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Supplementary Materials for

Early deprivation alters structural brain development from middle childhood to adolescence

Margaret A. Sheridan *et al.*

Corresponding author: Margaret A. Sheridan, sheridan.margaret@unc.edu

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Supplementary Results

Region of Interest analysis.

We sought to confirm our findings in the whole brain using an ROI approach because this allowed us to take a stricter approach to multiple comparisons. In this approach we took ROIs which overlapped with findings from (*28*) because this is the only paper reports findings from a sample of post-pubertal individuals who were exposed to institutionalization. Thus, these findings are likely to be most similar to what we would expect to observe here. Mackes and colleagues observed differences in cortical surface area and thickness associated with exposure to institutionalization in the inferior frontal gyrus, anterior cingulate cortex, and temporal pole(*28*). Using structurally defined regions of interest with the Desikan and Killiany atlas (*78*) we examined group (FCG vs CAUG) differences in thickness at age 16 in six regions: right and left caudal anterior cingulate cortex, left and right pars triangularis, and left and right temporal pole. We set our threshold for significance at $p < .008$ using a Bonferonni correction. We observed significant differences between CAUG and FCG in two regions of interest, the left caudal anterior cingulate cortex ($t_{79} = 3.06$, $p = .001$, $d = .21$) and pars triangularis ($t_{79} = 3.13$, $p = .001$, $d = .15$). These anatomically defined regions overlap significantly spatially with differences we observed in the whole brain analysis. No other regions were significantly different between groups (all p's > .07).

Impact of institutionalization on subcortical volume without controls for ICV

When not controlling for intracranial volume, ever-institutionalized children had significantly smaller right ($F_{1,111} = 6.10$, $p = .02$, $\eta^2 = .052$) and left ($F_{1,111} = 2.74$, $p = .10$, $\eta^2 = .024$) hippocampus, right ($F_{1,111} = 4.52$, $p = .04$, $\eta^2 = .039$) and left ($F_{1,111} = 4.36$, $p = .04$, $\eta^2 = .038$) amygdala, and right ($F_{1,111} = 8.09$, $p = .005$, $\eta^2 = .068$) and left ($F_{1,111} = 12.17$, $p < .001$, $\eta^2 = .099$) thalamus volume relative to never-institutionalized children following correction for multiple comparisons using false discovery rate(*75*) (FDR). However, none of these differences were significant after controlling for total intracranial volume.

Non-significant results (group effects)

We found no evidence for significant differences in subcortical volume at 16 years of age between children in the ever vs. never institutionalized groups in the right ($F_{1,111}$ = 1.88, *p* =.17, η^2 = .017) and left ($F_{1,111}$ = 1.02, *p* =.32, η^2 = .009) caudate, right ($F_{1,111}$ = .98, *p* =.32, η^2 = .009) and left ($F_{1,111}$ = .23, *p* =.64, η^2 = .002) putamen, or the right ($F_{1,111}$ = 1.95, *p* =.17, η^2 = .017) and left ($F_{1,111}$ = .67, *p* =.41, η^2 = .006) globus pallidus after controlling for multiple comparisons.

We found no evidence for the impact of foster care intervention on subcortical volume at 16 years of age in the right (t_{80} = 1.01, *p* = .16, *d* =.22) and left (t_{80} = 1.15, *p* = .13, *d* =.25) hippocampus, right (t_{80} = 1.30, *p* = .10, *d* =.29) and left (t_{80} = 1.61, *p* = .06, *d* =.36) amygdala, right (t_{80} = .19, *p* = .42, *d* =.043) and left (t_{80} = -.05, *p* = .48, *d* = -.01) caudate, right (t_{80} = .94, *p* = .18, *d* =.21) and left (t_{80} = 1.82, *p* = .04, *d* =.40) putamen, right (t_{80} = .90, *p* = .19, *d* =.19) and left (t_{80} = .06, *p* = .48, *d* =.014) globus pallidus, or right (t_{80} = .83, *p* = .21, *d* =.18) and left (t_{80} = .83, *p* = .20, *d* =.18) thalamus after controlling for multiple comparisons.

We found no evidence for the impact of randomization out of foster care intervention early vs. late on subcortical volume at 16 years of age in the right (t_{39} = .87, *p* = .20, *d* =.27) and left (t_{39} = .94, *p* = .18, *d* =.29) hippocampus, right (t_{39} = .58, *p* = .28, *d* =.18) and left (t_{39} = 1.21, *p* = .12, *d* =.38) amygdala, right (t_{39} = .60, *p* = .28, *d* =.19) and left (t_{39} = .36, *p* = .36, *d* =.11) caudate, right (t_{39} = 1.35, *p* = .09, *d* =.42) and left (t_{39} = 1.83, *p* = .04, *d* =.57) putamen, right (t_{39} = .32, *p* = .38, *d* =.10) and left (t_{39} = .96, *p* = .17, *d* =.29) globus pallidus, or right (t_{39} = -.37, *p* = .36, *d* = -.12) and left (t_{39} = -.21, *p* = .42, *d* = -.06) thalamus after controlling for multiple comparisons.

Associations between neural structure and psychopathology

We examined associations between psychopathology as measured by factor scores and cortical thickness in the two regions in the left hemisphere (ACC and IFG) which showed a significant impact of randomization to foster care on neural structure at age 16 controlling for age at scan and gender. As reported in the paper thickness in the ACC significantly predicted factor scores on the externalizing factor but not the ‘p’ factor, or internalizing factor. Thickness in the IFG did not significantly predict factor scores on the externalizing (β = .09, t = .82, p = .41, f^2= .008), internalizing (β = .11, t = .98, p = .33, f^2= .019) or 'p' factor (β = .14, t = 1.25, p = .21, f^2= .012).

Longitudinal change

Because acquisition parameters changed between 8 and 16 years, we wanted to document that we observed patterns of change in cortical volume from 9 -16 years which would be expected based on prior research. Here we report on change in volume and thickness across all participants regardless of group. Given that this sample is not representative of any specific population we report these findings only as a methods note to the overall paper. First, as expected based on previous work(*32,45*), we observed significant reductions in grey matter volume ($F_{1,61}$ = 9.32, p <.003) and increases in white matter volume ($F_{1,61}$ = 7.94, p <.007) from early to middle adolescence.

Second, as expected based on previous work, subcortical volume also changed from 9 to 16 years in this sample(*4*). We observed significant reductions over time in subcortical grey matter volume in the left ($F_{1,61}$ = 5.41, p = .02) and right ($F_{1,61}$ = 10.15, p = .002) hippocampus, right amygdala ($F_{1,61}$ = 3.99, p = .05), right thalamus ($F_{1,61}$ = 4.25, p = .04), left ($F_{1,61}$ = 11.98, p = .001) and right caudate ($F_{1,61}$ = 7.09, p = .01), and in the left ($F_{1,61}$ = 13.59, p < .001) and right ($F_{1,61}$ = 10.94, p = .002) pallidum. Of these regions, change in the right hippocampus, caudate, and pallidum remained significant after controlling for multiple comparisons.

Third, we examined change in cortical thickness and surface area from 9 to 16 years of age in a vertex-wise analysis that controlled for multiple comparisons. As predicted from the extant literature, cortical thickness decreased across age in most areas of cortex (Figure S3; Table S1). This change was prominent across temporal cortex, IFG, medial PFC and the post central gyrus.

Fig. S1.

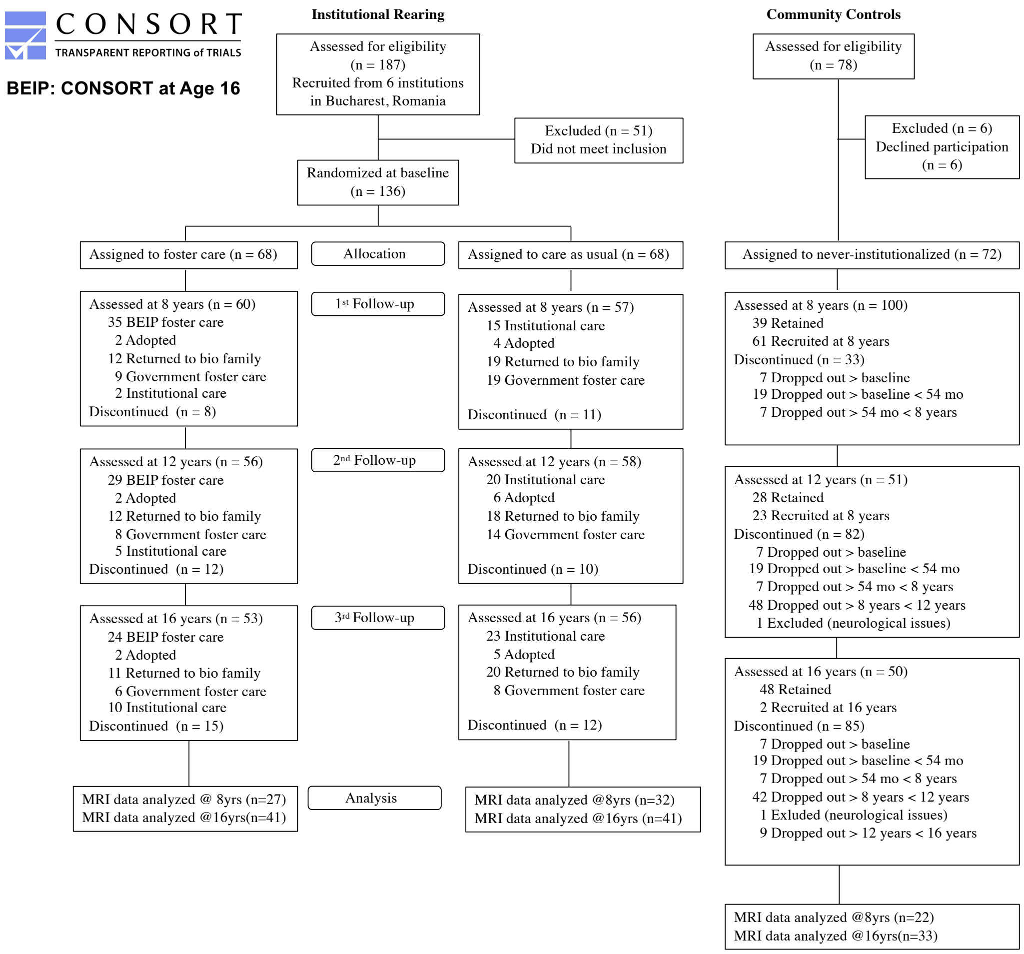

Figure S1. Consort diagram for the BEIP study through 16 years of age. At the third follow-up (16 years) the following participants were re-enrolled into the parent study (FCG n = 53; CAUG n = 56; NIG n = 50). At both 9 and 16 years, not every participant was able to be recruited into the MRI portion of the study, many refused to participate because of concerns about the MRI scanner, others because of time constraints with scheduling or funding. As a result, the final number of participants for the MRI portions of the study are smaller than for the parent study at both 9 and 16 years. More participants were successfully recruited into the MRI portion of the study at 16 relative to 9 years, primarily due to funding constraints at the 9 year time point. Many participants in the 'never institutionalized' group refused further participation in all portions of the study. This is indicated in the 'Community Controls' portion of the diagram. As can be observed, these participants left at every time point (for example, in the final sample at 16 years 7 dropped out before the baseline, 19 dropped out between the baseline and 54 month follow up, etc.).

Fig. S2.

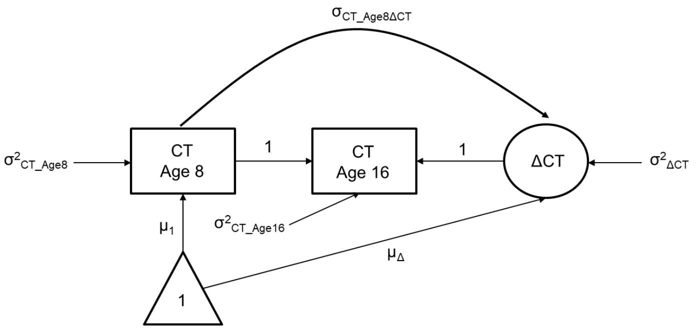

Figure S2. Latent Change Analysis. Structure of the latent change score (LCS) analysis with change in cortical thickness (CT) from age 8 to 16 years predicted by initial level of CT at age 8 years. Group membership (care-as-usual = 0, foster care = 1) was added as a predictor of change (ΔCT) in cortical thickness of the ACC and IFG (in separate models) given that these were the regions showing differences by intervention group. This analysis used a maximum likelihood with robust standard errors (MLR) estimator and used full-information maximum likelihood, meaning all participants with at least one data point at age 8 and/or 16 years were included in the analysis. This served as a test of robustness of the main results by

Fig. S3.

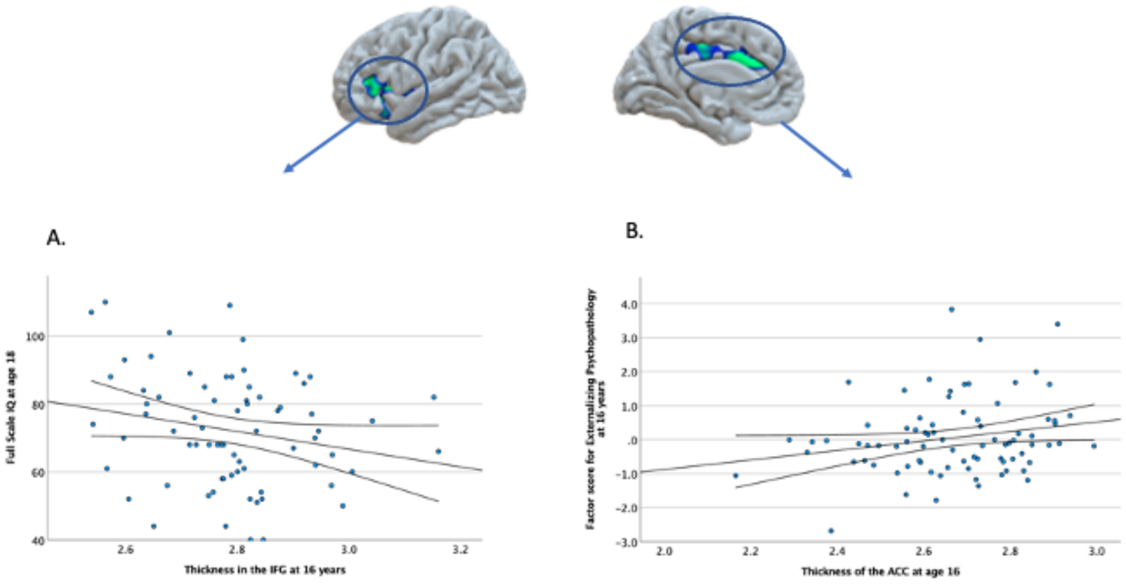

Figure S3. Cortical Thickness and Developmental Outcomes. Correlations between cortical thickness at age 16 in (A) the inferior frontal gyrus (IFG) and Full Scale IQ at age 18 years and (B) the anterior cingulate cortex (ACC) and externalizing factors scores at age 16.

Fig. S4.

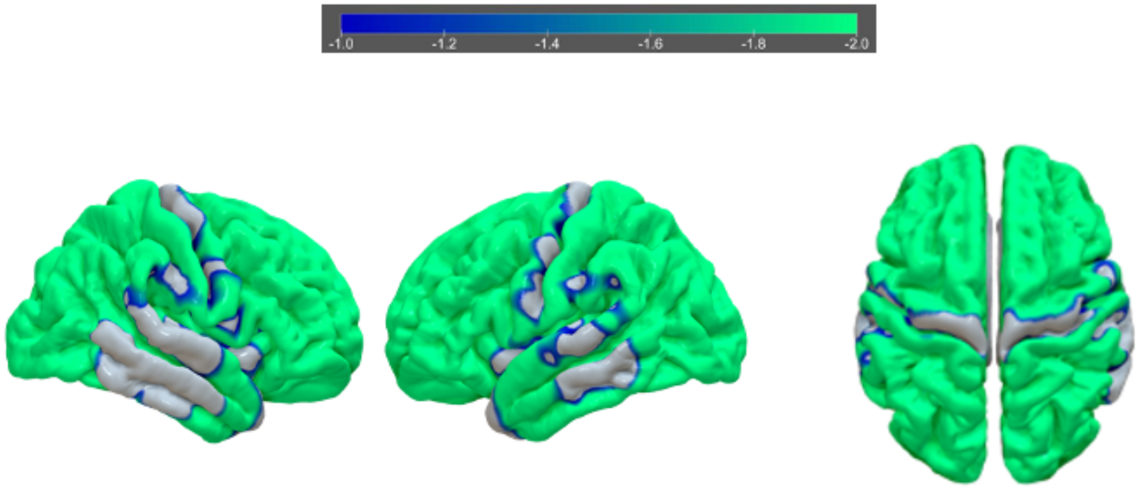

Figure S4. Developmental change in thickness regardless of group assignment. Areas of cortex showing significant decreases in thickness from 9 to 16 years regardless of experiences of institutionalization

Table S1.

	CAUG	**FCG**	**NIG**
Average age at 16 year follow up (SD)	200m (5.8m)	198m (6.2m)	201m (5.6m)
Months between Scan 1 and Scan 2	84m	82m	78m
Gender	54% female	49% female	42% female

Table S1. Demographic and sample information

Table S2.

Brain Area	Cluster size (mm^2)	Z-value of Max Vertex *z*	P-value of cluster *p*	Approximate Coordinates of Max Vertex in MNI space x	y	z
Change in thickness between 9 and 16 years across groups (n = 64)						
L Lat Orbital frontal cortex	71458	-18.16	>0.001	-19.3	30.1	-17.5
R Lingual cortex	67462	-15.35	>0.001	15.3	-53.0	-2.5

Table S2. Regions with significant differences in longitudinal cortical thickness (mm^2) among all subjects regardless of group membership.

Table S3.

		CAUG (n = 40)	FCG (n= 41)	NIG (n = 33)
Total grey matter volume (cubic centimeters)		469.3(48.6)	470.4 (43.6)	482.1 (51.5)
Total white matter volume		423.9 (49.1)	438.6 (48.7)	456.6 (56.6)
Amygdala	Right	1.5 (.2)	1.5 (.2)	1.5 (.2)
	Left	1.4 (.2)	1.5 (.2)	1.5 (.2)
Hippocampus	Right	4.0 (.4)	4.0 (.4)	4.1 (.4)
	Left	3.9 (.4)	4.0 (.4)	4.0 (.4)
Thalamus	Right	6.9 (.7)	7.0 (.8)	7.2 (.8)
	Left	7.4 (.7)	7.5 (.9)	7.9 (.8)
Caudate	Right	3.9 (.5)	3.9 (.6)	3.9 (.5)
	Left	3.7 (.4)	3.7 (.5)	3.7 (.5)
Putamen	Right	5.6 (.7)	5.7 (.5)	5.6 (.7)
	Left	5.6 (.8)	5.9 (.6)	5.8 (.9)
Globus Pallidus	Right	1.6 (.2)	1.6 (.2)	1.7 (.2)
	Left	1.7 (.3)	1.7 (.2)	1.7 (.3)

Table S3. Volume of total cortical grey and white matter as well as volume of six subcortical structures in cubic centimeters at the second (age 16 years) time point. Volume was measured using FreeSurfer analysis suite. Only differences between the EIG and NIG were significant for total grey and white matter volume.

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