Systemic inflammation during the first year of life is associated with brain functional connectivity and future cognitive outcomes

Ashley M. Bach [a,b], Wanze Xie [h,i,j], Laura Piazzoli [a,c], Sarah K.G. Jensen [d], Sajia Afreen [e], Rashidul Haque [e], William A. Petri [f], Charles A. Nelson [a,c,g,*]

[a] *Labs of Cognitive Neuroscience, Division of Developmental Medicine, Boston Children's Hospital, USA*
[b] *Harvard T.H. Chan School of Public Health, USA*
[c] *Harvard Medical School, USA*
[d] *Department of Social Work, Boston College, USA*
[e] *International Centre for Diarrhoeal Disease Research, Bangladesh*
[f] *Division of Infectious Diseases, University of Virginia School of Medicine, USA*
[g] *Harvard Graduate School of Education, USA*
[h] *School of Psychological and Cognitive Sciences, Peking University, China*
[i] *PKU-IDG/McGovern Institute for Brain Research, Peking University, China*
[j] *Beijing Key Laboratory of Behavior and Mental Health, Peking University, China*

ARTICLE INFO

ABSTRACT

The first years of life are a sensitive period of rapid neural and immune system development vulnerable to the impact of adverse experiences. Several studies support inflammation as a consequence of various adversities and an exposure negatively associated with developmental outcomes. The mechanism by which systemic inflammation may affect brain development and later cognitive outcomes remains unclear. In this longitudinal cohort study, we examine the associations between recurrent systemic inflammation, defined as C-reactive protein elevation on ≥ 2 of 4 measurements across the first year of life, electroencephalography (EEG) functional connectivity (FC) at 36 months, and composite cognitive outcomes at 3, 4, and 5 years among 122 children living in a limited-resource setting in Dhaka, Bangladesh. Recurrent systemic inflammation during the first year of life is significantly negatively associated with cognitive outcomes at 3, 4, and 5 years, after accounting for stunting and family care indicators (a measure of stimulation in the home environment). Recurrent systemic inflammation is significantly positively associated with parietal-occipital FC in the Beta band at 36 months, which in turn is significantly negatively associated with composite cognitive scores at 3 and 4 years. However, FC does not mediate the relationship between recurrent systemic inflammation and cognitive outcomes.

1. Introduction

Millions of children worldwide are exposed to early biological and psychosocial hazards that may limit their ability to reach their full developmental potential (McCoy et al., 2016). The first years of life represent a sensitive period of rapid development of neural, neuroendocrine, and immune systems that are vulnerable to adverse experiences that can alter biology with long-term influence on health and development (Wachs et al., 2014; Nelson, 2017; Walker et al., 2011; Jensen et al., 2017). This vulnerability is due, in part, to critical period closure, which can lead to a consolidation of effects. As a result, exposure to adverse experiences during critical periods of brain development are far more likely to have enduring rather than transient effects on children's outcomes (Early Adversity and Critical Periods, 2021). Children in low-resource environments are at heightened risk of exposure to compounding biological, environmental, and psychosocial adversities

including food insecurity, infectious disease, polluted environments, and psychosocial stressors, which together and separately may adversely impact neurodevelopment (Johnson et al., 2016; Council on Community Pediatrics, 2016; John et al., 2017; Kutlesic et al., 2017). The mechanism by which these exposures impact development remains unclear. One hypothesis is that inflammation is a common biological consequence of various adversities and involved in their negative effect on development.

Inflammation is defined as the physiologic response to infections, tissue injury, psychological stress, and other insults (Calder et al., 2009; Black, 2002). It may impact brain development directly, as in central nervous system infections, or indirectly, via systemic inflammation in response to an environmental exposure (Bilbo, 2009). Acute inflammation is a rapid, innate reaction to a variety of stressors that is short-lived and usually protective as it fights a pathogen or initiates healing of damaged tissue (Raiten et al., 2015). Chronic inflammation, by contrast, is an inflammatory response that fails to resolve and may be detrimental to the host. Chronic inflammation is characterized by persistent elevation in systemic plasma concentrations of several cytokines, including C-reactive protein (CRP), and may contribute to immunosuppression, oxidative stress, and cytotoxicity (Raiten et al., 2015; Kanterman et al., 2012).

Chronic inflammation may be caused by a variety of early adversities including recurrent infection, environmental exposures, and psychosocial stressors, with negative long-term health consequences (Danese et al., 2009; Shonkoff et al., 2012; Slopen et al., 2013). Persistent systemic inflammation has been associated with structural remodeling of multiple organ systems that increases risk for impaired long-term physical and mental health (Boyce et al., 2021). For example, early life adversity has been associated with elevated biomarkers of systemic inflammation, including CRP, that increase risk for later depression and cardiovascular and autoimmune disease (Danese and McEwen, 2012; Dube et al., 2009; Baumeister et al., 2016; Slopen et al., 2018).

Several aspects of brain development, including changes in synapse number and myelin integrity, extend from mid-fetal development through middle and late childhood and are subject to environmental influences including inflammation (John et al., 2017). Jiang et al. (2018) have described how the nature and timing of inflammatory insults may influence early brain development. During fetal development, maternal and/or fetal immune activation may negatively affect brain development if the inflammation occurs during a major neurodevelopmental process such as cell migration or dendritic sprouting (Marques et al., 2013). Maternal inflammation during pregnancy is associated with increased likelihood of neurodevelopmental and psychiatric disorders in children (Estes and McAllister, 2016). Inflammation and cytokine elevations due to infection in early postnatal life are associated with impaired neurodevelopment (Jiang et al., 2014; O'Shea et al., 2012; Dickson, 2000), and early life inflammation has been associated with a variety of neurodevelopmental disorders (Jiang et al., 2018). Among children enrolled in the Bangladesh Early Adversity Neuroimaging (BEAN) study, elevated inflammatory biomarkers in infancy are negatively associated with cognitive outcomes at 1, 2 and 5 years of age (Jiang et al., 2014; Jiang et al., 2017; Jensen et al., 2019).

Despite the many potential causes of early childhood adversity and inflammation in low-resource settings, there are few studies to date that examine the association of early postnatal inflammation with neurodevelopment among children in low- and middle-income countries. Even fewer utilize neuroimaging, which may help elucidate the mechanism by which systemic inflammation affects the developing brain. The present study examines the associations between inflammation, electroencephalogram (EEG) functional connectivity (FC), and cognitive outcomes among children living in a low-resource environment in Bangladesh to determine whether early life inflammation, a potential consequence of a variety of adversities, impacts cognitive outcomes, and whether changes in EEG FC mediate the impact of inflammation on the developing brain.

We assess changes in EEG FC based upon prior literature implicating changes in white matter and brain connectivity after exposure to inflammation (Rudolph et al., 2018; Gianaros et al., 2013). A previous study in this population reported associations of inflammation with event-related potentials to social stimuli and cognitive outcomes (Xie et al., 2019). Our analysis of EEG FC builds upon this by assessing the association of inflammation with brain network connectivity in multiple regions. EEG FC has been used to investigate the efficiency and organization of brain networks among typically developing children (Xie et al., 2019). Variation in FC is often attributed to changes in the organization and functioning of brain networks, and abnormal FC patterns associated with early exposure to systemic inflammation have been linked to deficits in later cognitive performance (Rudolph et al., 2018; Orekhova et al., 2014). It is therefore plausible that inflammation during early childhood disrupts communication between cortical areas through neural oscillations in different frequency bands, which in turn may lead to altered cognitive outcomes. Because there is no evidence of a single brain region or frequency band most affected by early exposure to inflammation, we adopt an exploratory approach to examining the associations of early life inflammation with EEG FC in multiple regions to better understand how and where early systemic inflammation may exert an effect on the developing brain. Specifically, we test the hypotheses that 1) recurrent systemic inflammation during the first year of life is associated with worse cognitive outcomes; 2) recurrent systemic inflammation is associated with changes in FC; and 3) these changes in FC mediate the effect of recurrent systemic inflammation on cognitive outcomes.

2. Methods

We examined the relationships between inflammation, EEG FC, and cognitive outcomes among children enrolled in a longitudinal prospective cohort in the BEAN study.

2.1. Participants and measurement of inflammation

Children in Dhaka, Bangladesh enrolled in the BEAN study within a week of birth (Median: 5d, Range: 1–7d) after voluntary informed consent was obtained from parents following a protocol approved by the International Centre for Diarrhoeal Disease Research, Bangladesh Institutional Review Board and the Boston Children's Hospital Institutional Review Board (Storrs, 2017). All children were born $\geq$ 34 gestational weeks and had no known history of neurological abnormalities, genetic disorders, or visual or auditory impairments. Other demographics are described in previous studies of this cohort (Jensen et al., 2019; Xie et al., 2019). Of 130 children in the cohort, the 122 with serum CRP concentration (mg/L) measured at 6, 18, 40, and 53 weeks of age using an enzyme linked immunosorbent assay (Immunidiagnostik AG) were included in the analysis. Samples from all subjects were analyzed simultaneously for each timepoint. CRP was selected as the inflammatory biomarker of interest because of its availability at multiple timepoints in this cohort, its use in previous studies of adversity exposure, chronic inflammation, and long-term outcomes (Slopen et al., 2018; Danese et al., 2007), and its association with childhood adversity greater than that of other inflammatory markers (Baumeister et al., 2016). All children received biweekly home visits for documentation of fever and recent illness. All data was collected by trained local research staff.

Recurrent systemic inflammation was defined as top-quartile CRP for age in this population on two or more occasions during the first year of life. The choice of top quartile for assigning status of protein elevation was made for the following reasons: 1) serum CRP varies according to postnatal age in our population (Supplemental Fig. 1); 2) normative data for serum CRP in this population of infants in Bangladesh are not available; and 3) serum CRP values do not conform to a normal distribution. Other investigators have defined sustained inflammation using

inflammatory proteins in the top quartile across multiple timepoints due to similar observations and limitations in their populations of interest (Kuban et al., 2019; O'Shea et al., 2013). CRP was defined as a dichotomous rather than a continuous variable to assess associations with recurrent CRP elevation rather than with the full range of CRP variation or with absolute frequency of CRP elevation.

2.2. EEG data collection and processing

EEG was recorded at age 36 months (Mean: 36.2, SD: 0.45) from a 128-channel HydroCel Geodesic Senso Net connected to a NetAmps 300 amplifier (Electrical Geodesic Inc., Eugene, OR) while children watched a screensaver with abstract shapes and soothing sounds for 2 min.

EEG recordings were preprocessed using EEGLAB (Delorme and Makeig, 2004) and ERPLAB (Lopez-Calderon and Luck, 2014) toolboxes in MATLAB (R2017a, the Mathworks, Inc.). The continuous EEG data were filtered with an 8th order Butterworth band-pass filter with a pass band of 1 – 50 Hz. The filtered data was then segmented into 1 s epochs. The EEG epochs were inspected for artifacts using both absolute (voltage $> 100\mu V$ or EEG $< -100\mu V$) and stepwise (voltage change $> 100\mu V$ within a 100 ms moving window with a 50 ms window step) algorithms. Channel interpolation was conducted using a spherical spline interpolation with the EEGLAB function "eeg_interp" if there were fewer than 18 (15%) electrodes that were missing or had bad data. Independent component analysis (ICA) was also conducted to remove components related to eye movements, blinks, and focal activity. Each child must have had at least 60 clean epochs (50%) to have been included in further analyses. For the participants included in the final samples, the mean number of clean epochs was 103.59 (SD = 16.64).

2.3. EEG FC analysis

EEG FC was estimated from the processed EEG recordings. The processing stream for the source-space FC analysis used is the same as described in previous studies of this population (Xie et al., 2019; Xie et al., 2019). Cortical source reconstruction was conducted for the scalp EEG data using realistic head models created using age-appropriate average MRI templates (Richards et al., 2016). Distributed source reconstruction of the EEG time-series was conducted, and reconstructed source activities were segmented into 48 cortical regions of interest (ROIs) using the LPBA40 brain atlas (Shattuck et al., 2008). FC between the 48 cortical ROIs was estimated using the weighted phase lag index (Vinck et al., 2011), a widely used measure of "phase-to-phase synchrony" for different frequency bands at 36 months: theta (3–7 Hz), alpha (7–10 Hz), beta (11–20 Hz), and gamma (20–40 Hz) (Development of infant sustained attention and its relation to EEG oscillations, 2020; Thorpe et al., 2016). The 48 ROIs were further categorized into frontal (F), temporal (T), parietal (P), and occipital (O) lobes, and the FC within and between them were calculated (Supplemental Fig. 2).

2.4. Cognitive outcomes

The Mullen Scales of Early Learning (MSEL) was used to measure outcomes at 3 years (Mullen, 1995). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was used to measure outcomes at 4 and 5 years, to avoid potential ceiling effects on the MSEL. Both are interactive assessments that provide global and subscale assessments of children's cognitive development (Supplemental Table 1).

The MSEL and WPPSI were developed and normed in the United States. Both have previously been used in low-income country settings (Koura et al., 2013; Bornman et al., 2018; Milosavljevic et al., 2019), and the WPPSI has been used to assess cognitive outcomes in 5-year-old children in Bangladesh (Wasserman et al., 2007; Kippler et al., 2012). To ensure that both were culturally-appropriate assessment tools, local staff translated and adapted them by substituting unfamiliar images and questions with objects and examples that Bangladeshi children would

recognize. Both assessments were administered by local psychologists and research assistants. Given the absence of local norms for these assessments, we standardized raw scores within our sample for each time point to obtain age-appropriate Z-scores in this population. MSEL composite scores were calculated as the Z-score of the summed subscale raw scores as in previous studies of this population (Xie et al., 2019; Jensen et al., 2019). WPPSI full-scale intelligence quotient (IQ) scores were standardized as Z-scores.

2.5. Covariates

Measures of stunting and environmental stimulation were included as covariates given their impact on neurodevelopment. Height was obtained at 36, 48, and 54 months of age. Children's height-for-age (HAZ) scores were calculated based upon World Health Organization (WHO) standards. Stunting, which is associated with worse cognitive outcomes, was defined as HAZ > 2 SD below the mean of the WHO reference (Perkins et al., 2017). Family care indicators (FCI), a survey measure of stimulation in the home environment, were assessed through oral interviews with caregivers conducted by local, native staff. Interviews took place at the time of a child's first cognitive assessment. The FCI uses items from UNICEF's Multiple Indictor Cluster Survey to assess stimulating activities that a caregiver engaged in with the child within the preceding 30 days (Jensen et al., 2019). The FCI measure has been widely used in low- in middle-income countries, including Bangladesh (Hamadani et al., 2010), and in previous studies of this population (Xie et al., 2019; Jensen et al., 2019). After controlling for socioeconomic factors, FCI is predictive of developmental outcomes, with higher score indicating greater stimulation associated with better outcomes (Hamadani et al., 2010).

2.6. Statistical analysis

Baseline characteristics were compared between children with and without exposure to recurrent systemic inflammation using the Kruskal-Wallis or Student t-test for continuous variables, and the χ^2 or Fisher exact test for categorical variables. Descriptive statistics and multiple linear regression were conducted in Stata (version 16.1) to assess associations between inflammation, EEG FC, and cognitive outcomes. In this exploratory analysis, linear regression models were used to examine the association of inflammation with FC in each frequency band within and between the four lobes. Multiple comparison is a limitation of this exploratory approach. To reduce risk of Type I error, p-values were adjusted using a false discovery rate (FDR) of 0.05 using the Benjamini & Yekutieli method by brain region (Benjamini and Yekutieli, 2001). Only the region significantly associated with inflammation was further evaluated for association with cognitive outcomes and in the longitudinal path analysis, controlling for covariates. Path analysis was used to assess indirect effects of inflammation on cognitive outcomes via EEG FC.

3. Results

3.1. Participant characteristics

Of 130 children in the cohort, 122 had serum CRP collected at 6, 18, 40, and 53 weeks of age (Supplemental Fig. 1) and received bi-weekly home visits and temperature measurements. Presence of fever ($\geq$38 C) in the 3 days before and after CRP measurement was identified. Only 4 of 122 children had a fever within 3 days of CRP collection.

Among these 122 children, 35 met criteria for recurrent systemic inflammation (two or more top-quartile CRP values), and 87 did not. There was no significant difference in prevalence of stunting nor FCI between those children with and without exposure to recurrent systemic inflammation (Table 1). 110 (90%) children had available parietal-occipital EEG FC data obtained at 36 months. 119 (98%) children underwent cognitive evaluation with MSEL at 36 months (Mean: 36.1

Table 1
Baseline Characteristics.

	Recurrent inflammation (N = 35)	No recurrent inflammation (N = 87)	P-Value
Gestational age ± SD (weeks)	37.7 ± 1.41	37.2 ± 1.35	0.08
Male (%)	20 (57%)	46 (53%)	0.67
Age at enrollment ± SD (days)	5 ± 1.80	5.1 ± 1.73	0.79
Weight at time of enrollment ± SD (kg)	2.82 ± 0.38	2.79 ± 0.41	0.71
Age at EEG, median months (IQR)	36 (36–37)	36 (36–36)	0.09
Family Care Indicators, median points (IQR)	8 (5–10)	8 (6–11)	0.42
Stunting (%) at 3 years	14 (40%)	27 (31%)	0.34
Stunting (%) at 4 years	9 (26%)	26 (30%)	0.62
Stunting (%) at 5 years	8 (23%)	20 (23%)	0.96
Age at MSEL ± SD (months)	36.1 ± 0.08	36.1 ± 0.11	0.48
Age at 4-year WPPSI ± SD (months)	48.5 ± 0.20	48.5 ± 0.21	0.80
Age at 5-year WPPSI ± SD (months)	60.3 ± 0.26	60.4 ± 0.21	0.38

SD: Standard Deviation. IQR: Interquartile Range. EEG: Electroencephalogram. MSEL: Mullen Scales of Early Learning. WPPSI: Wechsler Preschool and Primary Scale of Intelligence.

months, SD: 0.10). 118 (97%) and 116 (95%) children underwent cognitive evaluation with WPPSI at 48 months (Mean: 48.5 months, SD: 0.20) and 60 months of age (Mean: 60.4 months, SD: 0.23), respectively. There was no difference in timing of EEG or cognitive evaluations among children with and without exposure to recurrent systemic inflammation.

3.2. Inflammation and cognitive outcome

Recurrent systemic inflammation during the first year of life was negatively associated with MSEL Sum Z-score (Coefficient: −0.46, p = 0.01) at 3 years, after controlling for FCI and stunting (Table 2; Supplemental Table 2). Similarly, recurrent systemic inflammation was negatively associated with WPPSI Full-Scale IQ at 4 years (Coefficient: −0.47, p = 0.02) and 5 years (Coefficient: −0.69, p < 0.01), after controlling for FCI and stunting. The predicted probability of composite cognitive outcome more than 1 SD below the population mean varied by inflammation exposure and stunting in a similar pattern across 3, 4 and 5-year outcomes (Fig. 1).

3.3. Inflammation, EEG FC, and cognitive outcome

Recurrent systemic inflammation was associated with increased parietal-occipital EEG FC in the Beta band (Coefficient: 0.59, p < 0.01) before and after adjusting for FCI and stunting (Table 3; Supplemental Table 3). This association remained significant after correction for

multiple testing using a false discovery rate (FDR) of 0.05 using the Benjamini & Yekutieli method by brain region (adjusted p-value=0.032) (Benjamini and Yekutieli, 2001). Parietal-occipital FC in the Beta band was negatively associated with cognitive outcomes at 3 years (Coefficient: −0.21, p = 0.01) and 4 years (Coefficient: −0.24, p < 0.01), after adjusting for FCI and stunting at 36 and 48 months, respectively (Table 4; Supplemental Table 4).

The associations of recurrent systemic inflammation with cognitive outcomes at 3, 4, and 5 years were all decreased in magnitude and no longer significant for 3- and 4-year outcomes after adjustment for parietal-occipital FC (Table 2). Longitudinal path analysis was performed to test the hypothesized multivariate mediation model, wherein brain FC mediates the association of recurrent systemic inflammation with cognitive outcomes (Fig. 2). We found no significant indirect effects of recurrent systemic inflammation on composite cognitive outcomes via parietal-occipital FC in the Beta band at 3 years (Coefficient: −0.10; p = 0.09), 4 years (Coefficient: −0.16; p = 0.05), or 5 years (Coefficient: −0.07; p = 0.28).

Indirect effect of inflammation on cognitive outcomes via Beta-band parietal-occipital functional connectivity*

	β	P-value	95% CI
a) Inflammation → 3 y Sum Z-Score	-0.10	0.09	-0.22 – 0.02
b) Inflammation → 4 y Full Scale IQ Z-Score	-0.16	0.05	-0.31 – 0.00
c) Inflammation → 5 y Full Scale IQ Z-Score	-0.07	0.28	-0.21 – 0.06

*Adjusted for family care indictors and stunting at 36 months, 48 months, or 54 months for 3, 4, and 5-year outcomes, respectively
FC: Functional Connectivity. MSEL: Mullen Scales of Early Learning. WPPSI: Wechsler Preschool and Primary Scales of Intelligence. IQ: Intelligence Quotient.

4. Discussion

Our results demonstrate that recurrent systemic inflammation, as measured by two or more instances of elevated CRP across the first year of life, is associated with lower cognitive scores at 3, 4, and 5 years of age and increased parietal-occipital brain FC in the Beta band, after controlling for stunting and family care indicators. Increased parietal-occipital FC is associated with lower composite cognitive scores, but does not mediate the relationship between recurrent systemic inflammation and cognitive outcomes.

Our first finding that recurrent systemic inflammation is associated with lower cognitive scores supports previous literature (Jiang et al., 2014; Jiang et al., 2017; Jensen et al., 2019), and adds that the association persists at 3–5 years of age in this at-risk population of children in Bangladesh. Our consistent findings across three timepoints using both the MSEL and WPPSI strengthen the evidence for this association. The mechanism by which systemic inflammation may affect neurodevelopment remains unclear, but animal and human studies implicate changes in white matter and brain structure and connectivity. Fetal exposure to elevated maternal cytokines is associated with morphological brain abnormalities that adversely affect neurodevelopment
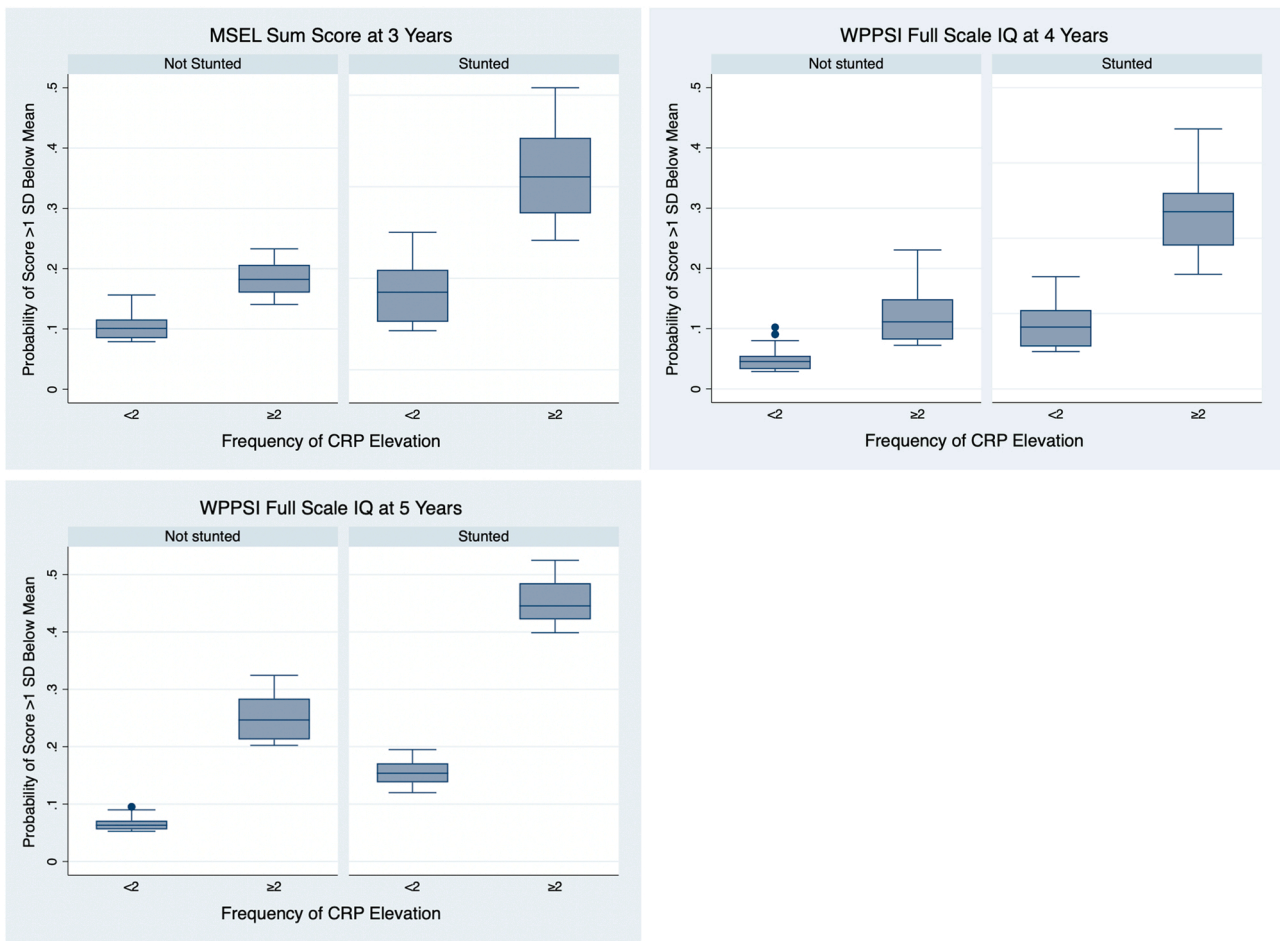
Table 2
Univariate and multivariate regression for the association of recurrent systemic inflammation with composite cognitive outcomes at 3, 4, and 5 years.

	Model 1			Model 2[a]			Model 3[b]		
	β	P-value	95% CI	β	P-value	95% CI	β	P-value	95% CI
3-year MSEL Sum Z-score	-0.51	**0.01**	-0.87 - −0.15	-0.46	**0.01**	-0.80 - −0.11	-0.27	0.17	-0.65 – 0.11
4-year WPPSI FSIQ Z-score	-0.46	**0.02**	-0.86 - −0.06	-0.47	**0.02**	-0.84 - −0.09	-0.20	0.35	-0.62 – 0.22
5-year WPPSI FSIQ Z-score	-0.71	**<0.01**	-1.09 - −0.33	-0.69	**<0.01**	-1.07 - −0.32	-0.52	**0.02**	-0.96 - −0.09

MSEL: Mullen Scales of Early Learning. WPPSI: Wechsler Preschool and Primary Scale of Intelligence. FSIQ: Full Scale Intelligence Quotient. CI: Confidence Interval. FCI: Family Care Indicators.
[a] Adjusted for FCI and stunting at 36, 48, or 54 months for 3-year, 4-year, and 5-year outcomes, respectively.
[b] Adjusted for parietal-occipital functional connectivity in the Beta band, FCI, and stunting at 36, 48, or 54 months for 3-year, 4-year, and 5-year outcomes, respectively.

Fig. 1. Predicted probability of cognitive outcome greater than one standard deviation below population mean by stunting status and exposure to recurrent systemic inflammation* .

Probability of cognitive outcome greater than one standard deviation below the population mean predicted by the full regression model, which is adjusted for stunting and family care indicators. Boxplots represent standard values (median, interquartile range, 1.5 times the interquartile range above the 75th percentile and below the 25th percentile). SD: Standard Deviation. CRP: C-reactive protein. MSEL: Mullen Scales of Early Learning. WPPSI: Wechsler Preschool and Primary Scale of Intelligence. IQ: Intelligence Quotient.

Table 3

Univariate and multivariate regression for the association of recurrent systemic inflammation with electroencephalogram functional connectivity.

	Model 1			Model 2[a]		
	β	P-value	95% CI	β	P-value	95% CI
Parietal-occipital Beta-band FC (Z-score)	0.59	**< 0.01**	0.16 – 1.02	0.59	**< 0.01**	0.17 – 1.02

FC: Functional Connectivity.
[a] Adjusted for FCI and stunting at 36 months.

Table 4

Univariate and multivariate regression for the association of Beta-band parietal-occipital electroencephalogram functional connectivity with composite cognitive outcomes at 3, 4, and 5 years.

	Model 1			Model 2[a]		
	β	P-value	95% CI	β	P-value	95% CI
3 y MSEL Sum (Z-score)	-0.23	**< 0.01**	-0.40 – − 0.07	-0.21	**0.01**	-0.38 - − 0.05
4 y WPPSI FSIQ (Z-score)	-0.23	**0.01**	-0.40 – − 0.05	-0.24	**< 0.01**	-0.41 – − 0.07
5 y WPPSI FSIQ (Z-score)	-0.16	0.09	-0.34 – 0.02	-0.17	0.06	-0.36–0.01

MSEL: Mullen Scales of Early Learning. WPPSI: Wechsler Preschool and Primary Scale of Intelligence. FSIQ: Full Scale Intelligence Quotient.
[a] Adjusted for FCI and stunting at 36, 48, or 54 months for 3-year, 4-year, and 5-year outcomes, respectively.

(Marques et al., 2013; O'Shea et al., 2012). Fetal mice exposed to exogenous inflammatory cytokine IL-1b have long-lasting myelination defects, reduced white matter fractional anisotropy and associated memory deficits (Favrais et al., 2011). Animal models of systemic postnatal inflammation have reduced hippocampal volume and behavioral deficits in hippocampus-dependent working memory (Malaeb et al., 2014), disruption of brain resting-state activity, and reduced connectivity in the motor and cingulate networks (Guevara et al., 2017). In humans, maternal systemic inflammation is associated with brain FC on neonatal fMRI and working memory at age 2 (Rudolph et al., 2018). Among preterm newborns, recurrent elevation of inflammatory

biomarkers including CRP, defined as biomarkers in the top quartile on two occasions in the early postnatal period, informs risk of poor cognitive outcomes at 2 years (O'Shea et al., 2012). Similarly, recurrent elevation of circulating inflammatory biomarkers in preterm newborns,
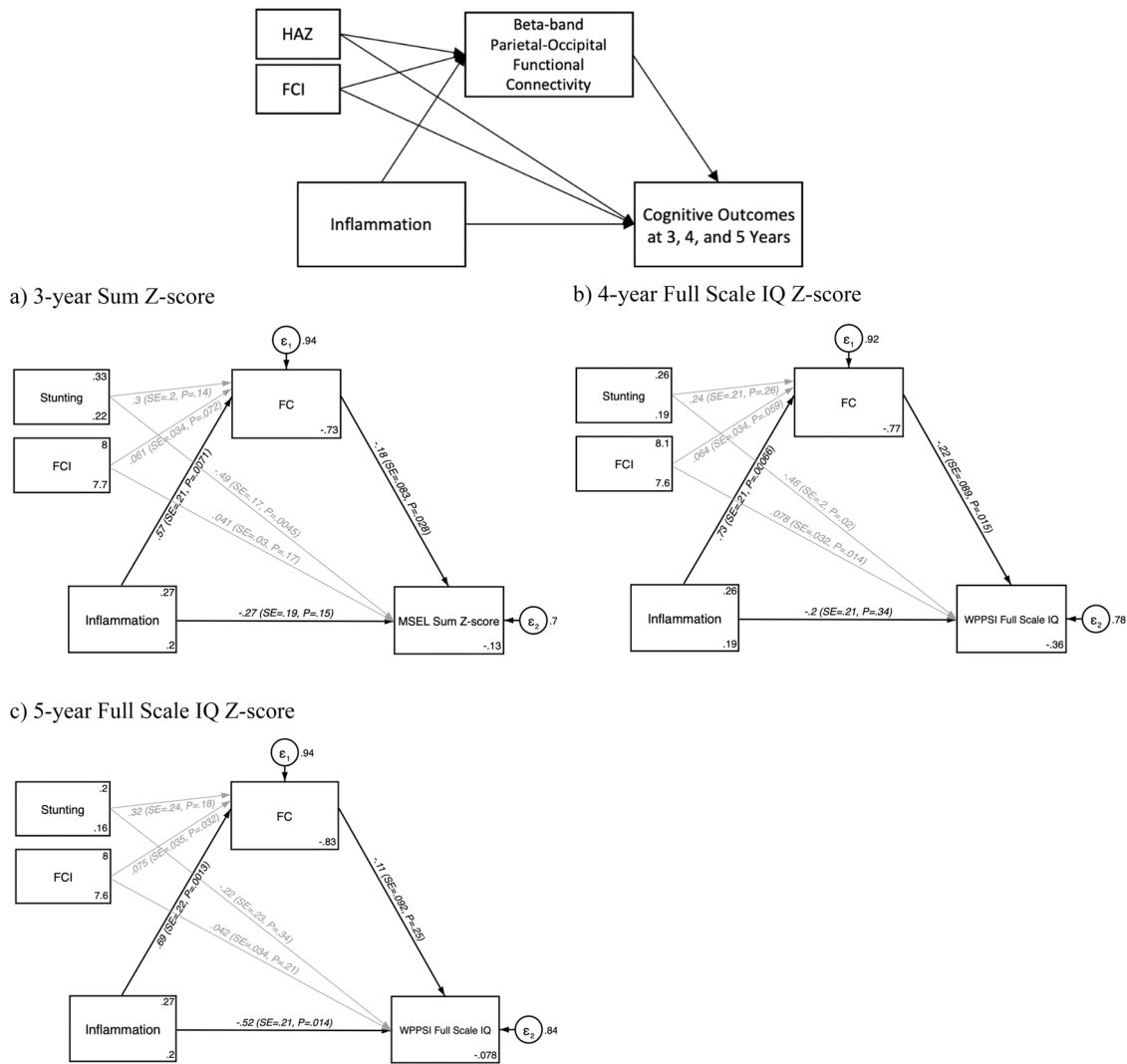
Fig. 2. Multivariate mediation models between recurrent systemic inflammation, Beta-band parietal-occipital functional connectivity, and cognitive outcomes at 3, 4, and 5 years tested with longitudinal path analysis.

defined as inflammatory proteins in the top quartile on two or more samples, is associated with brain volume on MRI and cognitive function at 10 years of age (Kuban et al., 2019). Nutrition and inflammation together impact myelination into early and middle childhood (John et al., 2017). To investigate the mechanism for the association of recurrent systemic inflammation with cognitive outcomes in our population, we next assessed the relationship between inflammation and brain connectivity.

Our second finding is that recurrent systemic inflammation is associated with increased parietal-occipital EEG FC in the Beta frequency band, after accounting for stunting and home care environment. Few studies to date have assessed the specific association of inflammation with EEG measures. The positive association of inflammation with FC reported here is consistent with a prior study reporting increased FC in association with stunting, another exposure associated with worse cognitive outcomes (Xie et al., 2019). A possible explanation for increased FC after exposure to recurrent systemic inflammation is disruption of the typical synaptic pruning process, which begins in infancy and eliminates unnecessary connections to develop robust and efficient neural networks (Zhan et al., 2014). Inflammatory cells in the brain, including microglia, are critical regulators of synaptic structure and elimination (Mottahedin et al., 2017). Immune activation during a critical period such as the first year of life may result in persistently

elevated FC. Alternatively, increased FC may reflect an adaptive response to lower efficiency of neural communications as a result of inflammation exposure (Spann et al., 2018). Neural oscillations in the Beta band are associated with cognitive functions including attention and working memory (Xie et al., 2018; Kopell et al., 2011; Gola et al., 2013). Changes in Beta-band FC have been associated with stunting, most prominently for connections involving the occipital lobe (Xie et al., 2019). Recurrent systemic inflammation during the first year of life may disrupt the progressive occipital-to-frontal myelination process that extends from in utero to age two. Parietal-occipital FC may be particularly affected as parietal and occipital myelination occurs at 4–6 postnatal months, after myelination of deeper brain structures but before myelination of the temporal and frontal cortex at 6–8 months (Deoni et al., 2011). Event related potentials in response to visual stimuli, which involve optic radiations (myelinated at 3–4 months) and the occipital region, have also been associated with inflammation exposure in this population (Xie et al., 2019), highlighting the potentially greater vulnerability of younger brains to inflammatory exposures. Further studies are needed to investigate the time-course of this vulnerability to inform critical windows for protection from inflammatory exposures.

Third, we found that increased parietal-occipital FC in the Beta band is negatively associated with cognitive scores at 3 and 4 years but does not significantly mediate the association of recurrent systemic

inflammation with cognitive outcomes. The directionality of this association is consistent with the hypothesis that increased FC is a maladaptive response to recurrent systemic inflammation during a critical period with negative consequences for cognitive outcomes. Several prior studies report associations of EEG measures with cognitive outcomes. Resting EEG power at birth is correlated with later memory and language skills at age 15 months (Brito et al., 2016). Regional and band-specific EEG power in early childhood is associated with language outcomes (Wilkinson et al., 2019), and longitudinal EEG measures across the first 1–2 years of life may estimate language development (Wilkinson et al., 2020). Several studies support that verbal and cognitive outcomes are correlated with changes in higher frequency (13–30 Hz) EEG measures (Brito et al., 2016; Gou et al., 2011; Tomalski et al., 2013). In a cohort of one-and-a-half to three-year-old children, Gamma power was associated with concurrent language skills and later language and cognition (Gou et al., 2011; Early Cognitive and Language Skills are Linked to Resting Frontal Gamma Power Across the First Three Years, 2020). However, there are few studies on EEG FC and outcomes (Orekhova et al., 2014), and none that report an association specific to parietal-occipital FC in the Beta band. EEG activity in the Beta band has been associated with cognitive functions (Xie et al., 2018; Kopell et al., 2011; Gola et al., 2013), but it is unclear why parietal-occipital FC specifically is associated with composite cognitive outcomes in our population, apart from that both parietal and occipital lobes are involved in many processes that contribute to a composite cognitive score. EEG measures may mediate the effect of exposures on outcomes (Xie et al., 2019; Cantiani et al., 2019), but our data do not support a significant mediation effect of EEG FC as there were no significant indirect effects of recurrent systemic inflammation on outcomes via FC. It is possible that our study is underpowered to detect such an effect, that EEG is not the appropriate neuroimaging modality to detect changes related to recurrent systemic inflammation, or that the timing of EEG did not capture changes related to prior recurrent systemic inflammation exposure or later cognitive function.

There are several limitations to our study, including the possibility of unmeasured confounders that affect the apparent associations we report. The disparate timing of inflammation exposure, EEG FC, and cognitive outcome measurement in this longitudinal cohort allows ample opportunity for influence of other variables that may also affect neurodevelopment. Chronic illness, family income and educational status are a few such possible confounders. FCI reflect these variables in part, and is included in our analysis as a more proximate measure of the environment that shapes a child's development. Although standardized assessments of cognition were adapted to the local context and administered by trained local research staff, the reliability of assessment was not specifically assessed and is thus a limitation of our study. Our exploratory approach to assessing the association of inflammation with brain FC carries risk of multiple testing, and is a limitation of this study. To address this limitation, we applied a FDR correction for multiple testing by brain region, and found that the association of inflammation with parietal-occipital FC in the Beta band remained significant. There was some loss to follow-up in our cohort such that EEG and cognitive outcome data were not available for all children, contributing to potential selection bias. Finally, our definition of recurrent systemic inflammation is limited by the type and frequency of available inflammatory biomarker data. CRP is a non-specific marker of acute inflammation, though large-scale prospective studies support its association with chronic inflammation and chronic inflammatory and neurodegenerative disease (Luan and Yao, 2018). It is possible that CRP elevations detected were secondary to acute infections. We evaluated presence of fever $\geq$ 38 C on biweekly temperatures and found that only 4 children had documented fever within 3 days of CRP collection, making it less likely that all CRP elevations were due to acute febrile illnesses alone. Though we modeled our definition of recurrent systemic inflammation after other studies, it is difficult to reliably assess the chronicity of systemic inflammation with only 4 serum samples across the span of 1 year.

Future investigations with more frequent inflammatory data collection and correlation with other inflammatory markers may better define sustained exposure to systemic inflammation.

In summary, this study strengthens the evidence that exposure to recurrent systemic inflammation during infancy is negatively associated with neurodevelopmental outcomes in early-to-middle childhood among at-risk children in a low-resource setting. Our results support growing evidence that recurrent systemic inflammation during early development is associated with changes to the developing brain with enduring effects. We identify relationships between early inflammation exposure, EEG FC, and cognitive outcomes that may begin to inform the definition of a critical window of time during which minimization of systemic inflammation may improve development. Further studies are needed to investigate how to best measure sustained systemic inflammation and evaluate the specific neurological changes that mediate the relationship between inflammation and developmental outcomes.

CRediT authorship contribution statement

Ashley Bach conceptualized and designed the study, carried out the analyses, and drafted the initial manuscript. Dr. Xie conceptualized and designed the study, carried out the analyses, and reviewed and revised the manuscript. Dr. Piazzoli contributed to data collection and data analysis, and reviewed and revised the manuscript. Dr. Jensen contributed to data collection and data analysis, and reviewed and revised the manuscript. Dr. Afreen led data collection in Bangladesh and reviewed and revised the manuscript. Drs. Haque and Petri obtained financial support for the study and reviewed and revised the manuscript. Dr. Nelson conceptualized and designed the study, obtained financial support for the study, led data collection and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors of this text have no conflicts of interest to disclose.

Potential conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Data Availability

Decisions for releasing the data collected for this study will be made on a case-by-case basis.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2021.101041.

References

McCoy, D.C., Peet, E.D., Ezzati, M., et al., 2016. Early childhood developmental status in low- and middle-income countries: national, regional, and global prevalence estimates using predictive modeling. PLoS Med. 13 (6), e1002034.

Wachs, T.D., Georgieff, M., Cusick, S., McEwen, B.S., 2014. Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience, and psychological research: timing of integrated early interventions. Ann. N.Y. Acad. Sci. 1308 (1), 89–106. https://doi.org/10.1111/nyas.12314.

Nelson, C.A., 2017. Hazards to early development: the biological embedding of early life adversity. Neuron 96 (2), 262–266. https://doi.org/10.1016/j.neuron.2017.09.027.

Walker, S.P., Wachs, T.D., Grantham-McGregor, S., Black, M.M., Nelson, C.A., Huffman, S.L., Baker-Henningham, H., Chang, S.M., Hamadani, J.D., Lozoff, B., Gardner, J.M., Powell, C.A., Rahman, A., Richter, L., 2011. Inequality in early childhood: risk and protective factors for early child development. Lancet 378 (9799), 1325–1338. https://doi.org/10.1016/S0140-6736(11)60555-2.

Jensen, S.K.G., Berens, A.E., Nelson, C.A., 2017. Effects of poverty on interacting biological systems underlying child development. Lancet Child Adolesc. Health 1 (3), 225–239. https://doi.org/10.1016/S2352-4642(17)30024-X.

Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment - ScienceDirect. Accessed February 20, 2021. ⟨https://www.sciencedirect.com/science/article/abs/pii/S0166223620300035⟩.

Johnson, S.B., Riis, J.L., Noble, K.G., 2016. State of the art review: poverty and the developing brain. Pediatrics 137 (4). https://doi.org/10.1542/peds.2015-3075.

Council on Community Pediatrics, 2016. Poverty and child health in the United States. Pediatrics 137 (4). https://doi.org/10.1542/peds.2016-0339.

John, C.C., Black, M.M., Nelson, C.A., 2017. Neurodevelopment: the impact of nutrition and inflammation during early to middle childhood in low-resource settings. Pediatrics 139 (Supplement 1), S59–S71. https://doi.org/10.1542/peds.2016–2828 H.

Kutlesic, V., Brewinski Isaacs, M., Freund, L.S., Hazra, R., Raiten, D.J., 2017. Executive summary: research gaps at the intersection of pediatric neurodevelopment, nutrition, and inflammation in low-resource settings. Pediatrics 139 (Supplement 1), S1–S11. https://doi.org/10.1542/peds.2016–2828 C.

Calder, P.C., Albers, R., Antoine, J.-M., Blum, S., Bourdet-Sicard, R., Ferns, G.A., Folkerts, G., Friedmann, P.S., Frost, G.S., Guarner, F., Løvik, M., Macfarlane, S., Meyer, P.D., M'Rabet, L., Serafini, M., van Eden, W., van Loo, J., Vas Dias, W., Vidry, S., Winklhofer-Roob, B.M., Zhao, J., 2009. Inflammatory Disease Processes and Interactions with Nutrition. Br. J. Nutr. 101 (S1), 1–45. https://doi.org/10.1017/S0007114509377867.

Black, P.H., 2002. Stress and the inflammatory response: a review of neurogenic inflammation. Brain Behav. Immun. 16 (6), 622–653. https://doi.org/10.1016/S0889-1591(02)00021-1.

Bilbo, S.D., 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. Front. Behav. Neurosci. 3, 3. https://doi.org/10.3389/neuro.08.014.2009.

Raiten, D.J., Sakr Ashour, F.A., Ross, A.C., Meydani, S.N., Dawson, H.D., Stephensen, C.B., Brabin, B.J., Suchdev, P.S., van Ommen, B., INSPIRE Consultative Group, 2015. Inflammation and nutritional science for programs/policies and interpretation of research evidence (INSPIRE). J. Nutr. 145 (5), 1039S–1108S. https://doi.org/10.3945/jn.114.194571.

Kanterman, J., Sade-Feldman, M., Baniyash, M., 2012. New insights into chronic inflammation-induced immunosuppression. Semin. Cancer Biol. 22 (4), 307–318. https://doi.org/10.1016/j.semcancer.2012.02.008.

Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., Poulton, R., Caspi, A., 2009. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch. Pediatr. Adolesc. Med. 163 (12), 1135–1143. https://doi.org/10.1001/archpediatrics.2009.214.

Shonkoff, J.P., Garner, A.S., Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics, 2012. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 129 (1), e232–e246. https://doi.org/10.1542/peds.2011-2663.

Slopen, N., Kubzansky, L.D., McLaughlin, K.A., Koenen, K.C., 2013. Childhood adversity and inflammatory processes in youth: a prospective study. Psychoneuroendocrinology 38 (2), 188–200. https://doi.org/10.1016/j.psyneuen.2012.05.013.

Boyce, W.T., Levitt, P., Martinez, F.D., McEwen, B.S., Shonkoff, J.P., 2021. Genes, environments, and time: the biology of adversity and resilience. Pediatrics 147. https://doi.org/10.1542/peds.2020-1651.

Danese, A., McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol. Behav. 106 (1), 29–39. https://doi.org/10.1016/j.physbeh.2011.08.019.

Dube, S.R., Fairweather, D., Pearson, W.S., Felitti, V.J., Anda, R.F., Croft, J.B., 2009. Cumulative childhood stress and autoimmune diseases in adults. Psychosom. Med. 71 (2), 243–250. https://doi.org/10.1097/PSY.0b013e3181907888.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol. Psychiatry 21 (5), 642–649. https://doi.org/10.1038/mp.2015.67.

Slopen, N., Zhang, J., Urlacher, S.S., De Silva, G., Mittal, M., 2018. Maternal experiences of intimate partner violence and C-reactive protein levels in young children in Tanzania. SSM Popul. Health 6, 107–115. https://doi.org/10.1016/j.ssmph.2018.09.002.

Jiang, N.M., Cowan, M., Moonah, S.N., Petri, W.A., 2018. The impact of systemic inflammation on neurodevelopment. Trends Mol. Med. 24 (9), 794–804. https://doi.org/10.1016/j.molmed.2018.06.008.

Marques, A.H., O'Connor, T.G., Roth, C., Susser, E., Bjørke-Monsen, A.-L., 2013. The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. Front. Neurosci. 7, 7. https://doi.org/10.3389/fnins.2013.00120.

Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353 (6301), 772–777. https://doi.org/10.1126/science.aag3194.

Jiang, N.M., Tofail, F., Moonah, S.N., Scharf, R.J., Taniuchi, M., Ma, J.Z., Hamadani, J.D., Gurley, E.S., Houpt, E.R., Azziz-Baumgartner, E., Haque, R., Petri WA, Jr, 2014. Febrile illness and pro-inflammatory cytokines are associated with lower neurodevelopmental scores in Bangladeshi infants living in poverty. BMC Pediatr. 14 (1), 50. https://doi.org/10.1186/1471-2431-14-50.

O'shea, T.M., Allred, E.N., Kuban, K.C., Dammann, O., Paneth, N., Fichorova, R., Hirtz, D., Leviton, A., Extremely Low Gestational Age Newborn (ELGAN) Study, I., 2012. Elevated concentrations of inflammation-related proteins in postnatal blood predict severe developmental delay at 2 years of age in extremely preterm infants. J. Pediatr. 160 (3), 395–401. https://doi.org/10.1016/j.jpeds.2011.08.069.

Dickson, R., 2000. Effects of treatment for intestinal helminth infection on growth and cognitive performance in children: systematic review of randomised trials. BMJ 320 (7251), 1697–1701. https://doi.org/10.1136/bmj.320.7251.1697.

Jiang, N.M., Tofail, F., Ma, J.Z., Haque, R., Kirkpatrick, B., Nelson, C.A., Petri, W.A., 2017. Early life inflammation and neurodevelopmental outcome in bangladeshi infants growing up in adversity. Am. J. Trop. Med. Hyg. 97 (3), 974–979. https://doi.org/10.4269/ajtmh.17-0083.

Jensen, S.K.G., Tofail, F., Haque, R., Petri, W.A., Nelson, C.A., 2019. Child development in the context of biological and psychosocial hazards among poor families in Bangladesh. PLoS One 14 (5), 0215304. https://doi.org/10.1371/journal.pone.0215304.

Rudolph, M.D., Graham, A.M., Feczko, E., Miranda-Dominguez, O., Rasmussen, J.M., Nardos, R., Entringer, S., Wadhwa, P.D., Buss, C., Fair, D.A., 2018. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nat. Neurosci. 21 (5), 765–772. https://doi.org/10.1038/s41593-018-0128-y.

Gianaros, P.J., Marsland, A.L., Sheu, L.K., Erickson, K.I., Verstynen, T.D., 2013. Inflammatory pathways link socioeconomic inequalities to white matter architecture. Cereb. Cortex. 23 (9), 2058–2071. https://doi.org/10.1093/cercor/bhs191.

Xie, W., Kumar, S., Kakon, S.H., Haque, R., Petri, W.A., Nelson, C.A., 2019. Chronic inflammation is associated with neural responses to faces in bangladeshi children. Neuroimage 202, 202. https://doi.org/10.1016/j.neuroimage.2019.116110.

Xie, W., Jensen, S.K.G., Wade, M., Kumar, S., Westerlund, A., Kakon, S.H., Haque, R., Petri, W.A., Nelson, C.A., 2019. Growth faltering is associated with altered brain functional connectivity and cognitive outcomes in urban Bangladeshi children exposed to early adversity. BMC Med. 17 (1), 199. https://doi.org/10.1186/s12916-019-1431-5.

Orekhova, E.V., Elsabbagh, M., Jones, E.J., Dawson, G., Charman, T., Johnson, M.H., BASIS, T., 2014. EEG hyper-connectivity in high-risk infants is associated with later autism. J. Neurodev. Disord. 6 (1), 40. https://doi.org/10.1186/1866-1955-6-40.

Storrs, C., 2017. How poverty affects the brain. Nat. News 547 (7662), 150–152. https://doi.org/10.1038/547150a.

Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. U.S.A. 104 (4), 1319–1324. https://doi.org/10.1073/pnas.0610362104.

Kuban, K.C.K., Jara, H., O'shea, T.M., Heeren, T., Joseph, R.M., Fichorova, R.N., Alshamrani, K., Aakil, A., Beaulieu, F., Horn, M., Douglass, L.M., Frazier, J.A., Hirtz, D., Rollins, J.V., Cochran, D., Paneth, N., ELGAN Study, I., 2019. Association of circulating proinflammatory and anti-inflammatory protein biomarkers in extremely preterm born children with subsequent brain magnetic resonance imaging volumes and cognitive function at age 10 years. J. Pediatr. 210, 81–90. https://doi.org/10.1016/j.jpeds.2019.03.018.

O'shea, T.M., Shah, B., Allred, E.N., Fichorova, R.N., Kuban, K., Dammann, O., Leviton, A., ELGAN Study, I., 2013. Inflammation-initiating illnesses, inflammation-related proteins, and cognitive impairment in extremely preterm infants. Brain Behav. Immun. 29, 104–112. https://doi.org/10.1016/j.bbi.2012.12.012.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134 (1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Lopez-Calderon, J., Luck, S.J., 2014. ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Hum. Neurosci. 8, 8. https://doi.org/10.3389/fnhum.2014.00213.

Xie, W., Mallin, B.M., Richards, J.E., 2019. Development of brain functional connectivity and its relation to infant sustained attention in the first year of life. Dev. Sci. 22 (1), e12703 https://doi.org/10.1111/desc.12703.

Richards, J.E., Sanchez, C., Phillips-Meek, M., Xie, W., 2016. A database of age-appropriate average MRI templates. NeuroImage 124 (Pt B), 1254–1259. https://doi.org/10.1016/j.neuroimage.2015.04.055.

Shattuck, D.W., Mirza, M., Adisetiyo, V., Hojatkashani, C., Salamon, G., Narr, K.L., Poldrack, R.A., Bilder, R.M., Toga, A.W., 2008. Construction of a 3D probabilistic atlas of human cortical structures. NeuroImage 39 (3), 1064–1080. https://doi.org/10.1016/j.neuroimage.2007.09.031.

Vinck, M., Oostenveld, R., van Wingerden, M., Battaglia, F., Pennartz, C.M.A., 2011. An improved index of phase-synchronization for electrophysiological data in the

presence of volume-conduction, noise and sample-size bias. NeuroImage 55 (4), 1548–1565. https://doi.org/10.1016/j.neuroimage.2011.01.055.

Development of infant sustained attention and its relation to EEG oscillations, an EEG and cortical source analysis study - Xie - 2018 - Developmental Science - Wiley Online Library. Accessed October 25, 2020. ⟨https://onlinelibrary.wiley.com/doi/abs/10.1111/desc.12562⟩.

Thorpe, S.G., Cannon, E.N., Fox, N.A., 2016. Spectral and source structural development of mu and alpha rhythms from infancy through adulthood. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 127 (1), 254–269. https://doi.org/10.1016/j.clinph.2015.03.004.

Mullen EM. Mullen Scales of Early Learning. Published online 1995.

Koura, K.G., Boivin, M.J., Davidson, L.L., Ouédraogo, S., Zoumenou, R., Alao, M.J., Garcia, A., Massougbodji, A., Cot, M., Bodeau-Livinec, F., 2013. Usefulness of child development assessments for low-resource settings in francophone Africa. J. Dev. Behav. Pediatr. JDBP 34 (7), 486–493. https://doi.org/10.1097/DBP.0b013e31829d211c.

Bornman, J., Romski, M., Tonsing, K., Sevcik, R., White, R., Barton-Hulsey, A., Morwane, R., 2018. Adapting and translating the mullen scales of early learning for the South African context. S. Afr. J. Commun. Disord. 65 (1), 1. https://doi.org/10.4102/sajcd.v65i1.571.

Milosavljevic, B., Vellekoop, P., Maris, H., Halliday, D., Drammeh, S., Sanyang, L., Darboe, M.K., Elwell, C., Moore, S.E., Lloyd-Fox, S., 2019. Adaptation of the Mullen Scales of Early Learning for use among infants aged 5– to 24–months in rural Gambia. Dev. Sci. 22 (5), e12808 https://doi.org/10.1111/desc.12808.

Wasserman, G.A., Liu, X., Parvez, F., Ahsan, H., Factor-Litvak, P., Kline, J., van Geen, A., Slavkovich, V., Loiacono, N.J., Levy, D., Cheng, Z., Graziano, J.H., 2007. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ. Health Perspect. 115 (2), 285–289. https://doi.org/10.1289/ehp.9501.

Kippler, M., Tofail, F., Hamadani, J.D., Gardner, R.M., Grantham-McGregor, S.M., Bottai, M., Vahter, M., 2012. Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. Environ. Health Perspect. 120 (10), 1462–1468. https://doi.org/10.1289/ehp.1104431.

Jensen, S.K.G., Kumar, S., Xie, W., Tofail, F., Haque, R., Petri, W.A., Nelson, C.A., 2019. Neural correlates of early adversity among Bangladeshi infants. Sci. Rep. 9, 9. https://doi.org/10.1038/s41598-019-39242-x.

Perkins, J.M., Kim, R., Krishna, A., McGovern, M., Aguayo, V.M., Subramanian, S.V., 2017. Understanding the association between stunting and child development in low- and middle-income countries: Next steps for research and intervention. Soc. Sci. Med. 193, 101–109. https://doi.org/10.1016/j.socscimed.2017.09.039.

Hamadani, J.D., Tofail, F., Hilaly, A., Huda, S.N., Engle, P., Grantham-McGregor, S.M., 2010. Use of family care indicators and their relationship with child development in Bangladesh. J. Health Popul. Nutr. 28 (1), 23–33.

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann. Stat. 29 (4), 1165–1188. https://doi.org/10.1214/aos/1013699998.

Favrais, G., van de Looij, Y., Fleiss, B., Ramanantsoa, N., Bonnin, P., Stoltenburg-Didinger, G., Lacaud, A., Saliba, E., Dammann, O., Gallego, J., Sizonenko, S., Hagberg, H., Lelièvre, V., Gressens, P., 2011. Systemic inflammation disrupts the developmental program of white matter. Ann. Neurol. 70 (4), 550–565. https://doi.org/10.1002/ana.22489.

Malaeb, S.N., Davis, J.M., Pinz, I.M., Newman, J.L., Dammann, O., Rios, M., 2014. Effect of sustained postnatal systemic inflammation on hippocampal volume and function in mice. Pediatr. Res. 76 (4), 363–369. https://doi.org/10.1038/pr.2014.106.

Guevara, E., Pierre, W.C., Tessier, C., Akakpo, L., Londono, I., Lesage, F., Lodygensky, G. A., 2017. Altered functional connectivity following an inflammatory white matter injury in the newborn rat: a high spatial and temporal resolution intrinsic optical imaging study. Front. Neurosci. 11, 11. https://doi.org/10.3389/fnins.2017.00358.

Zhan, Y., Paolicelli, R.C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., Vyssotski, A.L., Bifone, A., Gozzi, A., Ragozzino, D., Gross, C.T., 2014. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat. Neurosci. 17 (3), 400–406. https://doi.org/10.1038/nn.3641.

Mottahedin, A., Ardalan, M., Chumak, T., Riebe, I., Ek, J., Mallard, C., 2017. Effect of neuroinflammation on synaptic organization and function in the developing brain: implications for neurodevelopmental and neurodegenerative disorders. Front. Cell Neurosci. 11, 11. https://doi.org/10.3389/fncel.2017.00190.

Spann, M.N., Monk, C., Scheinost, D., Peterson, B.S., 2018. Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. J. Neurosci. 38 (11), 2877–2886. https://doi.org/10.1523/JNEUROSCI.2272-17.2018.

Xie, W., Mallin, B.M., Richards, J.E., 2018. Development of infant sustained attention and its relation to EEG oscillations: an EEG and cortical source analysis study. Dev. Sci. 21 (3), e12562 https://doi.org/10.1111/desc.12562.

Kopell, N., Whittington, M.A., Kramer, M.A., 2011. Neuronal assembly dynamics in the beta1 frequency range permits short-term memory. Proc. Natl. Acad. Sci. U.S.A. 108 (9), 3779–3784. https://doi.org/10.1073/pnas.1019676108.

Gola, M., Magnuski, M., Szumska, I., Wróbel, A., 2013. EEG beta band activity is related to attention and attentional deficits in the visual performance of elderly subjects. Int. J. Psychophysiol. 89 (3), 334–341. https://doi.org/10.1016/j.ijpsycho.2013.05.007.

Deoni, S.C., Mercure, E., Blasi, A., Gasston, D., Thomson, A., Johnson, M., Williams, S.C., Murphy, D.G., 2011. Mapping infant brain myelination with magnetic resonance imaging. J. Neurosci. 31 (2), 784–791. https://doi.org/10.1523/JNEUROSCI.2106-10.2011.

Brito, N.H., Fifer, W.P., Myers, M.M., Elliott, A.J., Noble, K.G., 2016. Associations among family socioeconomic status, EEG power at birth, and cognitive skills during infancy. Dev. Cogn. Neurosci. 19, 144–151. https://doi.org/10.1016/j.dcn.2016.03.004.

Wilkinson, C.L., Levin, A.R., Gabard-Durnam, L.J., Tager-Flusberg, H., Nelson, C.A., 2019. Reduced frontal gamma power at 24 months is associated with better expressive language in toddlers at risk for autism. Autism. Res. 12 (8), 1211–1224. https://doi.org/10.1002/aur.2131.

Wilkinson, C.L., Gabard-Durnam, L.J., Kapur, K., Tager-Flusberg, H., Levin, A.R., Nelson, C.A., 2020. Use of longitudinal EEG measures in estimating language development in infants with and without familial risk for autism spectrum disorder. Neurobiol. Lang. Camb. Mass. 1 (1), 33–53. https://doi.org/10.1162/nol_a_00002.

Gou, Z., Choudhury, N., Benasich, A.A., 2011. Resting frontal gamma power at 16, 24 and 36 months predicts individual differences in language and cognition at 4 and 5 years. Behav. Brain. Res. 220 (2), 263–270. https://doi.org/10.1016/j.bbr.2011.01.048.

Tomalski, P., Moore, D.G., Ribeiro, H., Axelsson, E.L., Murphy, E., Karmiloff-Smith, A., Johnson, M.H., Kushnerenko, E., 2013. Socioeconomic status and functional brain development - associations in early infancy. Dev. Sci. 16 (5), 676–687. https://doi.org/10.1111/desc.12079.

Early Cognitive and Language Skills are Linked to Resting Frontal Gamma Power Across the First Three Years , (Accessed 25 October 2020). ⟨https://www-ncbi-nlm-nih-gov.ucsf.idm.oclc.org/pmc/articles/PMC2610686/⟩.

Cantiani, C., Piazza, C., Mornati, G., Molteni, M., Riva, V., 2019. Oscillatory gamma activity mediates the pathway from socioeconomic status to language acquisition in infancy. Infant. Behav. Dev. 57, 101384 https://doi.org/10.1016/j.infbeh.2019.101384.

Luan, Y., Yao, Y., 2018. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front. Immunol. 9, 9. https://doi.org/10.3389/fimmu.2018.01302.