained, that is, time spent in institutions was significantly correlated with the gamma ($p = .01$, Wald statistic = 6.35), beta ($p = .0001$, Wald statistic = 15.13), alpha ($p < .0001$, Wald statistic = 17.89), and theta ($p = .03$, Wald statistic = 4.73) amplitude trajectories (see Table 4). Age at foster care placement had a significant effect on the trajectory of the beta and alpha oscillations ($p < .001$ for both, Wald statistic = 14.98 for beta and 11.69 for alpha) but a nonsignificant effect on all other trajectories ($p \geq .07$) and did not alter the statistical differences of the three groups for any trajectory. Similar results were obtained under the second nontask condition (the presentation of the bingo wheel), but only the models for data for lights-off and eyes-closed conditions are summarized in Tables 2–4.

Cross-frequency Coupling Trajectories

Median cross-frequency coupling at each time point, estimated from the cross-correlations between oscillations for gamma, beta, alpha, and theta are shown in Figure 2 as a function of oscillation frequency. Corresponding plots for the bingo wheel condition are shown in Appendix A, Figure A2. Note that independently of group and time, each cross-coupling trajectory had a distinct slope, that is, the gamma cross-coupling varied substantially less with frequency compared to beta, which in turn varied less than alpha and theta cross-coupling. This is expected given that oscillations closer in frequency range will be more highly

correlated than oscillations further apart in the spectrum. Summary statistics at 96 months are provided in Table 5. Cross-correlations between gamma or beta oscillations and lower frequencies were higher in the NIG compared to FCG and CAUG, whereas cross-correlations between alpha and lower frequencies were lower in the NIG compared to the other two groups. Cross-correlation measures the similarity of two signals as a function of a time delay (lag) between them. Here it was estimated for each pair of EMD components, in each electrode and each analysis window, then averaged over these windows, and the median over electrodes was selected as the relevant statistic. As an additional assessment of group-level coupling between oscillations, amplitude correlations for all pairs of oscillations were also estimated, that is, time-average amplitude was estimated for each identified EMD component in each electrode, resulting in five vectors of amplitudes for each participant (gamma to delta). The correlation between these vectors was quantified by Spearman's rho for all participants in each group. Corresponding scatter plots are shown in Figure 3. Substantial group differences in these correlations were detected across frequencies, and Spearman's rho was in the range 0.53–0.96 for NIG, 0.11–0.91 for CAUG, and 0.36–0.96 for FCG.

96 Months

To assess the significance of the interactions between oscillations, quantified by peak cross-correlation, we investigated cross-frequency couplings both at the 96-month assessment as well as their longitudinal trajectories from 42 to 96 months, using linear ordinary and mixed effects regression models, respectively. At 96 months, statistically significant group differences in cross-coupling were found for all gamma interactions ($p = .018$ for gamma–beta, Wald statistic = 5.71, $p = .003$ for gamma–alpha, Wald statistic = 9.17, $p = .016$ for gamma–theta, Wald statistic = 5.95, $p = .044$ for gamma–delta), beta–alpha ($p = .03$,

Table 2. Summary of Linear Mixed Effects Regression Model Statistics for Oscillation Amplitude as a Function of Time and Group

Parameter	*Regression Coefficient*	*Confidence Interval*	*SE*	*p*	*Wald Statistic*
Gamma Oscillation Amplitude Trajectory					
Intercept	34.80	[30.80, 38.21]	1.88	<.0001	337.82
Time (age)	−0.17	[−0.22, −0.12]	0.02	<.0001	49.84
Group	1.69	[0.01, 3.39]	0.86	.05	3.96
Beta Oscillation Amplitude Trajectory					
Intercept	34.01	[31.41, 36.60]	1.32	<.0001	666.65
Time (age)	−0.10	[−0.13, −0.07]	0.02	<.0001	34.76
Group	2.01	[0.82, 3.21]	0.61	.001	11.02
Alpha Oscillation Amplitude Trajectory					
Intercept	34.66	[32.07, 37.26]	1.32	<.0001	691.69
Time (age)	−0.14	[−0.18, −0.11]	0.02	<.0001	73.89
Group	1.34	[0.14, 2.53]	0.6	.03	4.84
Theta Oscillation Amplitude Trajectory					
Intercept	37.22	[33.12, 41.32]	2.08	<.0001	318.62
Time (age)	−0.19	[−0.24, −0.14]	0.03	<.0001	54.02
Group	0.68	[−1.21, 2.57]	0.96	.48	0.50
Delta Oscillation Amplitude Trajectory					
Intercept	49.17	[42.32, 56.02]	3.48	<.0001	199.66
Time (age)	−0.29	[−0.38, −0.21]	0.04	<.0001	45.16
Group	−0.23	[−3.38, 2.93]	1.60	.89	0.02

Table 3. Summary of Linear Mixed Effects Regression Model Statistics for Oscillation Amplitude as a Function of Time and Group and Adjusted for Birth Weight

Parameter	*Regression Coefficient*	*Confidence Interval*	*SE*	*p*	*Wald Statistic*
Gamma Oscillation Amplitude Trajectory					
Intercept	32.52	[27.37, 37.67]	2.61	<.0001	154.51
Time (age)	−0.15	[−0.18, −0.11]	0.02	<.0001	72.59
Group	2.18	[0.94, 3.42]	0.63	.0006	11.97
Birth weight	−0.0002	[−0.002, 0.001]	0.0007	.73	0.11
Beta Oscillation Amplitude Trajectory					
Intercept	38.52	[33.92, 43.1]	2.33	<.0001	272.25
Time (age)	−0.09	[−0.12, −0.06]	0.01	<.0001	36.6
Group	2.39	[1.29, 3.50]	0.56	<.0001	18.06
Birth weight	−0.002	[−0.003, −0.0007]	0.0007	.003	8.76
Alpha Oscillation Amplitude Trajectory					
Intercept	39.22	[35.20, 43.24]	2.04	<.0001	369.79
Time (age)	−0.13	[−0.16, −0.11]	0.01	<.0001	97.22
Group	1.83	[0.86, 2.80]	0.49	.0002	13.84
Birth weight	−0.002	[−0.003, −0.001]	0.0006	.0003	13.47
Theta Oscillation Amplitude Trajectory					
Intercept	40.37	[36.09, 44.65]	2.17	<.0001	345.59
Time (age)	−0.17	[−0.20, −0.14]	0.01	<.0001	136.26
Group	1.14	[0.11, 2.18]	0.52	.03	4.75
Birth weight	−0.002	[−0.004, −0.001]	0.0006	.0004	13.1
Delta Oscillation Amplitude Trajectory					
Intercept	50.98	[44.82, 57.14]	3.13	<.0001	265.69
Time (age)	−0.25	[−0.29, −0.21]	0.02	<.0001	143.66
Group	0.73	[−0.75, 2.22]	0.75	.33	0.94
Birth weight	−0.003	[−0.005, −0.0009]	0.0009	.004	8.63

Wald statistic = 4.93), and all other alpha interactions (p = .035 for alpha–theta, Wald statistic = 4.54, p = .006 for alpha–delta, Wald statistic = 7.90). Birth weight had a nonsignificant effect on these differences for all oscillations ($p \geq .4$), and head circumference at this age also had a nonsignificant effect ($p \geq .2$).

42–96 Months

Statistically significant group differences were also found for several coupling trajectories, including those for the interactions between gamma and all other oscillations (see Table 6). Similarly, significant group differences were also estimated for alpha–theta and alpha–delta coupling (p = .05, Wald statistic = 3.72 and p = .01, Wald statistic = 6.60, respectively). The time effect on all trajectories was also significant ($p < .0001$). The significance/nonsignificance of these group differences remained unchanged when models were adjusted for birth weight (its effect was nonsignificant), head circumference, or when age at foster care placement was included (its effect was also nonsignificant across oscillations except for the

alpha–beta coupling; $p = .04$, Wald statistic = 4.41). Percent of time spent at institutions at 42 and 96 months was correlated with the cross-coupling trajectories of gamma–alpha ($p = .002$, Wald statistic = 9.12), gamma–theta ($p = .018$, Wald statistic = 5.57), and gamma–delta ($p = .02$, Wald statistic = 5.23).

DISCUSSION

In this study, we investigated the effects of psychosocial deprivation associated with institutional rearing in early life as well as the effects of foster care intervention on dynamic trajectories of neural oscillations and their interactions. The brain's electrical activity is characterized by oscillations that play a critical role in neural computation, transmission of information, and communication between brain regions and are thus paramount to cognitive function. Coupling between neural oscillations is critical for cognitive processing as it facilitates hierarchical processing of information between local and long-distance networks. Deficits in neural oscillations and their interactions have been associated with a wide range of neuropsychiatric

Table 4. Summary of Linear Mixed Effects Regression Model Statistics for Oscillation Amplitude as a Function of Time and Percent of Time Spent in Institutions (Instead of Group) and Adjusted for Birth Weight

Parameter	*Regression Coefficient*	*Confidence Interval*	*SE*	*p*	*Wald Statistic*
Gamma Oscillation Amplitude Trajectory					
Intercept	35.14	[29.31, 40.97]	2.96	<.0001	141.13
Time (age)	−0.16	[−0.20, −0.13]	0.02	<.0001	79.03
% Time in institution	−0.04	[−0.07, −0.008]	0.02	.0120	6.35
Birth weight	0.0003	[−0.001, 0.002]	0.0008	.67	0.18
Beta Oscillation Amplitude Trajectory					
Intercept	41.51	[36.33, 46.69]	2.63	<.0001	249.64
Time (age)	−0.11	[−0.14, −0.08]	0.02	<.0001	44.42
% Time in institution	−0.05	[−0.08, −0.03]	0.01	.0001	15.13
Birth weight	−0.001	[−0.003, −1.4E-05]	0.0007	.047	3.97
Alpha Oscillation Amplitude Trajectory					
Intercept	41.37	[37.07, 45.66]	2.18	<.0001	359.67
Time (age)	−0.15	[−0.17, −0.12]	0.01	<.0001	117.68
% Time in institution	−0.05	[−0.07, −0.025]	0.01	<.0001	17.89
Birth weight	−0.002	[−0.003, −4.0E-04]	0.0006	.008	7.07
Theta Oscillation Amplitude Trajectory					
Intercept	40.07	[35.72, 44.41]	2.2	<.0001	330.51
Time (age)	−0.17	[−0.20, −0.14]	0.01	<.0001	158.86
% Time in institution	−0.02	[−0.05, −0.002]	0.01	.03	4.73
Birth weight	−0.002	[−0.003, −3.7E-04]	0.0006	.01	6.75
Delta Oscillation Amplitude Trajectory					
Intercept	49.51	[43.00, 56.02]	3.3	<.0001	224.94
Time (age)	−0.25	[−0.29, −0.21]	0.02	<.0001	149.33
% Time in institution	−0.01	[−0.05, 0.02]	0.02	.47	0.52
Birth weight	−0.002	[−0.004, −0.001]	0.0009	.030	4.54

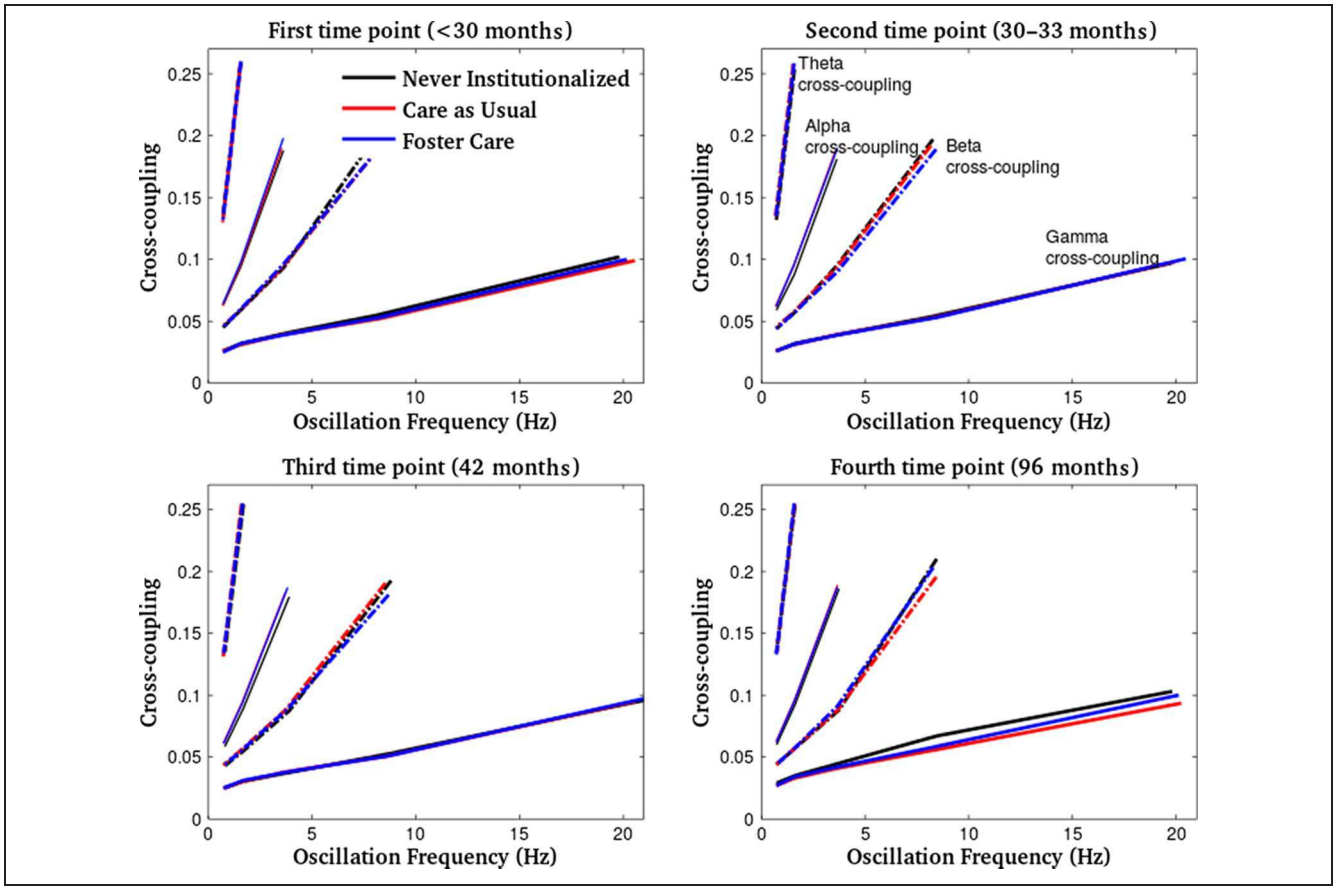

Figure 2. Median cross-frequency coupling as a function of frequency for the gamma, beta, alpha, and theta oscillations. Solid lines represent the gamma–beta, gamma–alpha, gamma–theta, and gamma–delta coupling and thus are the longest; dash-dotted lines represent the beta–alpha, beta–theta, and beta–delta coupling; light lines represent the alpha–theta and alpha–delta coupling; and dashed lines represent the theta–delta coupling. NIG is shown in black, CAUG in red, and FCG in blue.

and neurodevelopmental disorders. In the current study, three cohorts of children from the BEIP with longitudinal EEG recordings were studied and oscillation trajectories were estimated from 42 to 96 months, that is, after all children in the intervention arm of the trial had been placed in foster care.

Significant group differences in gamma, beta, alpha, and theta amplitude trajectories were estimated after

Table 5. Summary Statistics of Cross-frequency Coupling for All Oscillation Interactions, Separately for Each Group (NIG, FIG, and CAUG) at 96 Months

	NIG		*FCG*		*CAUG*	
	Median	*(25th, 75th) Quartiles*	*Median*	*(25th, 75th) Quartiles*	*Median*	*(25th, 75th) Quartiles*
Gamma–beta	0.103	(0.095, 0.119)	0.100	(0.090, 0.113)	0.094	(0.085, 0.103)
Gamma–alpha	0.067	(0.054, 0.080)	0.058	(0.054, 0.066)	0.056	(0.052, 0.062)
Gamma–theta	0.045	(0.039, 0.049)	0.042	(0.040, 0.045)	0.041	(0.039, 0.044)
Gamma–delta	0.035	(0.031, 0.038)	0.034	(0.032, 0.036)	0.033	(0.031, 0.035)
Beta–alpha	0.210	(0.196, 0.227)	0.203	(0.180, 0.217)	0.196	(0.173, 0.214)
Beta–theta	0.088	(0.086, 0.094)	0.091	(0.083, 0.097)	0.088	(0.083, 0.093)
Beta–delta	0.057	(0.055, 0.059)	0.057	(0.055, 0.060)	0.057	(0.055, 0.059)
Alpha–theta	0.186	(0.179, 0.192)	0.187	(0.179, 0.193)	0.189	(0.185, 0.198)
Alpha–delta	0.092	(0.088, 0.097)	0.095	(0.090, 0.098)	0.096	(0.092, 0.099)
Theta–delta	0.253	(0.248, 0.265)	0.255	(0.249, 0.260)	0.255	(0.247, 0.261)

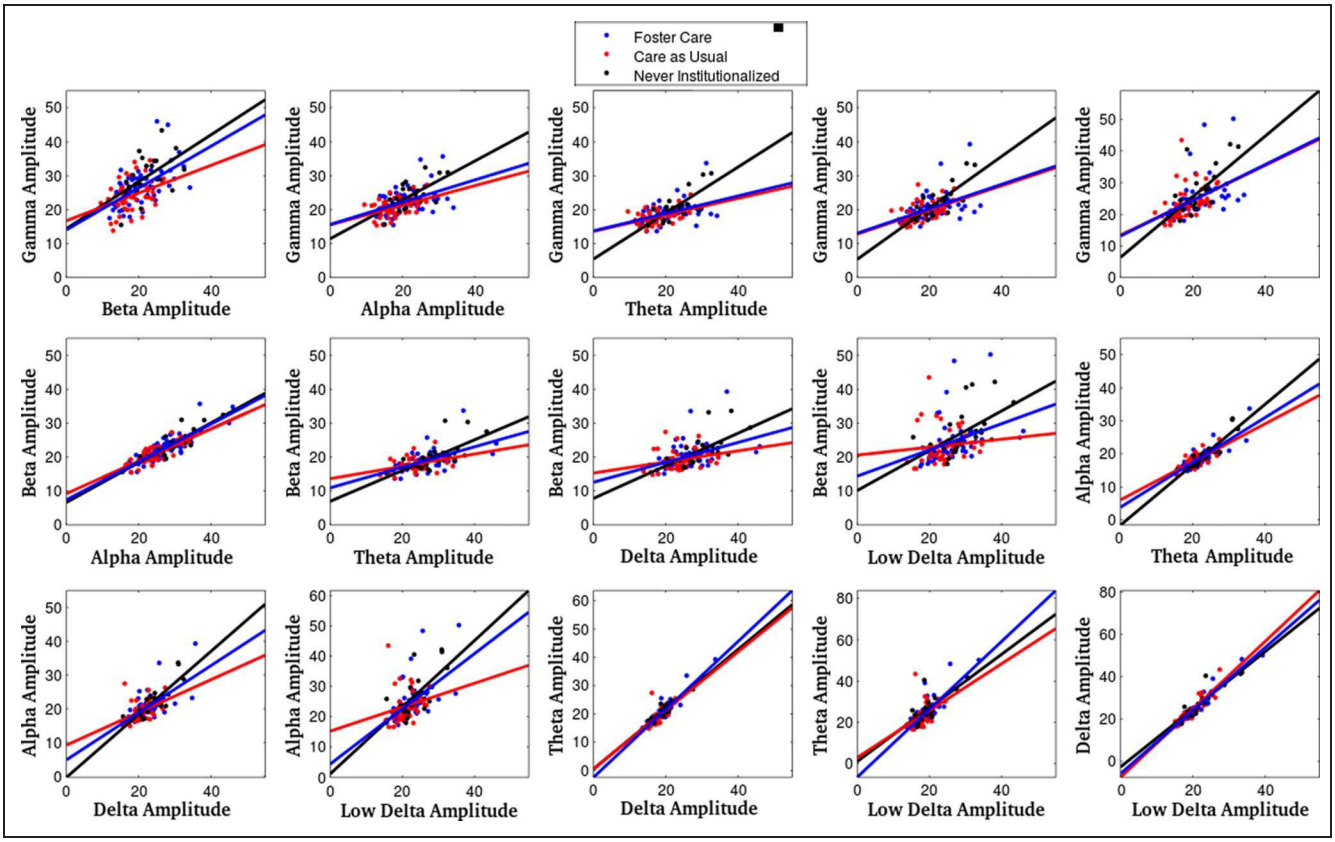

Figure 3. Amplitude scatter plots for all pairs of oscillations at 96 months. Each data point corresponds to an individual subject's median oscillation amplitude. The best-fit linear models are superimposed. NIG is shown in black, FCG in blue, and CAUG in red.

adjustment for birth weight. Similar differences were also identified as a function of time spent at institutions at 42 and 96 months. These results indicate that psychosocial deprivation and its extent, that is, the length of neglect, impact the developmental trajectories of neural oscillations across a broad frequency spectrum (from ~4 to >50 Hz). Altered oscillations in these bands may affect multiple aspects of cognitive function, including sensory processing, memory, and learning. Foster care intervention appears to have a positive impact, in that frequency–amplitude changes at 96 months in the FCG were closer to corresponding changes in the NIG than the CAUG (see Figure 1) and age at foster care placement was statistically correlated with the trajectories of the alpha and beta oscillations and their mutual coupling. However, despite this positive modulatory effect, identified trajectories of oscillation amplitudes from 42 to 96 months and their interactions remained statistically distinct in the three groups, indicating potentially differential neural maturation and developmental changes. These findings are in agreement with previous investigations of the BEIP EEG data that have also found significant group differences in alpha amplitude at 96 months (Vanderwert et al., 2010). This latter study also found statistical similarities in alpha amplitude between children in the FCG that were placed in foster care before 24 months and children in the NIG but did not assess age-related dynamics of this oscillation reported here. Given that the BEIP is an ongoing study, it will be important to assess the continuing effects of foster care at later time points.

Although the brain remains active in the absence of specific cognitive tasks, spatially distributed resting-state brain networks are typically weakly correlated to ensure flexibility and rapid recruitment of functional networks in response to cognitive demands or external inputs (Deco, Jirsa, & McIntosh, 2013). Correlations between neural oscillations at rest are, therefore, expected to be low relative to those during task performance. Nevertheless, the robustness of neural connections as a result of neural maturation may affect the amplitude of these correlations even at rest. Significant differences in multiple pairwise interactions between oscillations were estimated between the three groups, both at 96 months and longitudinally from 42 to 96 months. Specifically, significant group differences in cross-frequency coupling were estimated between gamma and all lower-frequency oscillations from the delta to the beta ranges and between alpha and all other oscillations. Also, time spent at institutions was significantly correlated with gamma–alpha, gamma–theta, and gamma–delta interactions. Overall lower coupling between gamma and lower frequencies in the CAUG compared to the FCG and NIG may be associated with weaker neural connections in this group, impaired communication between spatially distributed

Table 6. Linear Mixed Effects Model Parameters for Cross-frequency Coupling as a Function of Time and Group

Parameter	*Regression Coefficient*	*Confidence Interval*	*SE*	*p*	*Wald Statistic*
Gamma–Beta Coupling Trajectory					
Intercept	0.086	[0.08, 0.09]	0.003	<.0001	756.25
Time (age)	0.0001	[3.0E-05, 1.8E-04]	4.00E-005	.007	7.45
Group	0.004	[0.001, 0.007]	0.001	.003	8.94
Gamma–Alpha Coupling Trajectory					
Intercept	0.04	[0.036, 0.043]	0.002	<.0001	388.88
Time (age)	0.0002	[1.6E-04, 2.6E-04]	2.50E-005	<.0001	66.58
Group	0.003	[0.001, 0.005]	9.00E-004	.001	10.30
Gamma–Theta Coupling Trajectory					
Intercept	0.03	[0.029, 0.034]	0.0010	<.0001	897.60
Time (age)	0.0001	[7.45E-05, 1.4E-04]	1.30E-005	<.0001	57.15
Group	0.001	[2.0E-04, 0.002]	4.90E-004	.02	5.71
Gamma–Delta Coupling Trajectory					
Intercept	0.026	[0.025, 0.028]	7.60E-004	<.0001	318.62
Time (age)	6.70E-005	[4.82E-05, 8.6E-05]	9.70E-006	<.0001	48.30
Group	8.10E-004	[1.2E-04, 0.001]	3.50E-004	.02	5.38
Beta–Alpha Coupling Trajectory					
Intercept	0.18	[0.17, 0.19]	0.006	<.0001	1053.65
Time (age)	1.90E-004	[4.9E-05, 3.3E-04]	7.05E-005	.008	7.13
Group	0.002	[−0.003, 0.007]	0.003	.39	0.72
Beta–Theta Coupling Trajectory					
Intercept	0.09	[0.08, 0.1]	0.002	<.0001	2265.76
Time (age)	−2.00E-005	[−6.8E-05, 2.8E-05]	2.40E-005	.41	0.67
Group	2.30E-004	[−0.002, 0.001]	8.90E-004	.79	0.07
Beta–Delta Coupling					
Intercept	0.056	[0.055, 0.058]	7.70E-004	<.0001	5369.96
Time (age)	9.90E-006	[−9.2E-06, 2.9E-05]	9.70E-006	.31	1.04
Group	3.00E-004	[−0.001, 4.0E-04]	3.50E-004	.39	0.67
Alpha–Theta Coupling Trajectory					
Intercept	0.19	[0.183, 0.194]	0.003	<.0001	4853.90
Time (age)	1.70E-005	[−5.05E-05, 8.4E-05]	3.40E-005	.62	0.24
Group	−0.002	[−0.005, 4.4E-05]	0.001	.05	3.72

Table 6. (*continued*)

Parameter	*Regression Coefficient*	*Confidence Interval*	*SE*	*p*	*Wald Statistic*
Alpha–Delta Coupling Trajectory					
Intercept	0.094	[0.091, 0.097]	0.001	<.0001	3651.78
Time (age)	1.60E-005	[−2.3E-05, 5.5E-05]	2.00E-005	.41	0.67
Group	−0.002	[−0.003, −4.0E-04]	7.20E-004	.01	6.60
Theta–Delta Coupling Trajectory					
Intercept	0.260	[0.25, 0.27]	0.003	<.0001	5786.64
Time (age)	4.80E-005	[−1.3E-04, 3.7E-05]	4.30E-005	.27	1.23
Group	1.70E-004	[0.003, 0.003]	0.002	.91	0.01

brain networks and even reduced synaptic inhibition, which has been associated with various neuropsychiatric disorders (Liang et al., 2015; Yizhar et al., 2011).

Transient interactions between high- and low-frequency oscillations, such as gamma and theta, are critical for the transmission of locally processed neural information to distant brain regions during cognitive task performance. Impaired coupling between these oscillations even at rest may, therefore, be associated with a wide range of cognitive deficits, including decreased attention, slower RT, memory deficits, and impaired learning (Marshall et al., 2008; Buzsaki & Draguhn, 2004; Howard et al., 2003). Higher coupling between alpha and lower frequencies in the CAUG compared with the FCG and NIG may be the result of impaired suppression of the alpha and theta oscillations and their interactions, which has also been associated with neuropsychiatric disorders, including schizophrenia (Moran & Hong, 2011) and attention-deficit/hyperactivity disorder (Mazaheri et al., 2014). Attention-deficit/hyperactivity disorder has commonly been reported in children reared in institutions (McLaughlin et al., 2010; Biederman et al., 1995; Rutter & Quinton, 1977). Finally, impaired coupling between these lower frequencies may also be associated with impaired motivation, reward, and emotional processing and control (Bauer et al., 2009; Jacobs et al., 2006).

Finally, these widespread group differences in oscillation parameters and their interactions may be closely associated with previously reported structural brain differences in BEIP participants. For example, reduced integrity of large neural fiber tracts, such as the body of the corpus callosum, in the CAUG and FCG groups at 96 months (Bick et al., 2015) may be associated with corresponding deficits in specific oscillations, particularly alpha (Hinkley et al., 2012), that may not recover after the foster care intervention. The alpha oscillation has also been associated with other tracts, such as the superior corona radiata (Valdez-Hernandez et al., 2010), which was also found to be adversely affected by early institutionalization (Bick et al., 2015). Furthermore, impaired integrity of the fornix, previously reported in the CAUG and FCG groups (Bick et al., 2015), has also been associated with deficits in the theta rhythm (Mitchell, Rawlins, Steward, & Olton, 1982). In this study, the theta amplitude trajectory was also found to be statistically distinct in the three groups.

In summary, this study has identified significant and widespread differences in the developmental trajectories (from 42 to 96 months) of brain oscillations and their interactions in children reared in institutions. Given that these trajectories represent macroscale correlates of neural maturation, these findings suggest that early psychosocial neglect may adversely modulate fundamental aspects of the dynamic process of brain development. Furthermore, given the broad and critical role that neural oscillations play in the communication between brain regions, these findings suggest that institutionalization in early life may impact cognitive processing across multiple domains. Differences in neural communication reflected in these oscillations may be associated to structural differences reported in previous studies (Bick et al., 2015; Sheridan et al., 2012). Foster care placement appears to have a positive modulatory effect on several oscillation trajectories. However, by 96 months, these trajectories remained distinct from those of never-institutionalized children. Longer-term effects of this intervention could not be assessed in this study, but ongoing collection of EEG data in the BEIP makes it possible to investigate these effects at later ages. This study provides new findings on potentially profound effects of institutionalization of the developmental trajectories of fundamental properties of human brain activity across a broad frequency range. In turn, these findings may help elucidate the neurophysiological mechanisms associated with previously reported cognitive deficits in children reared in institutions.

APPENDIX A

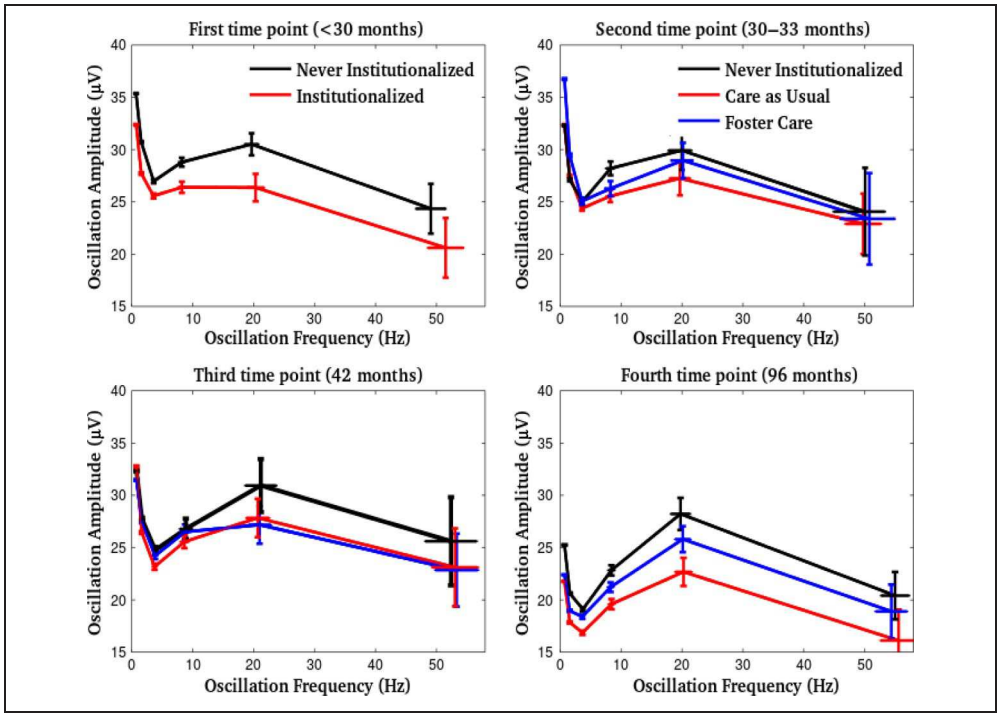

Figure A1. Frequency–amplitude plots of estimated oscillations at baseline (top left) and clockwise at ~30–33, 42, and 96 months, respectively. At the first three time points, nontask EEGs collected during the bingo wheel condition are shown. The 96-month data are the same as in Figure 1, because nontask EEGs were collected only under one condition at that age. Never-institutionalized children are shown in black, CAUG in red, and FCG in blue. Both frequency and amplitude interquartile ranges are superimposed (horizontal and vertical bars respectively).

Table A1. Summary of Linear Regression Model Parameters with Oscillation Frequency or Amplitude as the Outcome and Group as the Predictor (Categorized as Institutionalized = 1, Never Institutionalized = 0)

	Parameter	*Regression Coefficient*	*Confidence Interval (CI)*	*SE*	*p*	*Wald Statistic*
Baseline Gamma Oscillation Frequency						
Model 1	Intercept	48.27	[46.2, 50.33]	1.04	<.0001	2139.06
	Group	−0.98	[−1.52, −0.46]	0.27	.0003	13.47
	Age at measurement	0.15	[0.06, 0.24]	0.04	.0005	12.39
Model 2	Intercept	34.24	[25.69, 42.79]	4.32	<.0001	62.68
	Group	0.37	[0.19, 0.56]	0.09	.0001	15.83
	Head Circumference	−2.3	[−3.28, −1.33]	0.49	<.0001	21.72
Baseline Beta Oscillation Frequency						
Model 1	Intercept	19.01	[18.02, 20.00]	0.51	<.0001	1425.82
	Group	−0.27	[−0.56, −0.01]	0.13	.040	4.33
	Age at measurement	0.06	[0.02, 0.10]	0.02	.004	8.53
Model 2	Intercept	13.97	[9.84, 18.09]	2.09	<.0001	44.76
	Group	0.14	[0.05, 0.23]	0.05	.003	9.36
	Head Circumference	−0.72	[−1.19, −0.25]	0.24	.003	9.18
Baseline Gamma Oscillation Amplitude						
Model 1	Intercept	24.59	[15.93, 34.16]	4.84	<.0001	25.8
	Group	2.58	[0.12, 5.05]	1.25	.039	4.31
	Age at measurement	−0.02	[−0.42, 0.38]	0.2	.930	0.01

An adjustment for age at measurement was also included in the models (only statistically significant correlations are shown).

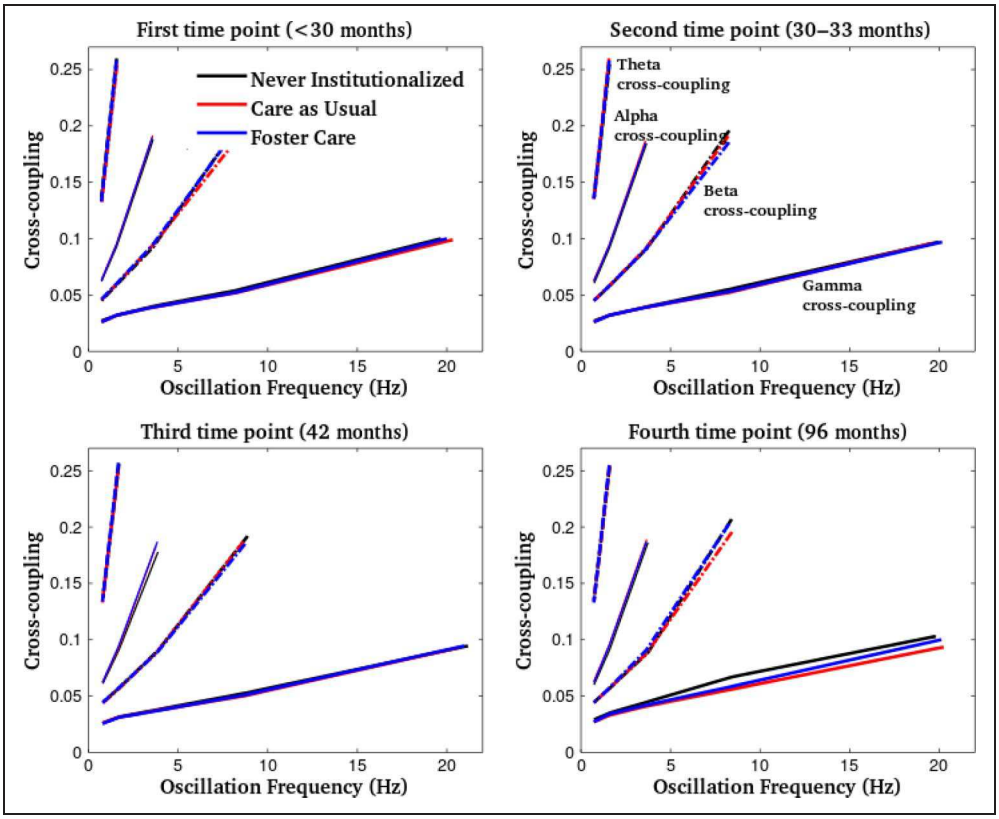

Figure A2. Median cross-frequency coupling as a function of frequency for the gamma, beta, alpha, and theta oscillations. At the first three time points, nontask EEGs collected during the bingo wheel condition are shown. The 96-month data are the same as in Figure 2, because nontask EEGs were collected only under one condition at that age. Solid lines represent the gamma–beta, gamma–alpha, gamma–theta, and gamma–delta coupling and thus are the longest; dash-dotted lines represent the beta–alpha, beta–theta, and beta–delta coupling; light lines represent the alpha–theta and alpha–delta coupling; and dashed lines represent the theta–delta coupling. NIG is shown in black, CAUG in red, and FCG in blue.

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