CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

ORCA – Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/103391/

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Stamoulis, Catherine, Vanderwert, Ross , Zeanah, Charles H., Fox, Nathan A. and Nelson, Charles A. 2017. Neuronal networks in the developing brain are adversely modulated by early psychosocial neglect. Journal of Neurophysiology , jn.00014.2017. 10.1152/jn.00014.2017

Publishers page: http://dx.doi.org/10.1152/jn.00014.2017

Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.

Articles in PresS. J Neurophysiol (July 5, 2017). doi:10.1152/jn.00014.2017

Neuronal networks in the developing brain are adversely modulated by early psychosocial neglect

Catherine Stamoulis[1,2,3*], Ross E. Vanderwert[8], Charles H. Zeanah[5], Nathan A. Fox[6], Charles, A. Nelson[1,4,7]

[1]Harvard Medical School, Boston MA, USA

[2]Division of Adolescent Medicine, Boston Children's Hospital, Boston MA, USA

[3]Department of Neurology, Boston Children's Hospital, Boston, MA, USA

[4]Divison of Developmental Medicine, Boston Children's Hospital, Boston MA USA

[5]Department of Psychiatry and Behavioral Sciences, Tulane University, New Orleans, LA, USA

[6]Department of Human Development and Quantitative Methodology, University of Maryland, College Park, MD, USA

[7]Graduate School of Education, Harvard University, Cambridge MA, USA

[8]School of Psychology, Cardiff University, UK

[*]To whom correspondence should be addressed: caterina.stamoulis@childrens.harvard.edu

Corresponding author address: Boston Children's Hospital, Division of Adolescent Medicine, 300 Longwood Avenue, Boston MA 02115

Running title: Effects of early psychosocial neglect on brain networks

Copyright © 2017 by the American Physiological Society.

Abstract

The brain's neural circuitry plays a ubiquitous role across domains in cognitive processing and undergoes extensive re-organization during the course of development in part as a result of experience. In this paper we investigated the effects of profound early psychosocial neglect associated with institutional rearing on the development of task-independent brain networks, estimated from longitudinally acquired electroencephalographic (EEG) data from <30 to 96 months, in three cohorts of children from the Bucharest Early Intervention Project (BEIP), including abandoned children reared in institutions who were randomly assigned either to a foster care intervention or to remain in care as usual and never institutionalized children.

Two aberrantly connected brain networks were identified in children that had been reared in institutions: 1) a hyper-connected parieto-occipital network, which included cortical hubs and connections that may partially overlap with default-mode network and 2) a hypo-connected network between left temporal and distributed bilateral regions, both of which were aberrantly connected across neural oscillations. This study provides the first evidence of the adverse effects of early psychosocial neglect on the wiring of the developing brain. Given these networks' potentially significant role in various cognitive processes, including memory, learning, social communication and language, these findings suggest that institutionalization in early life may profoundly impact the neural correlates underlying multiple cognitive domains, in ways that may not be fully reversible in the short term.

New and noteworthy

This paper provides first evidence that early psychosocial neglect associated with institutional rearing profoundly affects the development of the brain's neural circuitry. Using longitudinally-acquired electrophysiological data from the Bucharest Early Intervention Project (BEIP), the paper identifies multiple task-independent networks that are abnormally connected (hyper- or hypo-connected) in children reared in institutions compared to never-institutionalized children. These networks involve spatially distributed brain areas and their abnormal connections may adversely impact neural information processing across cognitive domains.

Keywords: Brain networks, EEG, early development, psychosocial neglect

Introduction

From the microscale of individual neurons to the macroscale of cortical regions, the brain's neuroarchitecture is characterized by networks organized into topologies that ensure flexible, rapid and efficient neural information processing (Bullmore & Sporns, 2009). These networks may be divided into two broad categories: task-related networks that are activated and coordinated in response to cognitive demands and external stimuli, and task-independent (resting-state or stimulus-independent) networks that are spontaneously active and coordinated when the brain is not actively engaged in specific cognitive tasks. In some cases, task-dependent networks increase their activity and coordination at the same time as specific task-independent networks decrease theirs (Fox et al., 2005). Thus, in part due to these inverse correlations, task-independent networks may play a critical role in cognitive function and neural information processing (Raichle et al., 2001, 2007; Dosenbach et al., 2008; Kelly et al., 2008). Predominantly fMRI studies in adults have identified several distinct, and in some cases inter-connected task-independent networks, including the default-mode network (DMN) (Greicius et al., 2003; Vincent et al., 2006; Mantini et al., 2007; Ward et al., 2014). The topologies of these networks, estimated from fMRI data with excellent spatial resolution, may be directly correlated with those of structural networks (Greicius et al., 2009; Barttfelt et al., 2015). Previous studies have associated disrupted task-independent networks, with neuropsychiatric disorders, including schizophrenia and autism (Kennedy et al., 2006, Bluhm et al., 2007).

The dynamic evolution of task-independent networks in the developing brain is poorly understood and our current knowledge is primarily based on fMRI studies. Elements of these networks come on line early in infancy (Fransson et al., 2007), but at least the DMN, which includes the ventral medial prefrontal cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), lateral temporal cortex, precuneus and lateral parietal inferior gyri and the hippocampal formation (Greicius et al., 2003; Buckner et al., 2008), may be incompletely connected even at ages 7-9 years (Fair et al., 2008). Negative early experiences and stressors,

including poverty, abuse and psychosocial neglect, may have profound effects on neural maturation and consequently brain structure and function. In fact, social and emotional deprivation associated with institutional rearing has been shown to adversely affect brain's structure (Eluvathingal et al., 2006; Bauer et al., 2009; Sheridan et al, 2012; Bick et al., 2015), metabolism (Chugani et al., 2001; Tottenham et al., 2011) and electrical activity (Marshall et al., 2004, 2008; Vanderwert et al., 2010; McLaughlin et al., 2010, 2011; Stamoulis et al, 2015). Earlier work on the Bucharest Early Intervention Project (BEIP), a longitudinal study of children with a history of severe early deprivation (see Zeanah et al., 2003; Nelson et al., 2014), has shown that early psychosocial deprivation significantly impacts age-related dynamics in the developing brain's rhythms (Stamoulis et al., 2015). In the same sample, Marshall et al. (2008) showed that removal from an institution and placement in a foster care home prior to 24 months of age resulted in higher local network synchrony and statistically higher power in the alpha band (8-12 Hz) in the first 4 years of life in comparison to children who remained in institutions. A positive modulatory effect of foster care placement was also reported in other oscillations (Stamoulis et al., 2015), although changes in these oscillations from 42 to 96 months were found to be distinct in children removed from institutions and placed in foster care compared to those who had never been institutionalized. These results highlight the profound adverse effects of early institutionalization on the developing brain.

There are very few studies that have investigated task-independent networks in the developing brain and no previous work on the effects of neglect on these networks. This study investigated the topologies of task-independent networks and their developmental trajectories in children participating in the BEIP. Longitudinal electrophysiological (EEG) data from 3 cohorts were analyzed, including a group of institutionalized children who were randomized to a high-quality foster care placement (the foster care group), a group randomized to remain in institutional care (care as usual group) and a group of children who had never been institutionalized and lived with their families in the Bucharest community (never institutionalized group). Although EEG has

excellent temporal resolution, it lacks the high spatial resolution of fMRI and cannot resolve network topologies with the same spatial specificity as fMRI. Consequently, brain network topologies estimated from fMRI (which measures hemodynamic responses) and EEG (which measures neural activity) are not directly comparable. Nevertheless, EEG may still provide spatially sparse connectivity information on task-independent networks that may overlap with those identified by fMRI. Here we hypothesized that the spatial organization, properties and age-related dynamics of these networks are significantly impacted by early neglect in a frequency-specific manner, resulting in aberrant topologies that impair the efficiency of neural information processing and consequently cognitive function.

Materials and Methods

1. Bucharest Early Intervention Project (BEIP)

The BEIP is an ongoing longitudinal study that started in 2001 as a randomized controlled trial with foster care as an intervention for young children who had been abandoned at birth and placed in institutions. Using multi-modal data, the study aims to investigate the effects of early psychosocial deprivation on the structure and function of the developing brain and potentially beneficial effects of removal from an institution and foster care placement (Zeanah et al, 2003, Nelson et al, 2014). One hundred thirty-six children who had been reared in institutions entered the trial at ages 6-30 months, and were randomized to two arms, care as usual (CAUG; n = 68), i.e., more prolonged institutional rearing and foster care (FCG; n = 68), i.e., placement in high-quality foster care specifically created for the project. A comparison group of 72 Romanian children who had never been institutionalized and lived with their families in Bucharest communities were also recruited (NIG).

2. Participants

The present study sought to quantify the age-related changes in task-independent networks using longitudinally acquired EEG signals from the BEIP cohorts, with an emphasis on 42 and 96 months (although

data at all ages were analyzed). Thus, only subgroups of the BEIP cohorts with measurements at a minimum of 2 time points were included. Also, 4 children in the CAUG with diagnosed Autism Spectrum Disorder (ASD) were excluded. The characteristics of these groups are described in more detail in (Stamoulis et al., 2015). Sixty-two children in the CAUG (median age at study entry = 23.0 months, inter-quartile range (IQR) = 9 months), 61 children in the FCG (median age at study entry = 23.0 months, IQR = 11 months), and 44 children in the NIG (median age at study entry = 21.5 months, IQR = 12 months) were studied.

3. Demographic data

Age, which varied between participants both at study entry and the second assessment (30-33 months) but not at 42 or 96 months, gender, age at foster care placement for children in the FCG, percent time spent in institutions for children in the FGC and CAUG, birth weight and head circumference were included in the analysis as potential covariates. All missing data were assumed to be missing at random, mainly as a result of longitudinal attrition. Eighty-four females and 83 males were studied. Birth weight varied in the range 0.9 – 4.5 kg (median = 3.0 kg, IQR = 0.8 kg). These data were missing in 15 children. There were no statistically significant differences in birth weight between the CAUG and FCG (median of CAUG = 2.8 kg, median of FCG = 2.6 kg, $p = 0.14$) but both groups had statistically lower birth weights than the NIG (median of NIG = 3.3 kg, $p<0.001$). Head circumference was measured at all 4 time points. These data were missing for 17 children at baseline, 16 at 30 months, 25 at 42 months and 32 at 96 months. Median circumference at baseline was 46.8 cm, IQR = 2.5 cm, 48.0 cm at 30 months IQR = 2.0 cm, 48.6 cm at 42 months, IQR = 1.6 cm, and 51.0 cm at 96 months, IQR = 2 cm. There were no significant differences in head circumference between the CAUG and FCG at any age ($p = 0.18$ at baseline, $p = 0.07$ at 30 months, $p = 0.09$ at 42 months, $p = 0.38$ at 96 months). In the FCG, age at foster care placement was in the range 6.8 – 33 months, median = 24.8 months, IQR = 10.1 months. Time spent at institutions at baseline, 42 and 96 months is summarized in Table S1.

4. EEG data characteristics and pre-processing

EEGs were collected at study entry (baseline) as well as at 30-33, 42 and 96 months, using an Electro-Cap (Electro-Cap International Inc) system (12 scalp electrodes: F3, F4, Fz, C3, C4, P3, P4, Pz, T7, T8, O1, O2). The characteristics of these data are described in detail in (Marshall et al, 2008, Vanderwert et al, 2010, Stamoulis et al, 2015). At baseline, 30-33 months and 42 month assessments, task-independent EEG signals were recorded while lights were turned off for ~1-3 min. At 96 months, task-independent EEG signals were recorded during 1-min intervals of eyes-closed (EC) and eyes-open (EO). Only signals recorded under the EC condition were included in the analysis. Data were sampled at 512 samples/s and bandpass filtered during acquisition in the range 0.1- 100 Hz. Prior to analysis all signals were referenced to an average reference. Previous work has shown that in the absence of appropriate source modeling, which is difficult with a small number of electrodes, an average reference results in substantially lower connectivity errors than a mastoid or Cz reference (Chella et al, 2016). However, similar to all referencing approaches, an average reference has shortcomings, too, particularly for localizing specific EEG waveforms such as event-related potentials (ERP). Here, the issue of localization is of less concern. Also, several studies have shown that for connectivity analyses, even with a low number of EEG electrodes average referencing is preferable to the use of a common reference (Dien, 1998). A stopband filterbank of 3^{rd} order elliptical filters with a 1-Hz bandwidth, 0.5 dB ripple in the passband and 20 dB in the stopband was used to suppress the power line noise at 50 Hz and its 100-Hz harmonic. Artifacts associated with eye blinking were locally suppressed using a matched-filtering approach, where signal templates for eye blinks were used to detect intervals containing these artifacts (Stamoulis et al., 2009). Individual EEG signals were further denoised via signal decomposition and elimination of random components identified based on their autocorrelation function (Stamoulis et al., 2014). Finally, signals containing extreme amplitude outliers, i.e., above a threshold equal to the median plus 3 times the inter-quartile difference (Tukey, 1977) were also eliminated. These outliers are likely to be associated with broadband muscle and/or other non-neural activity. Consequently, 1-s intervals containing outliers were

excluded from the signal decomposition and mutual information estimations.

5. Signal analysis

5a. Estimation of narrowband EEG signal components (individual oscillations): Neural oscillations in the developing brain may have characteristic frequencies that do not fall within the limits of traditional biological bands (delta to ripple), established based on adult brain signals. Thus, frequency domain analysis of bandpass filtered signals in these bands may not be appropriate. Instead, a fully unsupervised, time-domain approach based on the Ensemble Empirical Mode Decomposition method (EEMD, Wu et al, 2005) was used to estimate neural oscillations and their dominant frequencies. The EEMD is a modification of the classical EMD method (Huang et al, 1998) and accounts of the problem of mode (component) mixing. The estimation process has been descried in detail in previous work (Stamoulis et al., 2015). Task-independent network connectivity was estimated for individual oscillations of the EEG to construct frequency-specific networks. Briefly, each EEG signal was decomposed into a small set of narrowband components that significantly contributed to the broadband signal amplitude. The cost function proposed in (Stamoulis et al, 2011) was also used to select non-random components and eliminate noise-related signal contributions with substantial amplitude. A sliding 1-s window was used in all estimations. In exploratory analyses of the data, the window length was varied between 1 and 4 s, yielding similar estimates in oscillation amplitude, frequency and connectivity.

Glossary of terms: The following network parameters were estimated for each identified oscillation in the EEG: a) *spatially averaged connectivity* (over the entire brain and over individual networks identified in models to be statistically distinct between groups), b) non-directional *edge-specific connectivity* for each edge connecting pair of network nodes and c) *node centrality*, a measure of the importance of each node in the network. Each electrode was treated as a network node. Spatially-averaged and edge-specific connectivities were quantified using *mutual information*, an information theoretic measure (see 5b). Two types of

connectivity matrices were estimated for each child at each time point and each oscillation, a *weighted connectivity matrix* containing the actual mutual information values and thus the actual connection strengths between pairs of nodes and the *adjacency matrix,* a binary matrix of edge connection/non-connection obtained by appropriately thresholding the weighted connectivity matrix. Based on connectivity thresholds two sets of networks were identified, *hyper-* and *hypo-connected networks* (see 5c and 5d). Node centrality was quantified using *node strength*, a measure of the sum of its connections based the adjacency matrix (see 5e).

5b. Estimation of oscillation-specific connectivity: In the case of a large number of electrodes, connectivity analysis may be best conducted at the source level, to appropriately address issues of volume conduction which may impact various connectivity measures. The adequacy and accuracy of source connectivity analysis in the case of 12 electrodes are questionable, independently of the source separation or localization methods used. Information-based connectivity measures have been shown to be relatively robust to volume conduction (Vicente et al, 2011) and were used in this electrode-level analysis. Mutual information was used to quantify undirected pairwise network connectivity. Together with other information theoretic measures, it has been previously used in a number of studies to quantify correlation between electrophysiological signals and may be more robust to the inherent noise of these signals than other measures such as coherence (Vejmelka et al, 2008; Schreiber, 2000; Palus et al, 2001; Stamoulis et al, 2013). Mutual information $I(X,Y) = \sum_{x,y} p(x, y) \log \frac{p(x,y)}{p(x)\,p(y)} \geq 0$, between random variables X and Y measures their mutual dependence (Cover & Thomas, 2004). It is a function of their joint and marginal probability density functions $p(x, y)$, $p(x)$ and $p(y)$, which were estimated using a kernel-based method (assuming a Gaussian kernel) following segmentation of EEG signals in 1-s windows. Across ages and participants, a kernel bandwdith of 0.8 was used in the estimation and the probability density functions were evaluated at 200 points.

5c. Connectivity threshold estimation: Edge-specific mutual information thresholds were estimated as

follows: for each oscillation and network edge, the median (across subjects) mutual information for the NIG (and thus each age-matched oscillation and edges in the control group) was calculated as well as corresponding 95% confidence intervals (CI), using bootstrapping with replacement (2000 draws and an accelerated, bias-corrected percentile method (Efron, 1993)). The edge-specific upper CI for the NIG median mutual information was selected as an edge's threshold for edge hyper-connectivity, and the corresponding lower CI was selected as the threshold for edge hypo-connectivity.

5d. Adjacency matrix estimation for relative hyper- and hypo-connectivity: Based on the above thresholds, two sets of adjacency matrices - with elements *(i, j)* for edges connecting nodes *i* and *j*, for each oscillation-specific undirected graph were estimated for the CAUG and FCG, 1) the *hyper-connectivity adjacency matrices,* with elements that were equal to 1 for edges that exceeded the upper CI for median connectivity of the NIG and zeros elsewhere, 2) the *hypo-connectivity adjacency matrices,* with elements that were equal to 1 for edges that were below the lower CI for median connectivity of the NIG and 0 elsewhere.

5e. Estimation of node centrality: The maximum number of possible connections of each node in the estimated networks is 12 (a self-connection and 11 connections to all other nodes). There are several ways to define *node centrality*, i.e., the importance of a node in a network. Here it is defined in two ways: 1) in terms of *node strength*, i.e. the ratio of the sum of all edge weights for a node over the maximum possible sum of weights, so for node $c_i = \frac{\sum_j I_{ij}}{max\sum_j I_{ij}}$; 2) in terms of *node connectedness*, i.e., the ratio of the sum of all binary edge values for a node over the maximum possible sum of weights i.e., $c_i = \frac{\sum_j A_{ij}}{max\sum_j A_{ij}}$. Based on these topological measures it is possible to identify potential *hubs*, i.e., highly connected nodes that are critical for information processing through the network. Note that the adjacency matrices for the CAUG and FCG

were estimated as described in sub-section 5d. The adjacency matrices for subjects in the NIG were estimated assuming the median (across subjects and electrodes) MI as the corresponding connectivity threshold.

6. Statistical analysis

Differences in network characteristics at individual ages were assessed using ordinary linear regression models, with edge connectivity or node centrality as the dependent variable, and group (using criterion coding to avoid including several group variables given the relatively small sample), time spent in institutions, birth weight, head circumference, age at foster care placement and gender (categorized as female = 0, male = 1) as independent variables. In these models (as well as in mixed effects models used to assess age-related parameter changes), each edge or node parameter were assessed independently, i.e., nodes/edges were not compared to each other. Instead, their individual (independent) correlation with the predictors and confounders were assessed. Therefore, corrections for multiple comparisons were not necessary, particularly in mixed effects models (Gelman et al, 2012). Combinations of independent variables were included in separate models. Logistic regression models with group as the dependent variable (assuming the NIG as the reference category) and network measures as independent variables were also developed. Finally, in cases where network parameters were found to be statistically distinct among the 3 groups, their relationship was also investigated through logistic regression models that included only the CAUG (= 0) and FCG (= 1), i.e., the groups in the two arms of the randomized trial. All modeling approaches yielded consistent results. Note that at baseline (prior to the randomization) there were only two groups, institutionalized and never-institutionalized.

Linear mixed effects models were developed to investigate temporal trajectories of network characteristics. 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 changes in network parameters between 42 and 96 months. Thus, the models included a subject-specific intercept and a subject-specific age slope, to account

for potential subject-specific variabilities. Independent variables included gender, birth weight, head circumference, group, age at foster care placement and percent time spent at institutions. Given the sample size, only relatively small models were developed with combinations of 1-3 independent variables. All analyses were done using the software Matlab (Mathworks, Inc, Natick MA, USA).

Results

We investigated oscillation-specific network properties at all 4 age assessments, and their developmental changes from 42 to 96 months. We first examined spatially-averaged (global) connectivity followed by edge-specific connectivity and node centrality. We conducted two complementary analyses: 1) Using connectivity thresholds derived from the NIG, we compared the FCG and the CAUG relative to NIG. We thus present results on abnormal networks in the FCG and CAUG that were found to be *hyper-connected* or *hypo-connected* relative to the NIG; 2) We compared all 3 groups to each other via statistical models that included adjustments for birth weight or head circumference. We report network measures only for subnetworks that were found to be statistically distinct in the 3 groups. As previously noted, regression models were also developed to compare only the CAUG and FCG, separately from the NIG. Statistically significant group differences in network parameters identified in these models were consistent with those identified using models that included the NIG.

1. Brain-wide (spatially-averaged) connectivity

First, median (over electrodes) mutual information (MI) that had been averaged in time was compared between groups for each estimated oscillation at each assessment age, to assess potential differences in brain/hemisphere-wide connectivity. Corresponding frequency-connectivity relationships at these ages (unadjusted for confounders or other covariates) are shown in Figure 1. Inter-quartile ranges (vertical bars for MI and horizontal bars for frequency) are shown. In these unadjusted connectivity data, no significant

differences were found between groups except for the gamma oscillation at 96 months ($p = 0.012$), and the alpha and theta oscillations at baseline (study entry) ($p = 0.002$ and $p = 0.016$ for alpha and theta connectivity respectively). When adjusted for birth weight or head circumference, significant differences in whole brain and hemisphere-specific connectivity were estimated between institutionalized and never institutionalized children in the theta band at baseline ($p = 0.006$ for the entire brain, $p = 0.002$ for the left-hemisphere and $p = 0.034$ for the right hemisphere). When adjusted for age at foster care placement, significant group differences in left-hemisphere theta connectivity were estimated at 96 months ($p = 0.035$). When adjusted for head circumference, significant group differences in beta connectivity were also estimated in the left hemisphere at 96 months ($p = 0.044$). The statistics of oscillation frequencies at each assessment age are summarized in Table S1.

2. Network topologies at 4 assessment ages

All reported connectivity parameters in the CAUG and FCG are relative to the corresponding NIG parameters. For each assessment age and oscillation, network topologies for the two groups are shown in Figure 2. Note that these connectivities are unadjusted for potential confounders and are solely based on thresholding of the MI matrices. Appropriate adjustments were included in the analysis and are described in the next section. For each oscillation, topologically distinct hyper- and hypo-connected subnetworks were identified in the CAUG and FCG with some overlap of their elements across oscillations. At baseline, both groups had a large number of hyper-connected edges (up to ~85% of all possible edges) and a small number of hypo-connected edges. This number decreased significantly from baseline to the second assessment (from more than 75% to ~25% of all possible connections), potentially due to neural maturation and elimination of redundant connections. No substantial topological differences were estimated between the two groups at those ages. At 42 months, an even lower number of hyper-connected edges were identified in both groups, asymmetrically clustered in the left hemisphere and primarily in temporo-parietal and parieto-occipital regions in the gamma and beta

networks, but less consistently (in space) in other networks. For some oscillations, a small number of hypo-connected edges were also identified. Finally, at 96 months, more consistent topologies were identified in both groups: a) a hyper-connected gamma network with aberrant connections between bilateral parietal and occipital regions; b) relatively larger hypo-connected beta and alpha networks with aberrant connections primarily between left and right temporal regions, left temporal and bilateral frontal and occipital regions.

3. Network topologies and parameters at 42 and 96 months

To validate the findings of the above threshold-based analysis and include appropriate adjustments for potential confounders, all 3 groups were explicitly compared at 42 and 96 months using statistical models. Statistically distinct networks based on the models are shown in Figure 3. No significant gender effects were found in any parameter at any age ($p \geq 0.40$).

3a. Network connectivity

i) Forty-two months: Although the above threshold-based analysis identified statistically distinct edges between the NIG and both the CAUG and FCG, when adjusted for birth weight or head circumference at that age in the models, no statistically distinct edges were identified between the 3 groups. The effect of age at foster care placement was found to be significant for right fronto-central (F4, C4) and centro-parietal (C4, P4) regions in the gamma networks, with statistically higher connections in the CAUG followed by the FCG and the NIG ($p = 0.007$, Wald statistic = 7.74 for group, $p = 0.006$, Wald statistic = 7.63 for age at foster care placement). Connectivity between occipital regions was also statistically higher in the CAUG followed by the FCG and the NIG and in the alpha and theta networks ($p = 0.013$, Wald statistic = 6.39 for group, $p = 0.027$, Wald statistic = 5.04 for age at foster care placement in the alpha network, and $p = 0.030$, Wald statistic = 4.87 for group, $p = 0.047$, Wald statistic = 4.07 for foster care placement in the theta network).

ii) <u>Ninety-six months:</u> The majority of aberrantly connected edges identified by the threshold-based analysis were also found to be distinct in the 3 groups through the statistical models. For oscillations in the gamma to theta ranges, statistically distinct sub-networks/edges and corresponding brain regions are summarized in Table 1. Related model statistics for these edges and sub-networks are summarized in Table S3. Adjustments for birth weight and age at foster care placement were non-significant in all models ($p>0.17$ for birth weight and $p>0.06$ for age at placement). Similarly, the adjustment for head circumference was non-significant for all models for gamma connectivity ($p>0.2$), all models for beta connectivity with the exception of the (F3, T7) connectivity ($p=0.047$) and marginally for the (F4, T7) connectivity ($p = 0.056$), all models for alpha connectivity with the exception of the (P3, Pz), (P4, Pz) and (T7, 02) connectivities ($p = 0.028$, $p = 0.019$ and $p = 0.030$ respectively), and all models for theta with the exception of the (P3, P4) connectivity ($p = 0.020$ for theta). Median mutual information for each group is shown in column 2.

Within the *<u>gamma network</u>*, the parieto-occipital sub-network (P3, Pz, P4, O1, O2 and averaged connectivity in this subnetwork) was found to be statistically distinct in the 3 groups with highest connectivity in the CAUG followed by FCG. Elements of this subnetwork were also hyper-connected across frequency ranges. In the *<u>beta network</u>*, the left temporal region (T7) in the CAUG and FCG was statistically hypo-connected to several other brain regions, including bilateral frontal (F3, Fz, F4), right temporal (T8), bilateral parietal (P3, Pz, P4), bilateral occipital (O1, O2) and right central (C4). These connectivities, as well as averaged connectivity in the corresponding subnetwork were distinct in the 3 groups, with statistically lowest values in the CAUG. We examined the raw signal from electrode T7 across subjects to ensure that the observed laterality of these aberrant connectivities was not associated with artifacts or noise. No significant signal variance differences were found between groups or subjects. All hypo-connections from the beta network were also found to be distinct between groups in the *<u>alpha network</u>*, with the exception of bilateral frontal, bilateral temporal and the right central – left temporal connections. Averaged connectivity in this subnetwork was also

found to be statistically lowest in the CAUG. In the *theta network*, fronto-parietal (Fz, Pz), bilateral centro-parietal (C3, P3) and (C4, P4), and most edges of the aberrant gamma subnetwork were statistically distinct between groups, with highest connectivities in the CAUG followed by the FCG. Also, elements of the hypo-connected beta subnetwork were distinct in the 3 groups, with lowest connectivities in the CAUG. Finally, centro-parietal connections in the theta network were also found to be statistically distinct between groups in the *delta network,* with highest connectivities in the CAUG.

3b. Node centrality

A few nodes with statistically distinct *connectedness* across the 3 groups were found both at 42 and 96 months and are summarized in Tables 1 (96 months) and S4 (both ages). At 42 months, these included T7 in the gamma network; Fz, T7 and T8 in the beta network; Pz in the alpha network; and Fz and Pz in the theta network. At 96 months, Pz had the highest connectedness in all networks except delta, similarly for C3, C4 and P4 but only in the beta and alpha networks and Fz in the theta network. T7 had the lowest connectedness in the beta and alpha networks. We examined the raw signals in electrode Pz across subjects to ensure that increased connectedness was not due to spurious correlations between signals. No significant signal differences were found between this and other electrodes. Birth weight, head circumference and age at foster care placement all had a non-significant effects ($p > 0.08$ for birth weight, $p > 0.13$ for head circumference and $p > 0.05$ for age at foster care placement).

A subset of nodes with distinct connectedness among groups also had distinct *node strengths* but only at 96 months. The statistics of corresponding models are summarized in Table S5. Similarly to connectedness, node Pz had statistically higher strength in the CAUG in the gamma, beta and alpha networks and node T7 the lowest strength in the beta to delta networks. Nodes F3, F4, Fz, and T7 all had the lowest strengths in the CAUG followed by the FCG in the beta network. Finally, P4 was also found to have statistically distinct

strength in the 3 groups both in the alpha and theta networks, with highest strength in the CAUG. Birth weight and age at foster care placement had non-significant effects in all networks and nodes ($p \geq 0.09$ for both), and head circumference also had a non-significant effect ($p \geq 0.08$) except for node P4 in the alpha network ($p = 0.016$). The spatial distribution of all nodes with distinct strengths in gamma, beta, alpha and theta networks is shown in Figure 4. In addition to edges that were distinct between groups (those of Figure 3), edges that exceeded the median (over subjects) NIG connectivity but were not significantly different between groups are also superimposed (dashed lines). Independently of significance, a higher number of connections were estimated in the CAUG followed by FCG across oscillations. In summary, a few nodes in previously identified distinct subnetworks among groups were found to be either aberrant hubs or to have abnormally low centrality in the CAUG and FCG, suggesting additional topological differences between these groups.

4. Network parameter trajectories from 42 to 96 months

All previous analyses investigated network properties at individual assessment ages. To assess the impact of early neglect on the development of these networks, we also investigated the age-related changes in estimated parameters from 42 to 96 months using appropriate statistical models for repeated measures.

4a. Connectivity trajectories

For each oscillation, the changes in all network edges were estimated and compared between groups, using mixed effects regression models that included time (age), group and birth weight or head circumference (and/or age at foster care placement) as independent variables and pairwise MI as the dependent connectivity variable. The statistics of these models for edges that were distinct between groups are summarized in Table S6a. The effect of time (age) was significant in all these models ($p \leq 0.01$). Birth weight, and head circumference had non-significant effects in all models ($p > 0.17$ for birth weight, $p > 0.26$ for circumference). A small number of network connections had distinct age-related changes across groups, including (P3, Pz) and

(P4, O2) across oscillations except delta, and (C3, P3), (P3, O2), (P4, O1) and (Pz, O2) in the gamma network. Note that with the exception of (C3, P3) these edges were also found to be distinct at 96 months and were part of the parieto-occipital hyper-connected subnetwork in the CAUG and FCG compared to NIG.

4b. Node centrality

With the exception of node P3 in the gamma network with marginally significant age-related changes across groups ($p = 0.053$, Wald statistic = 3.77) no other node strength changed significantly from 42 to 96 months. However, connectedness in nodes P4 and Pz in the alpha and theta networks changed in a statistically distinct way across groups. Both nodes belong to the subset of nodes with distinct connectedness at 96 months in the 3 groups (Pz also had statistically distinct connectedness at 42 months; see Table S6b). Birth weight and head circumference had non-significant effects ($p > 0.21$ for birth weight, $p > 0.05$ for head circumference). These results suggest that at least elements (nodes and edges) of task-independent networks develop abnormally as a function of age in children reared in institutions, resulting in significant differences at 96 months.

Discussion

In this paper we report the impact of early psychosocial deprivation associated with institutionalization on the topologies and age-related dynamics of frequency (oscillation)-specific, task-independent brain networks in three groups of children from the BEIP. To investigate these topologies, we have used multiple statistical modeling approaches and network measures. Our present findings extend previous work (Stamoulis et al, 2015), which has shown that early institutionalization has profound and widespread effects on broadband neural activity.

In children reared in institutions and thus subjected to early neglect, this study has identified two aberrantly connected networks, particularly at 96 months: 1) the *aberrantly hyper-connected parieto-occipital gamma network* in the CAUG and FCG, both with statistically higher connectivity than the NIG, but also with distinctly different connectivity from each other. Elements of this subnetwork were also aberrantly hyper-connected at lower frequencies (beta, alpha and theta networks); 2) the *hypo-connected fronto-temporal network* at frequencies below the gamma range (beta to delta) in the CAUG and FCG compared to NIG at 96 months, but also distinctly different from each other. Although the adverse effects of early stressors on neural maturation and the development of human brain networks remain elusive, there is substantial evidence that brain development is significantly impacted by early experiences (Nelson et al, 2006). Therefore, negative experiences may significantly and differentially affect the maturation of the brain's neural circuitry, impairing both selective connection strengthening (leading to hypo-connected networks), and/or connection pruning (leading to networks that appear aberrantly hyper-connected at the macroscale). Both types of aberrant networks may prevent efficient neural information processing.

It is important to note the statistically lower connectivity in the FCG (although still statistically higher than NIG) compared to CAUG in the parieto-occipital network, suggesting a positive effect of the foster care

intervention in lowering aberrant hyper-connectivity. Previous work has shown that this network is synchronized in the gamma band during visual processing (Helfrich et al, 2014). Abnormally high connectivity may imply reduced flexibility of this network to modulate its activity during visual task performance. In fMRI studies, elements of this network have been previously identified as major cortical hubs (Tomasi et al., 2011). Here, parietal nodes, which may overlap with this network, were found to be aberrant hubs at multiple frequencies, with abnormally high connectivities in the CAUG and FCG compared to the NIG. These regions are involved in a wide range of cognitive processes. For example, parietal regions are often activated during episodic memory retrieval (Cabeza, et al 2008) and are involved in self-projection (Buckner et al., 2007) as well as visuo-spatial processing (Tosoni et al, 2014). Furthermore, spatial attention has been shown to modulate the coordination between parietal and occipital regions during top-down processing of spatial attention information (Lauritzen et al., 2009). Thus, abnormally high task-independent connectivity between these areas may adversely impact these cognitive processes.

Although elements of the hyper-connected parieto-occipital network had distinct connectivities in the 3 groups across frequencies, the largest number of aberrant edges in this subnetwork was estimated in the gamma frequency range. Gamma synchrony in parietal regions has been associated with visuo-motor learning and object representation (e.g., Bertrand et al., 2000; Perfetti et al., 2001; Galletti et al., 2003; Tallon-Baudry, 2009). Previous studies have shown that children reared in institutions have decreased performance on tests of visual memory and attention (Bos et al., 2009; Pollack et al, 2010; Bick et al., in press), which may be explained by decreased flexibility in the underlying neural circuitry. At lower frequencies, particularly the theta and delta ranges, fronto-parietal regions, which appeared to be aberrantly hyper-connected in the CAUG and FCG, have been shown to be part of a network that is characterized by spontaneous low-frequency activity and is anti-correlated with the DMN (Fox et al., 2005; Konrad et al., 2010), which implies that it should be weakly correlated at rest, in contrast to the DMN. Although neuronal networks identified in this study with

low spatial resolution-EEG are not directly comparable with high-resolution fMRI networks, similar anti-correlations between task-dependent and task-independent networks may be measurable by both modalities. Therefore, aberrantly high task-independent connectivity in the identified parieto-occipital network may prevent suppression of its resting activity and inhibit its functional activation.

The second major finding of this study is the *hypo-connected fronto-temporal network* at frequencies below the gamma range (beta to delta) in the CAUG and FCG compared to NIG at 96 months. Several elements of this network may overlap with previously identified task-independent networks, e.g., the resting-state auditory-phonological and visual networks reported by Mantini et al. (2007). Left middle and transverse temporal regions, covered by electrode T7, were found to be significantly hypo-connected with bilateral frontal (F3, Fz, F4), bilateral occipital (O1, O2) and right temporal (T8) regions. This node was also found to have statistically lower important (centrality) in the network in the CAUG and FCG. Left temporal regions are associated with hearing, language processing and memory. The parietal-temporal-occipital association area is responsible for integrating visual and auditory information and is involved in language comprehension. Left fronto-temporal connectivity has also been shown to be an essential network involved in syntactic processing (Tyler et al, 2011; Papoutsi et al, 2011). Note that spatially-averaged connectivity in the left hemisphere was also found to be distinct in the 3 groups at 96 months, in the beta and theta networks. Again, our findings may tap an underlying aberrant network associated with the behavioral evidence of impaired language development as a result of early institutionalization. It is important to note the distinct connectivity in this subnetwork in the CAUG and FCG, suggesting a positive effect of the foster care intervention in increasing connectivity in this subnetwork. Thus, this change could be associated with the observed improvements in language learning as a result of the foster care intervention and age of that intervention (Croft et al., 2007; Windsor et al, 2011, 2013). A previous study of structural brain connectivity in the BEIP cohort (Bick et al, 2015) has shown impaired integrity of the corpus callosum in children reared in institutions, which would in part explain lower inter-

503 hemispheric connectivity between temporal regions in the CAUG and FCG.

504

505 Although all network analyses in this study have consistently identified both the hyper-connected parieto-
506 occipital network and the hypo-connected primarily left temporal network across several frequency bands at
507 96 months, corresponding findings at 42 months were less clear. A few elements of the parieto-occipital
508 subnetwork with aberrant characteristics at 42 months remained atypically connected at 96 months, with
509 distinct properties in the 3 groups. The dynamic trajectories of part of this subnetwork were also distinct
510 among groups, potentially due to differential neural maturation rates. It is possible that additional network
511 differences were difficult to detect at 42 months due to incomplete and heterogeneous maturation of task-
512 independent networks at this age, which could make it more difficult to detect connectivity group differences.

513

514 Finally, the frequency specificity of our findings varied between networks (e.g., a larger hyper-connected
515 network in the gamma range compared to lower frequencies). Although higher-frequency networks imply
516 spatially localized processing, lower-frequency oscillations facilitate the communication (or binding) between
517 these networks. The presence of smaller numbers of aberrant connections at lower frequencies could in part be
518 due to impaired binding between high- and lower-frequency oscillations within corresponding networks. Our
519 previous work has shown decreased coupling between task-independent gamma and lower-frequency
520 oscillations, which could in part explain these findings (Stamoulis et al., 2015). Furthermore, substantial
521 topological overlap between aberrantly hypo-connected edges were observed in the alpha and beta networks.
522 Significant correlations between alpha and beta oscillations have been reported in task-independent EEGs,
523 which may explain the topological similarities between the two networks (Carlqvist et al., 2005).

524

525 Despite its many methodological strengths (including its randomized control trial design), this study is not
526 without limitations, including its relatively small sample size. Nevertheless, data from multiple time points

were included in parts of the statistical analysis, and multiple statistical models were developed to compare the cohorts, all yielding consistent results, which supports the robustness of the findings. It is, however, possible that smaller network-level differences between groups were not detectable in this sample. Second, a small number of electrodes was used to record brain activity, which prevented appropriate source-level analyses to explicitly address the issue of volume conduction. However, information-based measures of connectivity were used in this study, which have been previously been shown to be relatively robust to volume conduction. Also, the low spatial resolution of the EEG limits the estimation of detailed network topologies possible by other modalities, particularly fMRI. Despite these limitations, to the best of our knowledge, this study provides the first evidence of multiple, significantly impacted and aberrantly connected task-independent brain networks in children who have experienced severe psychosocial deprivation. Considering these networks' potential involvement in cognitive processing, including memory, visuo-motor learning, visual processing, social communication and language, these findings suggest that early psychosocial neglect associated with institutionalization may have profound adverse effects on the brain's wiring and communication, which may not be fully reversible, at least not within a few years from the intervention. Nevertheless, statistical differences between the CAUG and FCG also suggest significant positive effects of foster care on improving neural information processing facilitated by these networks.

Funding

This study was supported in part by NIH Grant R01MH091363 (Nelson) and NSF BRAIN EAGER Grant 1451480 (Stamoulis).

References

[1] Andreou, C, Nolter, G, Leight, G, Polomac, N, Hanganu-Opatz IL, Lambert, M, Engel, AK, Mulert, C (2015), Increased Resting-State Gamma-Band Connectivity in First-Episode Schizophrenia, *Schizophr Bull*, 41(4):930-939.

[2] Bauer PM, Hanson JL, Pierson RK, Davidson RJ, Pollak SD (2009) Cerebellar volume and cognitive functioning in children who experienced early deprivation, *Biol Psychiatry* 66: 1100–1106.

[3] Barttfeld, P, Uhrig, L, Sitt, JD, Sigman, M, Jarraya, B, Dehane, S (2015), Signature of consciousness in the dynamics of resting-state activity, *Proc Nat Acad Sci* , 112(3): 887-892.

[4] Bertrand, O, Tallon-Baudry, C (2000) Oscillatory gamma activity in humans: a possible role for object representation, *Int J Psychophysiol*, 38(3): 211-223.

[5] Bick, J., Zhu, T., Stamoulis, C., Fox, NA, Zeanah, C., Nelson, CA (2015), Effect of Early Institutionalization and Foster Care on Long-term White Matter Development: A Randomized Clinical Trial, *JAMA Pediatr*, 169(3): 211-9.

[6] Bick, J, Zeanah CH, Fox NA, & Nelson CA (in press). Memory and executive functioning in 12-Year-Old children with histories of institutional rearing. *Child Development*.

[7] Bluhm, RL, Miller, J, Lanius, RA, Osuch, EA, Boksman, EA (2007), Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenia patients: anomalies in the default networks, Schizophr. Bull.,

571 33: 1004-1012.
572
573 [8] Bos, K, Zeanah, CH, Fox, NA, Drury, SS, McLaughlin, KA, Nelson CA (2011), Psychiatric Outcomes in
574 Young Children with a History of Institutionalization, *Harv Rev Psychiatry,* 19(1): 15–24.
575
576 [9] Bos K, Fox NA, Zeanah CH, & Nelson CA (2009), Effects of early psychosocial deprivation on the
577 development of memory and executive function. *Frontiers in Behavioral Neuroscience*, 3:16.
578
579 [10] Buckner, RL, Carroll, DC (2007), Self-projection and the brain, *Trends Cogn Sci,* 11: 49-57.
580
581 [11] Buckner, RL, Andrews-Hanna, JR, Schachter, DL (2008), The brain's default network: anatomy, function,
582 and relevance to disease, Ann NY Acad Sci, 1124: 1-38.
583
584 [12] Bullmore, E., Sporns, O (2009), Complex brain networks: graph theoretical analysis of structural and
585 functional systems, *Nat Rev Neurosci*, 10(3):186-98.
586
587 [13] Carey, PD, Warwick, J, Niehaus, DJ, van der Linden, G, van Heerden, BB, Harvey, BH, Seedat, S., Stein,
588 DJ (2004), Single photon emission computed tomography (SPECT) of anxiety disorders before and after
589 treatment with citalopram. BMC Psychiatry 4, 30.
590
591 [14] Cabeza, R, Ciaramelli, E, Olson, IR, Moscovitch, M (2008), Parietal cortex and episodic memory: an
592 attentional account, *Nat Rev Neurosci*, 9(8): 613-625.
593
594 [15] Calqvist, H, Nikulin, VV, Stromberg, JO, Brismar, T (2005), Amplitude and phase relationship between

595 alpha and beta oscillations in the human electroencephalogram, *Med Biol Eng Comput*, 43(5):599-607.
596
597 [16] Chella, F, Pizzella, V, Zappasodi, F, Marzetti, L (2016), Impact of the reference choice on scalp EEG
598 connectivity estimation, *J Neural Eng,* 13: 1-21.
599
600 [17] Chugani HT, Behen ME, Muzik O, Juhasz C, Nagy F, et al. (2001) Local brain functional activity
601 following early deprivation: A study of post-institutionalized Romanian orphans. *NeuroImage* 14: 1290–1301.
602
603 [18] Croft, C, Beckett C, Rutter M, Castle J, Colvert E, Groothues C, et al (2007). Early adolescent outcomes
604 of institutionally deprived and non-deprived adoptees. II: Language as a protective factor and a vulnerable
605 outcome. *J Child Psychol Psychiatry*, 48:31–44.
606
607 [19] Courchesne, E., Pierce, K (2005), Why the frontal cortex in autism might be talking only to itself: local
608 over-connectivity but long-distance disconnection, *Curr Op Neurobiol,* 15: 225-230.
609
610 [20] Dien, J (1998), Issues in the application ofthe average reference: Review, critiques, and
611 recommendations, *Behavior Research Methods. Instruments. & Computers,* 30 (l). 34-43.
612
613 [21] Dosenbach, NU, Fair, DA, Cohen, AL, Schlaggar, BL, Petersen, SE (2008), A dual-networks architecture
614 of top-down control, *Trends Cogn Sci*, 12(3): 99–105
615
616 [22] Efron, B, Tibshirani, R (1993), An introduction to the bootstrap, New York: Chapman and Hall
617
618 [23] Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE,

619 Schlaggar BL (2008), The maturing architecture of the brain's default network. *Proc Natl Acad Sci USA*
620 105:4028–4032.
621
622 [24] Fox, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is
623 intrinsically organized into dynamic, anti-correlated functional networks. *Proc Natl Acad Sci* USA 102:9673–
624 9678.
625
626 [25] Fransson, P, Sklold, B, Horsh, S, Nordell, A, Blennow, M, Lagercrantz, H, Aden, U (2007) , Resting-
627 state networks in the infant brain, *Proc Nat Acad Sci*, 104(39): 15531–15536.
628
629 [26] Galletti, C, Kutz, DF, Gamberini, M, Breveglieri, R, Fattori, P (2003), P, Role of the medial parieto-
630 occipital cortex in the control of reaching and grasping movements, *Exp Brain Res* 153(2):158-170.
631
632 [27] Gelman, A, Hill, J, Yajima, M (2012), Why we (usually) don't have to worry about multiple comparisons,
633 J Res Educ Eff, 5: 189-211.
634
635 [28] Gentili, C., Ricciardi, E., Gobbini, MI., Santarelli, MF., Haxby, JV., Pietrini, P., Guazzelli, M (2009),
636 Beyond amygdala: Default Mode Network activity differs between patients with social phobia and healthy
637 controls. *Brain Res. Bull*. 79: 409–413
638
639 [29] Greicius, MD, Krasnow, B, Reiss, AL, Menon, V (2003), Functional connectivity in the resting brain: A
640 network analysis of the default mode hypothesis, *Proc Natl Acad Sci* (100): 253-258.
641
642 [30] Greicius, MD, Flores, BH, Menon, V, Glover, GH, Solvason, HB, Kenna, H, Reiss, AL, Schatzberg, AF

643 (2007), Resting-state functional connectivity in major depression: abnormally increased contributions from
644 subgenual cingulate cortex and thalamus, *Biol Psychiatry*, 62(5): 429-437.
645
646 [31] Greicius, MD, Supekar, K, Menon, V, Dougherty, RF (2009), Resting-state functional connectivity
647 reflects structural connectivity in the default mode network, *Cerebr Cort* 19: 72-78.
648
649 [32] Helfrich RF, Knepper H, Nolte G, Strüber D, Rach S, (2014) Selective modulation of inter-hemispheric
650 functional connectivity by HD-tACS shapes perception. *PLoS Biol 12*: e1002031
651
652 [33] Huang, NE, Shen, Z, Long, SR, Wu, MC, Shih, HH, Zheng, Q, Yen, NC, Tung, CC, Liu, HH (1998)
653 The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series
654 analysis, *Proc Royal Soc A,* 454 (1971): 903–995.
655
656 [34] Kelly, C, Uddin, LQ, Biswal, BB, Castellanos, FX, Milham, MP (2008), Competition between functional
657 brain networks mediates behavioral variability, *Neuroimage*, (39): 527-537.
658
659 [35] Kennedy, DP, Courchesne, E (2008) Failing to deactivate: resting functional abnormalities in autism, *Proc*
660 *Natl Acad Sci*, 103: 8275-8280.
661
662 [35] Konrad, K, Eickhoff, SB (2010) Is the ADHD Brain Wired Differently? A Review on Structural and
663 Functional Connectivity in Attention Deficit Hyperactivity Disorder, *Hum Brain Mapp*, 31(6):904-16.
664
665 [36] Levin, AR, Fox, NA, Zeanah, CH, Nelson CA (2015), Social communication difficulties and autism in
666 previously institutionalized children, *J Am Acad Child Adolesc Psychiatry*, 54(2): 108-115.
667

668 [37] Lauriten, TZ, D'Esposito, M, Heeger, DJ, Solver, MA, Top-down flow of visual spatial attention signals
669 from parietal to occipital, Journal of Vision 9(13): 1-14.
670
671 [38] Liao, W, Chen, H, Feng, Y, Mantini, D, Gentili, C, Pan, Z, Ding J, Duan, X, Qiu, C, Liu, S, Gong, Q,
672 Zhang, W (2010) Selective aberrant functional connectivity of resting state networks in social anxiety
673 disorder, *Neuroimage*, 52: 1549–1558.
674
675 [39] Marshall, PJ, Reeb, BC, Fox, NA, Nelson CA, Zeanah CH (2008) Effects of early intervention of EEG
676 power and coherence in previously institutionalized children in Romania, *Dev Psychopathol.*, 20(3):861-80.
677
678 [40] Marshall PJ, Fox NA and Bucharest Early Intervention Project Core Group, A comparison of the
679 electroencephalogram between institutionalized and community children in Romania (2004), *J Cogn*
680 *Neurosci*., 16(8):1327-38.
681
682 [41] McLaughlin, KA, Fox, NA, Zeanah, CH, Sheridan MA, Marshall, P, Nelson CA (2010), Delayed
683 maturation in brain electrical activity partially explains the association between early environmental
684 deprivation and symptoms of attention-deficit/hyper-activity disorders, *Biol Psychiatry*, 15:68(4): 239-336.
685
686 [42] McLaughlin, KA, Fox, NA, Zeanah, CH, Sheridan MA, Nelson CA (2011) Adverse rearing environments
687 and neural development in children: the development of frontal electroencephalogram asymmetry, *Biol*
688 *Psychiatry,* 70:1008-1015
689
690 [43] Nelson, CA, Fox, Na, Zeanah, CH (2014), Romania's abandoned children: Deprivation, brain
691 development and the struggle for recovery, Cambridge, MA, Harvard University Press.

692

693 [44] Nelson, CA, de Haan, M, Thomas, KM (2006), Neuroscience of Cognitive Development: The Role of
694 Experience and the Developing Brain, Wiley, NY.

695

696 [45] Nickl-Jockschat, Rottschy, C, Thommes, J, Schneider, F, Laird, AR, Fox, PT, Eickhoff, SB (2015), Neural
697 networks related to dysfunctional face processing in autism spectrum disorder, *Brain Struct Func*, 220(4):
698 2355-237

699

700 [46] Northam, GB, Liegeois, F, Tournier, JD, Croft, LJ, Johns, PN, Ching ,WK, Wyatt, JS, Baldeweg, T
701 (2012), Inter-hemispheric temporal lobe connectivity predicts language impairment in adolescents born
702 preterm, *Brain,* 135(Pt 12):3781-3798.

703

704 [47] Palus, M, Komarek, V, Prochazka, T, Hrncir, Z, Sterbova, K (2001), *IEEE Eng. Med. Biol. Mag*,
705 20(5):65-71.

706

707 [48] Papoutsi, M, Stamatakis, EA, Griffiths, J, Marslen-Wilson WD, Tyler, LK(2011) Is left fronto-temporal
708 connectivity essential for syntax? Effective connectivity, tractography and performance in left-hemisphere
709 damaged patients, *Neuroimage,* 58(2):656-64

710

711 [49] Perfetti, B, Moisello, C, Landsnesors, EC, Kvint, S, Lanzafame, S, Onofri, M, Di Rocco, A, Tononi, G,
712 Ghilardi, MF (2011), Modulation of gamma and theta spectral amplitude and phase synchronization is
713 associated with the development of visuo-motor learning, *J Neurosci,* 31(41): 14810-14819.

714

715 [50] Pollack, S, Nelson, CA, Schlaak, MF, Roeber, BJ, Wewerka, SS, Wilk, KL, Frenn, KA, Loman, MM,

716 Gunnar, MR, Neurodevelopmental effects of early deprivation in post-institutionalized children, Child Dev
717 81(1): 224- 236.
718
719 [51] Raichle, ME, MacLeod, AM, Snyder, AZ, Powers,WJ, Gusnard, DA, Shulman, GL (2001), A default
720 mode of brain function. *Proc Natl Acad Sci,* (98):676–682.
721
722 [52] Raichle, ME., Snyder, AZ (2007), A default mode of brain function: a brief history of an evolving idea,
723 *NeuroImage* 237:1083–1090.
724
725 [53] Schreiber, T (2000), Measuring information transfer, *Phys. Rev. Lett.,* 85(2):461-464.
726
727 [54] Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA (2012), Variation in neural
728 development as a result of exposure to institutionalization early in childhood, *Proc Nat Acad Sci*,
729 109(32):12927-32.
730
731 [54] Stamoulis, C, Chang, BS (2009)., Application of matched-filtering to extract EEG features and decouple
732 signal contributions from multiple seizure foci in brain malformations, *IEEE Proc 4th International*
733 *IEEE/EBMS Conf Neural Eng*, 514-517.
734
735 [55] Stamoulis, C**.,** Betensky, RA (2011), A novel signal processing approach for the detection of copy-number
736 variations in the human genome, *Bionformatics,* 27(17):2338-2345.
737
738 [55] Stamoulis, C., Schomer, D.L., Chang, B.S (2013), Information theoretic measures of network
739 coordination in high-frequency scalp EEG reveal dynamic patterns associated with seizure termination,

Epilepsy Res. 105(3):299-315.

[56] Stamoulis, C., Vanderwert, RE, Zeanah, CH, Fox, NA, Nelson, CA (2015), Early psychosocial deprivation adversely impacts developmental trajectories of brain rhythms and their interactions, *J Cogn Neurosci,* 27(12): 2512-2528.

[57] Stamoulis, C, Vogel-Farley, V. Degregorio, G., Jeste, SS., Nelson, C.A (2014), Resting and Task-Modulated High-Frequency Brain Rhythms Measured by Scalp Encephalograms in Infants with Tuberous Sclerosis Complex, J Autism Develop Disord, 45(2):336-532014.

[58] Tallon-Baudry, C (2009), The roles of gamma-band oscillatory synchrony in human visual cognition *Front Biosci,* 14: 321-332.

[59] Tomasi, D, Volkow, ND (2011), Association between functional connectivity hubs and brain networks, *Cereb Cortex*, 21(9): 2003-2013.

[60] Tononi, J., Sporns, O., Edelman, GM (1994), A measure for brain complexity: Relating functional segregation and integration in the nervous system, *Proc Natl Acad Sci* (91): 5033-5037.

[61] Tosoni, A, Pitzalis, S, Committeri, G, Fattori, P, Galletti, C, Galati, G (2015), Resting-state connectivity and functional specialization in human medial parieto-occipital cortex*, Brain Struct Func,* 220(6): 3307-3321.

[62] Tottenham, N, Hare, TA, Millner, A, Gilhooly, T, Zevin, JD, Casey, BJ (2011), Elevated amygdala response to faces following early deprivation, *Dev Sci*, 14(2): 190-204.

[63] Tukey, JW (1977) Exploratory data analysis, Addison-Wesley.

[64] Tyler, LK, Marslen-Wilson, WD, Randall, B, Devereaux, BJ, Zhuand, J, Papoutsi, M, Stamatakis, EA (2011) Left inferior frontal cortex and syntax: function, structure and behavior in patients with left hemisphere damage, *Brain,* 134(Pt 2):415-31.

[65] Vanderwert RE, Marshall PJ, Nelson CA 3rd, Zeanah CH, Fox NA (2010), Timing of Intervention Effects Affects Brain Electrical Activity in Children Exposed to Severe Psychosocial Neglect, PloS One, 5(7): e11415.

[66] Vejmelka, M, Palus, M (2008), Inferring the directionality of coupling with conditional mutual information, *Phys. Rev. E*, 77:026214.

[67] Vicente, R., Wibral M., Lindner M., Pipa G. (2011). Transfer entropy–a model-free measure of effective connectivity for the neurosciences. *J. Comput. Neurosci*. 30, 45–67.

[68] Vincent, JL, Snyder, AZ, Fox, MD, Shannon, BJ, Andrews, JR, Raichle, ME, Buckner, RL (2006), Coherent spontaneous activity identifies a hippocampal–parietal memory network. J. *Neurophysiol,* 96, 3517–3531

[69] Ward, AM, Schultz, AP, Huijbers, W, Van Dijk, KR, Hedden, T, Sperling, RA (2014), The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system, *Hum Brain Mapp*, 35(3): 1061-1073.

[70] Warwick, JM, Carey, P, Jordaan, GP, Dupont, P, Stein, DJ (2008), Resting brain perfusion in social anxiety disorder: a voxel-wise whole brain comparison with healthy control subjects. Prog. *Neuropsychopharmacol. Biol. Psychiatry* 32: 1251–1256.

[71] Widom CS, DuMont K, Czaja SJ (2007). A prospective investigation of major depressive disorder and co-morbidity in abused and neglected children grown up. *Arch Gen Psychiatry,* 64:49–56.

[72] Windsor J, Benigno JP, Wing CA, Carroll PJ, Koga SF, Nelson CA 3rd, Fox NA, Zeanah CH (2011), Effects of foster care on young children's language learning, *Child Dev*, 82(4):1040-6.

[73] Windsor, J, Morary, A, Nelson, CA, Fox, NA, Zeanah, CH (2013), Effect of foster care on language learning at eight years: findings from the Bucharest Early Intervention Project, *J Child Lang,* 40(3):605-27.

[74] Wu, Z, Huang, N (2009), Ensemble Empirical Mode Decomposition: A Noise Assisted Data Analysis Method, Advances in Adaptive Data Analysis, 1-41, World Scientific Publishing Company.

[75] Zeanah, CH, Nelson CA, Fox NA, Smyke, AT, Marshall, PJ, Parker, SW, Koga, S (2003) Designing research to study the effects on institutionalization on brain and behavioral development: The Bucharest Early Intervention Project, *Dev Psychopathol*, 15:885-907.

Tables

	Edge Connectivity		Node Centrality	
Oscillation/Network	**Hyper-connected**	**Hypo-connected**	**Highest**	**Lowest**
Gamma-range (52.0-57.0 Hz)	**Regions:** Parietal; Parieto-occipital	–	Pz	
	Edges: P3-Pz; P4-O1, O2; Pz-O1,O2			
Beta-range (20.0-23.0 Hz)	**Regions:** Parietal	**Regions:** Left temporal; Bilateral frontal; Parietal; Occipital	Pz, C3, C4, P4	T7, F3, F4, Fz
	Edges: P3-Pz	**Edges:** T7-F3, Fz, F4, C4, P3, Pz,P4, O1, O2; F3-F4; T7-T8		
Alpha-range (8.0-10.0 Hz)	**Regions:** Parietal; Parieto-occipital	**Regions:** Left temporal; Bilateral frontal; Parietal; Occipital	Pz, C3, C4, P4	T7
	Edges: P3-Pz, P4-Pz, P4-O2	**Edges:** T7-F3, Fz,F4, C4, P3, Pz,P4, O1, O2		
Theta-range (3.6-4.3 Hz)	**Regions:** Midline; Centro-parietal; Parietal; Parieto-occipital	**Regions:** Left, bilateral temporal; Bilateral Centro-parietal; Parietal; Occipital	Pz, Fz, C3, C4, P4	T7
	Edges: Fz-Pz, C3-P3, C3-P4, O1-O2, P3-P4, P4-O1, P4-O2, P3-Pz	**Edges:** Fz-T7, Pz; C3-P3, C4-P4, P3-Pz, P4; P4-O1,O2; T7-T8; O1-O2		

Table 1: Summary of aberrantly connected and statistically distinct network elements (edges and nodes) in the three groups. For each oscillation frequency range, hyper- and hypo-connected brain regions and sets of network edges as well as aberrantly connected nodes (based on their centrality estimated either as node strength or connectedness) are listed.

Figures Legends

Figure 1: Frequency-connectivity (measured by mutual information) plots for all estimated oscillations at baseline (top left panel), and clockwise at ~30-33, 42, and 96 months respectively. At the first 3 time points connectivity was estimated from task-independent EEGs under the lights off recording condition and at 96 months under the eyes-closed condition. The 3 groups are superimposed: Care as Usual group (CAUG, red), Foster Care group (FCG, blue) and Never Institutionalized group (NIG, black). At baseline, and thus prior to randomization, children in the CAUG and FCG were part of the 'Institutionalized' group.

Figure 2: Hyper- and hypo-connected network edges and subnetworks in the CAUG and FCG relative to the NIG, for each estimated oscillation and at each assessment age (baseline to 96 months from left to right). Edges with mutual information (MI) values higher than the upper MI threshold are marked in red, and edges with MI values below the lower MI threshold are marked in green.

Figure 3: Oscillation-specific network edges for which connectivity was statistically distinct in the 3 groups, adjusted for birth weight and head circumference at each age. Left panel plots correspond to the CAUG (red), middle panels to the FCG (blue) and right panels to the NIG (black). Distinct line widths represent differential median (across the group) mutual information values, with thickest lines representing the highest median connectivity among groups and the thinnest lines representing the lowest connectivity.

Figure 4: Network nodes with aberrant strength (centrality) across groups, in the gamma, beta, alpha and theta networks. Larger circles and thicker lines reflect aberrantly and significantly higher node strength and connectivity (edge weight). Dashed lines correspond to edges above the NIG median connectivity threshold, which were not, however, statistically distinct between groups. Colors correspond to individual groups (CAUG - red, FCG - blue and NIG - black).

Supplemental Material

Assessment	Baseline		42 months		96 months	
Group	Median % time; Actual time (months)	(25^{th}, 75^{th}) quartiles	Median time; Actual time (months)	(25^{th}, 75^{th}) quartiles	Median time; Actual time (months)	(25^{th}, 75^{th}) quartiles
CAUG	98.6%	(81.6, 100.0)%	85.0%	(64.4, 97.1)%	53.0%	(36.2, 79.8)%
	19 mo	(16.9, 25.0) mo	35.7 mo	(27.0, 40.8) mo	50.9 mo	(31.2, 67.6) mo
FCG	95.9%	(69.4, 100.0)%	48.9%	(35.0, 61.8) %	23.40%	(18.3, 28.6)%
	18.3 mo	(16.3, 23.0) mo	20.5 mo	(14.7, 26.0) mo	22.5 mo	(15.0, 26.5) mo
NIG	0	0	0	0	0	0

Table S1: Summary statistics of percent time since birth spent in institutions and corresponding time in months, for each group at baseline, 42 and 96 months.

		Care as Usual Group		Foster Care Group		Never-Institutionalized Group	
Age (months)	Band range	Median (Hz)	(25^{th}, 75^{th}) quartiles	Median (Hz)	(25^{th}, 75^{th}) quartiles	Median (Hz)	(25^{th}, 75^{th}) quartiles
Baseline (< 30)	Gamma	51.82	(49.93, 53.65)	50.89	(49.71, 51.82)	49.12	(48.21, 50.35)
	Beta	20.57	(19.27, 21.30)	20.18	(19.58, 20.89)	19.82	(18.87, 20.21)
	Alpha	8.24	(7.85, 8.58)	8.23	(7.96, 8.56)	8.14	(7.87, 8.45)
	Theta	3.55	(3.42, 3.69)	3.61	(3.43, 3.70)	3.61	(3.46, 3.72)
	Delta	1.54	(1.46, 1.59)	1.56	(1.47, 1.61)	1.56	(1.50, 1.61)
30-33	Gamma	50.14	(48.41, 52.47)	51.34	(48.84, 53.69)	50.01	(48.44, 53.24)
	Beta	19.94	(18.79, 21.11)	20.47	(19.39, 21.70)	19.78	(18.55, 21.47)
	Alpha	8.20	(7.73, 8.64)	8.43	(7.92, 8.88)	8.28	(7.86, 8.82)
	Theta	3.60	(3.40, 3.79)	3.66	(3.42, 3.95)	3.64	(3.47, 3.85)
	Delta	1.54	(1.45, 1.63)	1.58	(1.49, 1.72)	1.60	(1.51, 1.64)
42	Gamma	52.96	(50.16, 55.25)	53.55	(50.59, 56.54)	53.14	(48.20, 56.59
	Beta	20.58	(19.46, 22.01)	21.47	(19.70, 22.62)	21.34	(18.56, 22.88)
	Alpha	8.54	(8.13, 9.04)	8.69	(8.30, 9.32)	8.81	(8.17, 9.58)
	Theta	3.71	(3.56, 3.96)	3.82	(3.58, 4.14)	3.90	(3.62, 4.25)
	Delta	1.60	(1.52, 1.70)	1.65	(1.51, 1.80)	1.69	(1.56, 1.83)
96	Gamma	55.54	(53.19, 57.20)	54.34	(52.25, 55.83)	55.10	(53.26, 56.37)
	Beta	20.25	(19.43, 21.16)	20.13	(19.31, 20.86)	19.81	(18.93, 21.08)
	Alpha	8.43	(8.15, 8.76)	8.28	(8.06, 8.63)	8.45	(8.05, 8.82)
	Theta	3.67	(3.56, 3.81)	3.66	(3.53, 3.83)	3.74	(3.60, 3.90)
	Delta	1.61	(1.53, 1.66)	1.58	(1.53, 1.65)	1.61	(1.55, 1.69)

Table S2: Characteristic oscillation frequency summary statistics (medians and (25^{th}, 75^{th}) quartiles) for each group at each assessment age.

894

895

Node pair	Median Mutual Information (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
Gamma Oscillation Connectivity						
(P3, Pz)	0.096, 0.084, 0.073	-0.009	[-0.017, -5E-04]	0.004	0.037	4.44
(P4, O1)	0.024, 0.018, 0.014	-0.005	[-0.009, -3E-04]	0.002	0.038	4.40
(P4, O2)	0.059, 0.048, 0.040	-0.009	[-0.014, -0.003]	0.003	0.002	9.66
(Pz, O1)	0.051, 0.042, 0.036	-0.006	[-0.012, -0.002]	0.003	0.008	7.27
(Pz, O2)	0.053, 0.044, 0.037	-0.007	[-0.012, -0.002]	0.003	0.007	7.58
Network	0.054, 0.048, 0.041	-0.007	[-0.011, -0.003]	0.001	0.002	9.76
Beta Oscillation Connectivity						
(F3, F4)	0.028, 0.034, 0.047	0.005	[2.00E-04, 0.009]	0.002	0.042	4.25
(F3, T7)	0.016, 0.021, 0.031	0.005	[0.002, 0.009]	0.002	0.005	8.32
(F4, T7)	0.005, 0.009, 0.013	0.003	[0.001, 0.005]	0.001	0.002	9.83
(Fz, T7)	0.006, 0.010, 0.015	0.003	[0.001, 0.005]	9.20E-004	0.002	10.02
(C4, T7)	0.003, 0.005, 0.010	0.001	[1.00E-04, 0.003]	6.30E-004	0.030	4.82
(P3, Pz)	0.115, 0.096, 0.080	-0.008	[-0.014, -0.002]	0.003	0.016	5.98
(P3, T7)	0.018, 0.027, 0.035	0.004	[4.00E-04, 0.007]	0.002	0.030	4.86
(T7, T8)	0.008, 0.012, 0.019	0.004	[0.001, 0.007]	0.001	0.004	8.60
(T7, O1)	0.010, 0.017, 0.029	0.005	[0.001, 0.009]	0.002	0.008	7.23

(T7, O2)	0.008, 0.012, 0.022	0.004	[5.00E-04, 0.007]	0.002	0.023	5.36
Network	0.012, 0.016, 0.021	0.003	[5.00E-04, 0.006]	0.001	0.021	5.44
Alpha Oscillation Connectivity						
(F3, T7)	0.038, 0.047, 0.059	0.005	[3.00E-04, 0.009]	0.002	0.036	4.50
(F4, T7)	0.022, 0.028, 0.036	0.004	[3.00E-04, 0.007]	0.002	0.031	4.78
(Fz, T7)	0.021, 0.028, 0.035	0.004	[4.00E-04, 0.007]	0.002	0.029	4.89
(P3, Pz)	0.087, 0.073, 0.063	-0.007	[-0.011, -0.002]	0.002	0.009	6.99
(P4, Pz)	0.076, 0.067, 0.057	-0.005	[-0.010, -3.0E-04]	0.002	0.036	4.52
(P4, O2)	0.070, 0.062, 0.053	-0.005	[-0.009, -0.001]	0.002	0.012	6.56
(T7, O1)	0.026, 0.040, 0.051	0.005	[9.00E-04, 0.009]	0.002	0.018	5.76
(T7, O2)	0.021, 0.027, 0.037	0.005	[0.001, 0.009]	0.002	0.013	6.37
Network	0.022, 0.029, 0.038	0.004	[7.00E-04, 0.007]	0.001	0.017	5.9
Theta Oscillation Connectivity						
(Fz, Pz)	0.011, 0.010, 0.008	-0.001	[-0.0025,-2.0E-04]	5.70E-04	0.024	5.21
(Fz, T7)	0.019, 0.022, 0.027	0.002	[2.0E-04, 0.005]	0.001	0.031	4.80
(C3, P3)	0.047, 0.041, 0.035	-0.004	[-0.008, -3.0E-04]	0.002	0.032	4.71
(C4, P4)	0.046, 0.040, 0.035	-0.003	[-0.006, -2.0E-04]	0.001	0.036	4.53
(P3, P4)	0.059, 0.053, 0.047	-0.003	[-0.006, -3.0E-04]	0.001	0.030	4.80
(P3, Pz)	0.088, 0.081, 0.073	-0.005	[-0.009, -4.0E-04]	0.002	0.032	4.73
(P4, O1)	0.051, 0.043, 0.037	-0.004	[-0.007, -7.0E-04]	0.002	0.016	5.94

(P4, O2)	0.073, 0.063, 0.056	-0.007	[-0.011, -0.002]	0.002	0.003	9.28
(T7, T8)	0.035, 0.041, 0.050	0.004	[4.0E-04, 0.008]	0.002	0.027	4.98
(O1, O2)	0.118, 0.104, 0.097	-0.006	[-0.012, -6.0E-04]	0.003	0.031	4.78
Network	0.048, 0.043, 0.040	-0.002	[0.013, -7.0E-04]	9.0E-04	0.043	4.20

Table S3: Summary of statistics for linear regression models for pairwise connectivities at 96 months as a function of group with an adjustment for birth weight or head circumference at that age. Only the statistics for pairs of nodes with statistically distinct connectivity (edge) among 3 groups are shown, as well as averaged connectivity over the subnetwork defined by these nodes/edge pairs. Median MI values for each group are provided in column 2.

Node	Median Node Centrality (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
42 MONTHS						
Gamma Oscillation Node Connectedness						
T7	0.50, 0.42, 0.17	-0.117	[-0.187, -0.047]	0.035	0.001	10.89
Beta Oscillation Node Connectedness						
Fz	0.50, 0.42, 0.33	-0.086	[-0.153, -0.019]	0.034	0.012	6.41
T7	0.67, 0.50, 0.33	-0.115	[-0.192, -0.039]	0.039	0.003	9.00
T8	0.67, 0.42, 0.17	-0.078	[-0.152, -0.004]	0.038	0.040	4.28
Alpha Oscillation Node Connectedness						
Pz	0.67, 0.50, 0.42	-0.078	[-0.143, -0.014]	0.033	0.018	5.75
Theta Oscillation Node Connectedness						
Fz	0.50, 0.33, 0.25	-0.092	[-0.152, -0.033]	0.030	0.002	9.56
Pz	0.58, 0.50, 0.42	-0.101	[-0.165, -0.037]	0.032	0.002	9.77
96 MONTHS						
Gamma Oscillation Node Connectedness						
Pz	0.50, 0.42, 0.33	-0.080	[-0.149, -0.011]	0.035	0.024	5.23
Beta Oscillation Node Connectedness						
Pz	0.58, 0.5, 0.42	-0.094	[-0.156, -0.033]	0.031	0.003	9.22
T7	0.08, 0.17, 0.25	0.079	[0.016, 0.142]	0.032	0.015	6.09

Alpha Oscillation Node Connectedness						
C3	0.50, 0.33, 0.25	-0.089	[-0.162, -0.016]	0.037	0.017	5.87
C4	0.42, 0.33, 0.17	-0.082	[-0.152, -0.013]	0.035	0.021	5.48
P4	0.50, 0.42, 0.33	-0.068	[-0.134, -0.001]	0.034	0.047	4.00
Pz	0.58, 0.42, 0.33	-0.083	[-0.147, -0.020]	0.032	0.011	6.68
T7	0.17, 0.42, 0.50	0.070	[0.001, 0.140]	0.035	0.048	3.98
Theta Oscillation Node Connectedness						
Fz	0.42, 0.33, 0.25	-0.077	[-0.135, -0.018]	0.030	0.011	6.58
C3	0.50, 0.42, 0.33	-0.085	[-0.158, -0.012]	0.037	0.022	5.32
C4	0.42, 0.33, 0.25	-0.070	[-0.140, -0.001]	0.035	0.047	4.00
P4	0.50, 0.42, 0.33	-0.067	[-0.130, -0.005]	0.032	0.035	4.51
Pz	0.58, 0.50, 0.33	-0.094	[-0.160, -0.030]	0.033	0.005	8.28

Table S4: Summary of statistics for linear regression models node connectedness (centrality based on the total number of connections), for each oscillation network at 42 and 96 months. Only the statistics for the 'group' parameter are shown, for nodes that were statistically distinct in the 3 groups when adjusted for birth weight or head circumference. Median connectedness values for each group are provided in column 2.

Node	Median Node Centrality (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
Gamma Oscillation Node Strength						
Pz	0.1165, 0.1091, 0.1032	-0.004	[-0.008, -7E-04]	0.002	0.048	3.99
Beta Oscillation Node Strength						
F3	0.1019, 0.1037, 0.1056	0.002	[1E-04, 0.004]	0.001	0.034	4.63

F4	0.1005, 0.1024, 0.1047	0.002	[3E-04, 0.004]	0.001	0.019	5.69
Fz	0.1007, 0.1021, 0.1038	0.001	[1E-04, 0.003]	0.001	0.036	4.51
Pz	0.1122, 0.1106, 0.1084	-0.002	[-0.004, -1E-04]	0.001	0.048	3.99
T7	0.0943, 0.0974, 0.1011	0.003	[0.001, 0.005]	0.001	0.002	10.55
Alpha Oscillation Node Strength						
P4	0.1146, 0.1100, 0.1061	-0.002	[-0.003, -1E-04]	0.001	0.041	4.28
Pz	0.1125, 0.1084, 0.1050	-0.002	[-0.003, -9E-05]	0.001	0.050	3.84
T7	0.1095, 0.1123, 0.1146	0.003	[2E-04, 0.005]	0.001	0.038	4.40
Theta Oscillation Node Strength						
P4	0.1173, 0.1151, 0.1139	-0.002	[-0.003, -4E-04]	0.001	0.012	6.49
T7	0.1067, 0.1104, 0.1143	0.002	[1E-04, 0.004]	0.001	0.040	4.33

Table S5: Summary of statistics for linear regression models node strength (centrality based on the sum of node weights), for each gamma, beta, alpha and theta networks at 96 months. Only the statistics for nodes that were statistically distinct in the 3 groups when adjusted for birth weight or head circumference are shown. Median node strength values for each group are provided in column 2.

Node pair	Regression	Confidence	Standard Error	p-value	Wald statistic

	Coefficient	Interval (CI)	(SE)		
	Gamma Oscillation Connectivity (Network Edge) Trajectory				
(C3, P3)	-0.016	[-0.030, -0.002]	0.007	0.024	5.13
(P3, Pz)	-0.019	[-0.033, -0.005]	0.007	0.007	7.29
(P3, O2)	-0.012	[-0.023, -0.001]	0.006	0.029	4.80
(P4, O1)	-0.011	[-0.022, -0.001]	0.005	0.032	4.65
(P4, O2)	-0.014	[-0.025, -0.003]	0.006	0.014	6.10
(Pz, O2)	-0.011	[-0.022, -0.001]	0.005	0.031	4.69
	Beta Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.005	[-0.011, -1E-04]	0.003	0.050	3.80
	Alpha Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.006	[-0.011, -0.001]	0.003	0.049	3.90
(P4, O2)	-0.006	[-0.011, -0.001]	0.003	0.05	3.89
	Theta Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.008	[-0.012, -0.002]	0.002	0.015	6.03
(P4, O2)	-0.007	[-0.012, -0.002]	0.002	0.010	6.82

Table S6a: Summary of linear mixed effects regression models statistics for pairwise connectivity trajectories from 42 to 96 months, as a function of time and group, adjusted for birth weight and/or head circumference. Only the statistics for the 'group' parameter are shown, for pairs of nodes for which their connectivity (edge) was statistically distinct in the 3 groups.

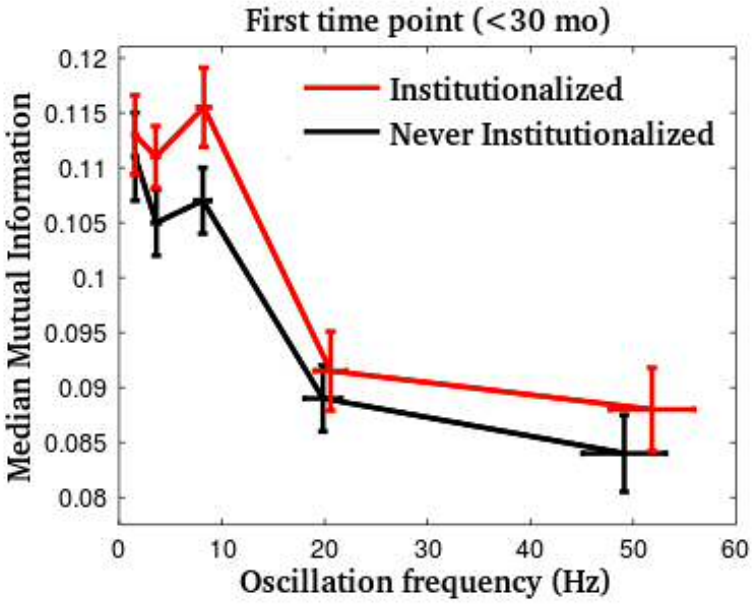
Node	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
	Alpha Oscillation Node Connectedness Trajectory				
P4	-0.053	[-0.088, -0.017]	0.018	0.004	8.60
Pz	-0.035	[-0.066, -0.003]	0.016	0.030	4.77
	Theta Oscillation Node Connectedness Trajectory				
P4	-0.045	[-0.087, -0.003]	0.021	0.036	4.44
Pz	-0.040	[-0.073, -0.007]	0.017	0.018	5.71

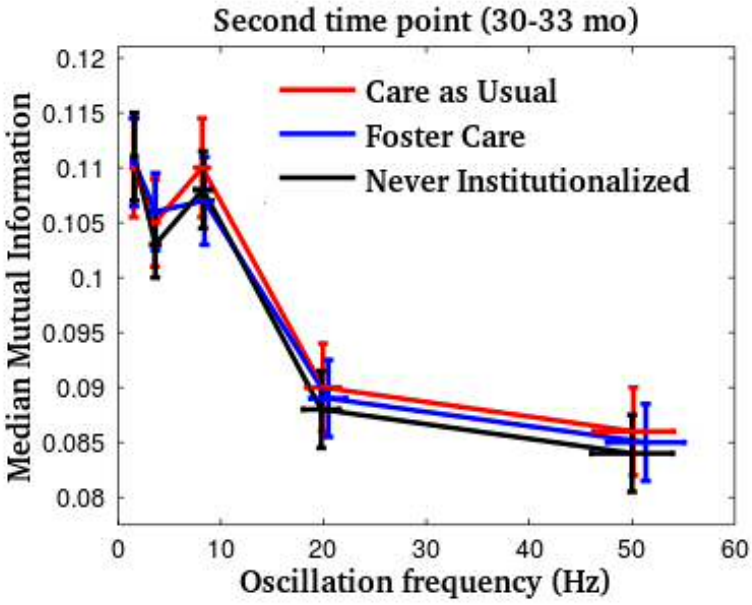
Table S6b: Summary of linear mixed effects regression models statistics for the trajectories of node connectedness from 42 to 96 months, as a function of time and group, adjusted for birth weight and/or head circumference. Only the statistics for the 'group' parameter are shown, for pairs of nodes that were statistically distinct in the 3 groups.

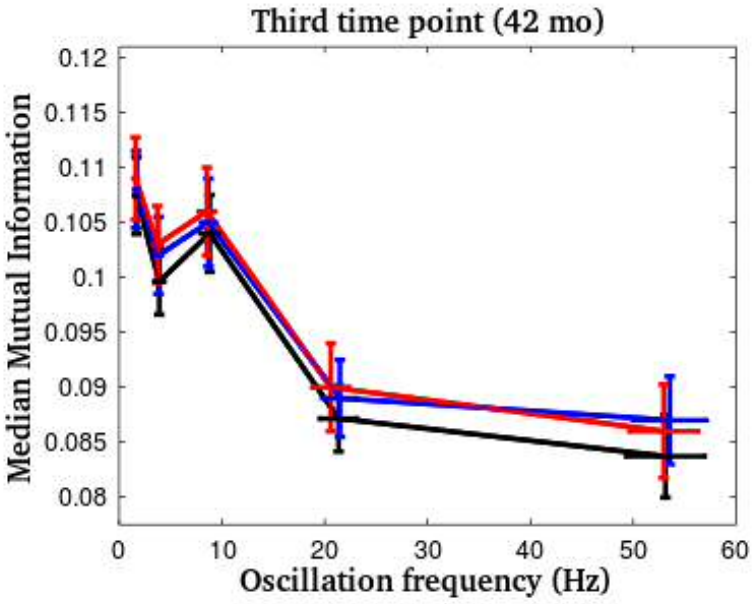
971

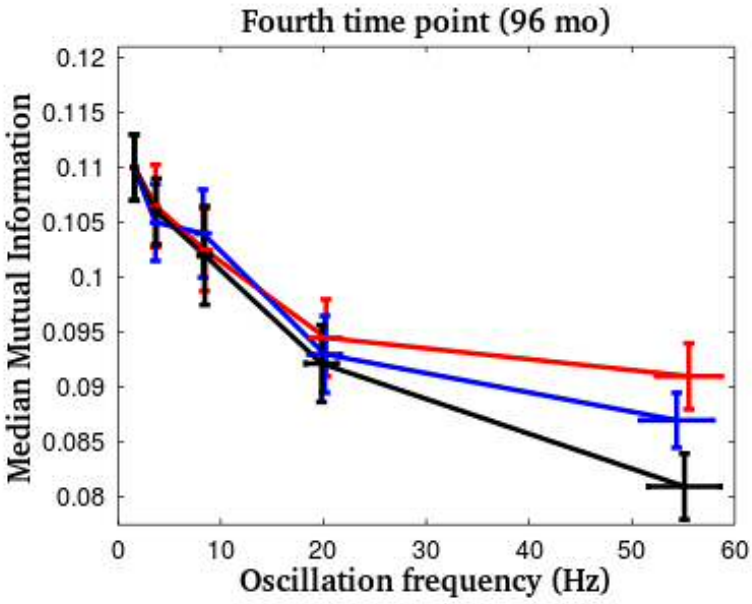
972

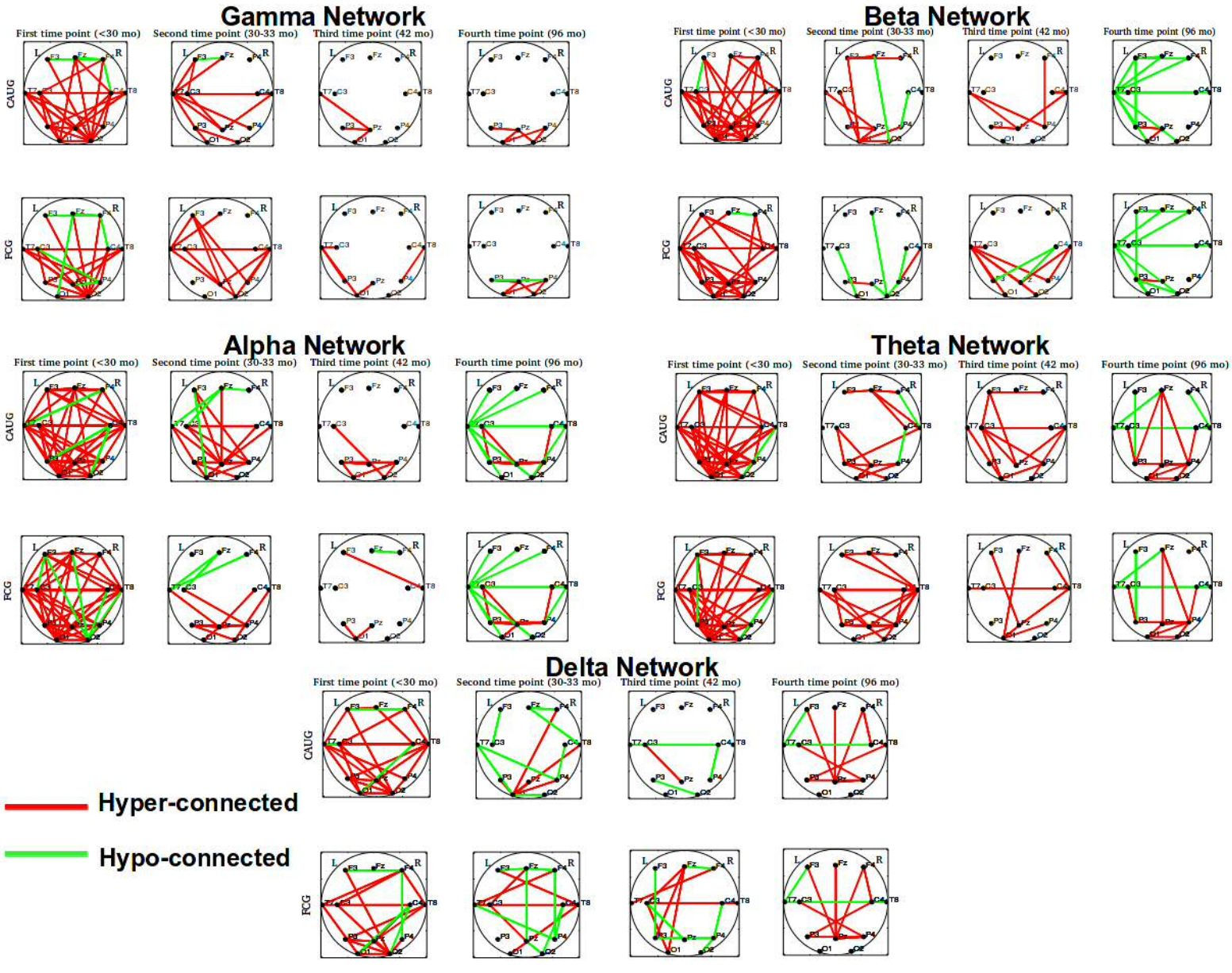
973

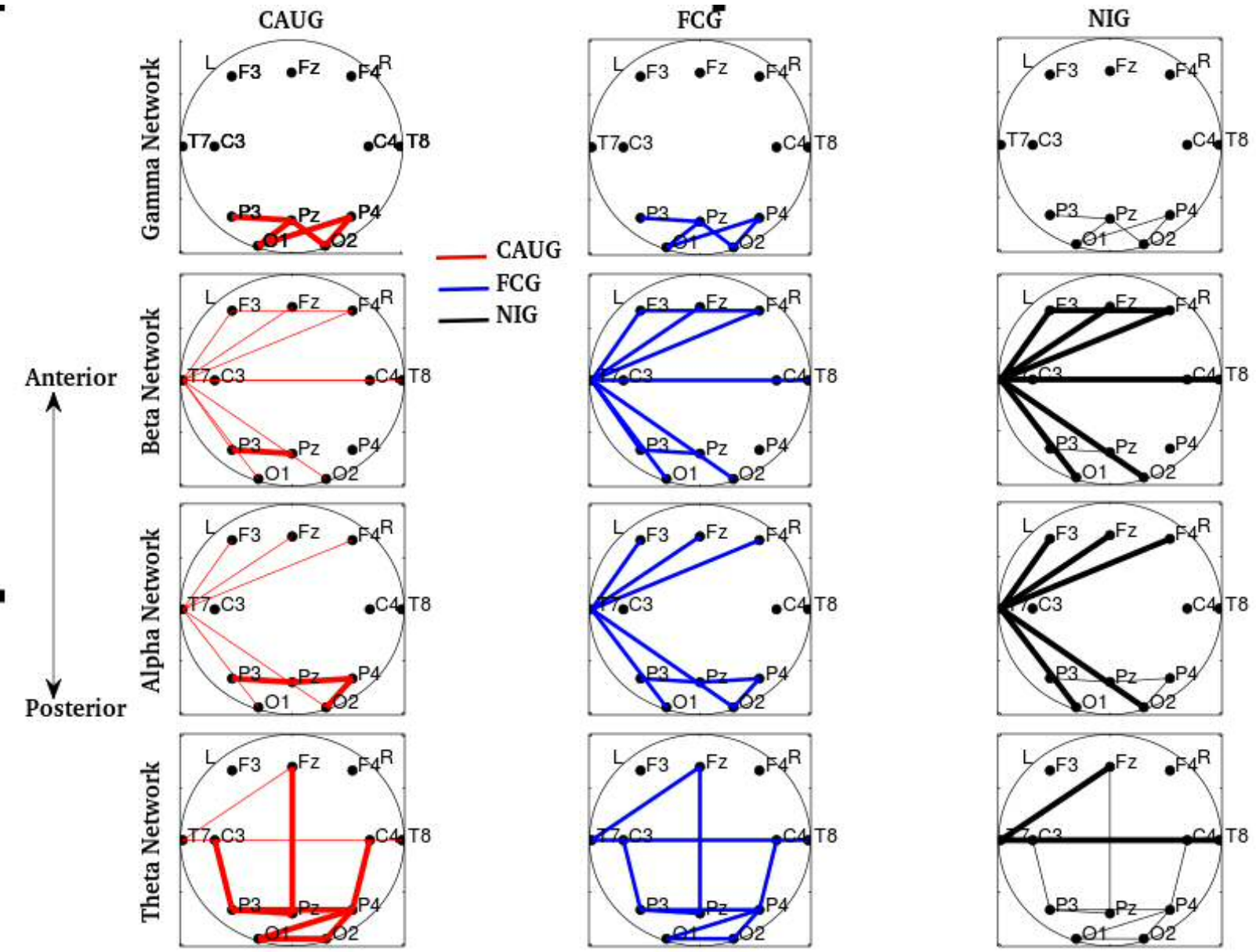

First time point (<30 mo)
Institutionalized
Never Institutionalized
Median Mutual Information
Oscillation frequency (Hz)

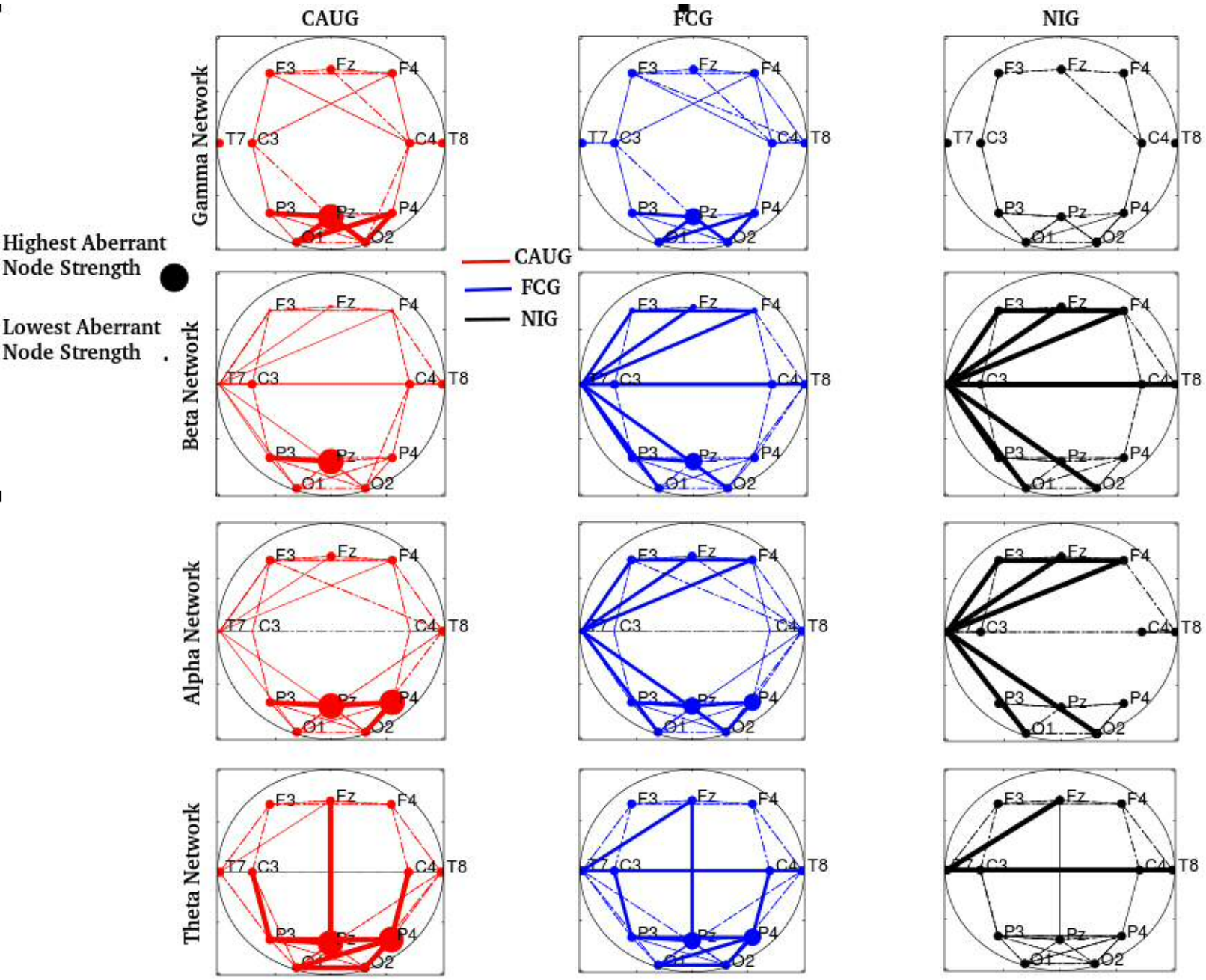

Second time point (30-33 mo)
Care as Usual
Foster Care
Never Institutionalized
Median Mutual Information
Oscillation frequency (Hz)


Third time point (42 mo)
Median Mutual Information
Oscillation frequency (Hz)


Fourth time point (96 mo)
Median Mutual Information
Oscillation frequency (Hz)


Gamma Network
First time point (<30 mo)
Second time point (30-33 mo)
Third time point (42 mo)
Fourth time point (96 mo)
CAUG
FCG
Beta Network
First time point (<30 mo)
Second time point (30-33 mo)
Third time point (42 mo)
Fourth time point (96 mo)
CAUG
FCG
Alpha Network
First time point (<30 mo)
Second time point (30-33 mo)
Third time point (42 mo)
Fourth time point (96 mo)
CAUG
FCG
Theta Network
First time point (<30 mo)
Second time point (30-33 mo)
Third time point (42 mo)
Fourth time point (96 mo)
CAUG
FCG
Delta Network
First time point (<30 mo)
Second time point (30-33 mo)
Third time point (42 mo)
Fourth time point (96 mo)
CAUG
FCG
Hyper-connected
Hypo-connected


CAUG
FCG
NIG
Gamma Network
Beta Network
Alpha Network
Theta Network
Anterior
Posterior
CAUG
FCG
NIG
L
R
F3
Fz
F4
T7
C3
C4
T8
P3
Pz
P4
O1
O2


CAUG
FCG
NIG
Gamma Network
Beta Network
Alpha Network
Theta Network
Highest Aberrant Node Strength
Lowest Aberrant Node Strength
CAUG
FCG
NIG
Fz
F3
F4
T7
C3
C4
T8
P3
Pz
P4
O1
O2