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Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to ADHD

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Abstract

Background—Children exposed to early-life psychosocial deprivation associated with institutional rearing are at markedly elevated risk of developing ADHD. Neurodevelopmental mechanisms that explain the high prevalence of ADHD in children exposed to institutionalization are unknown. We examined whether abnormalities in cortical thickness and sub-cortical volume were mechanisms explaining elevations in ADHD among children raised in institutional settings.

Methods—Data were drawn from the Bucharest Early Intervention Project, a cohort of children raised from early infancy in institutions in Romania (n=58) and age-matched community controls (n=22). Magnetic resonance imaging data were acquired when children were aged 8–10 years, and ADHD symptoms were assessed using the Health and Behavior Questionnaire (HBQ).

Results—Children reared in institutions exhibited widespread reductions in cortical thickness across prefrontal, parietal, and temporal regions relative to community controls. No group differences were found in the volume of sub-cortical structures. Reduced thickness across numerous cortical areas was associated with higher levels of ADHD symptoms. Cortical thickness in lateral orbitofrontal cortex, insula, inferior parietal cortex, precuneus, superior temporal cortex, and lingual gyrus mediated the association of institutionalization with inattention and impulsivity; additionally, supramarginal gyrus thickness mediated the association with inattention and fusiform gyrus thickness mediated the association with impulsivity.

Conclusion—Severe early-life deprivation disrupts cortical development resulting in reduced thickness in regions with atypical function during attention tasks in children with ADHD,

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including the inferior parietal cortex, precuneus, and superior temporal cortex. These reductions in thickness are a neurodevelopmental mechanism explaining elevated ADHD symptoms in children exposed to institutional rearing.

Keywords

cortical development; institutionalization; deprivation; childhood adversity; attention-deficit/hyperactivity disorder (ADHD); brain development

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder estimated to affect approximately 5% of children worldwide. (1–3) Children with ADHD exhibit deficits in numerous aspects of executive functioning including working memory, response inhibition, attentional and motor control, and planning. (4–9) Meta-analyses of fMRI studies have identified abnormalities in neural function among children with ADHD including blunted activation in right hemisphere dorsolateral prefrontal cortex (PFC), striatum, and thalamus during inhibition and attention tasks, reduced inferior parietal cortex, precuneus, and superior temporal cortex activation during attention tasks, and hypo-activation in left hemisphere frontal-parietal-cerebellar circuits during timing tasks. (10, 11).

ADHD is also associated with atypical neural structure, including smaller volume of the PFC and basal ganglia (12–14) and reductions in cortical thickness across the prefrontal, parietal, and temporal cortex. (15, 16) Children with ADHD experience 2–5 year delays in reaching peak cortical thickness in these regions, (17) and cortical thickness in children with ADHD does not “catch up” to levels seen in typically developing children in most areas. (16, 18). Children with ADHD whose developmental trajectory of cortical thickness is more similar to that of typically developing children have better functional outcomes than children with persistent thickness reductions, (16) suggesting that this pattern of cortical development may be central to the pathophysiology of ADHD.

What factors lead to these neurodevelopmental deficits in children with ADHD? The high heritability of the disorder and early age-of-onset suggest strong genetic underpinnings. (19, 20) However, early-life psychosocial deprivation is also associated with ADHD, (21–23) indicating that adverse early experiences may contribute to atypical patterns of brain development. The prevalence of ADHD among children raised in institutional settings is 4–5 times higher than in the general population, raising questions about neurodevelopmental mechanisms involved in ADHD following psychosocial deprivation. (21–23) Institutional rearing is associated with atypical structural development that might contribute to ADHD risk in previously-institutionalized children. Reduced cerebral and cortical white and grey matter volumes have been observed in institutionally-reared children (24, 25), as well as white matter microstructure abnormalities in tracts linking the PFC to temporal and parietal regions. (26–28) Larger right amygdala volume was reported in one study of institutionally-reared children, (24) and another found larger amygdala volume among late-adopted children compared to early-adopted and control children. (29) Reduced cerebellar volume has also been observed in previously-institutionalized children. (30)

We investigated whether atypical neural structure is responsible for elevations in ADHD among children raised in institutional settings. We anticipated that institutional rearing

would be associated with reduced cortical thickness and sub-cortical volume in regions implicated in ADHD pathology, including the dorsolateral PFC, inferior parietal cortex, superior temporal cortex, and striatum. In addition, we hypothesized that reduced cortical thickness and sub-cortical volume in these regions would be associated with ADHD pathology. Finally, we investigated whether disrupted cortical and sub-cortical development is a mechanism explaining the association between early psychosocial deprivation and ADHD.

Methods

Sample

The Bucharest Early Intervention Project (BEIP) is a longitudinal study of early institutionalization of young children in Bucharest, Romania. (31) A sample of 136 children (age range 6–30 months, *M* = 23 months) was recruited from each of the six institutions for young children in Bucharest, excluding participants with genetic syndromes (e.g., Down syndrome), fetal alcohol syndrome, and microcephaly. (31) An age-matched sample of 72 community-reared children was recruited from pediatric clinics in Bucharest and comprised the never-institutionalized group (NIG). Half of children in the institutionalized group were randomized to a foster care intervention, resulting in two groups: the foster care group (FCG) and the group who received care as usual (prolonged institutional care [CAUG]). The study design and methods have been described in detail previously. (31)

Structural magnetic resonance imaging (MRI) was acquired when children were between 8 and 10 years of age for all children whose guardians provided consent for imaging. Of the 86 children who completed MRI assessments, 80 were included in analysis: 31 CAUG children (15 female), 27 FCG children (13 female), and 22 NIG children (12 female). Four participants were excluded from analysis because of poor scan quality (2 CAUG, 1 FCG, and 1 NIG) and two children were excluded due to frank neurological abnormality (1 FCG, 1 NIG). Four participants were taking stimulant medication for ADHD at the time of the scan (3 CAUG, 1 FCG).

No differences in ADHD symptoms of inattention, $t(51) = 0.46$, $p = .646$, or impulsivity, $t(51) = 0.69$, $p = .497$, or in cortical thickness or sub-cortical volume were observed at age 8–10 years based on foster care placement. As such, children in the FCG and CAUG were collapsed into one ever-institutionalized group (EIG) for all analysis. No differences in gender distribution or age were observed for EIG and NIG children, although differences in IQ, birth weight, and cerebral gray and white matter were present across groups (Table 1).

Image acquisition

Structural magnetic resonance images were acquired at Regina Maria Health Center on a Siemens Magnetom Avanto 1.5 Tesla syngo system. Images were obtained using a transverse magnetization-prepared rapid gradient echo three-dimensional sequence (TE=2.98ms, TI=1000ms, flip angle= 8°, 176 slices with 1×1×1 mm isometric voxels) with a 16-channel head coil. The TR for this sequence was 1710 ms for most participants (n=59) and varied between 1650–1910 ms for remaining participants. Four subjects were acquired

in the sagittal plane; one was acquired in the coronal plane. Acquisition parameters did not differ by group membership nor were they associated with scan quality; all scans were therefore considered together and a covariate for TR length was included in all analysis.

Image Processing

Cortical reconstruction and volumetric segmentation were performed with FreeSurfer (Version 5.0, http://surfer.nmr.mgh.harvard.edu). Technical details of these procedures have been described previously. (32–36) Gray/white matter and gray matter/CSF boundaries are constructed using spatial intensity gradients across tissue classes. A segmentation process is used to identify sub-cortical grey matter structures. Following reconstruction, the cerebral cortex is parcellated into regions based on the structure of gyri and sulci. (34, 37) Intensity and continuity information is used to generate measurements of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface. (33) The resulting surface maps are not restricted to the voxel resolution of the original data and are capable of detecting sub-millimeter differences between groups.

FreeSurfer morphometric procedures have demonstrated good test-retest reliability across scanner manufacturers and field strengths, (38, 39) and methods for measuring cortical thickness have been validated against manual measurement (40, 41) and histological analysis, (42) and have been used in studies of children aged 8–10 years. (25,29–43) The results of the automated segmentation and parcellation process were manually inspected for all participants. Where necessary, manual edits were performed as recommended to optimize accurate placement of gray/white and gray/CSF borders based on shifts in the image intensity gradient. (32, 33) No differences were present in the degree to which manual edits were required across groups.

ADHD

The MacArthur Health and Behavior Questionnaire (HBQ) (44) was completed by the primary teacher of each child when they were between 8 and 10 years old (M = 8.5 years, SD = 0.4 years). The HBQ assesses emotional and behavior problems and has been widely used in studies of children ranging from preschool age to adolescence, including previously-institutionalized children. (45) The ADHD sub-scale assesses inattention and impulsivity. Teacher reports of ADHD behaviors on the HBQ have demonstrated excellent test-retest reliability in community and clinical samples, acceptable concordance with parent reports, and high discriminant validity. (44, 46)

Statistical Analysis

We investigated whether elevations in ADHD symptoms among institutionalized children relative to controls were accounted for by differences in brain structure using standard tests of statistical mediation. To provide evidence for mediation, four criteria must be met. (47, 48) First, an association between the exposure and outcome must be established. Here, we examined differences in ADHD symptoms between children reared in institutions versus the community using univariate ANOVAs with group (EIG, NIG) as a between-subjects factor.

Second, the exposure must be associated with the mediator. We examined group differences in brain structure using the Qdec surface-based group analysis tool (Version 1.4) in FreeSurfer. Following spatial normalization to an averaged spherical surface and smoothing with a 10mm full-width half-maximum Gaussian kernel, Qdec applies a general linear model (GLM) to cortical thickness at each vertex, separately by hemisphere. A discrete variable for group was included in the GLM, along with covariates for age, gender, total brain volume, and TR. No interactions were found between group and any of these covariates. To reduce Type I error associated with multiple comparisons, we applied a false discovery rate (FDR) correction. (49) Group differences in sub-cortical volume was examined using univariate ANOVAs with group as a between-subjects factor and the covariates outlined above for the caudate, putamen, globus pallidus, nucleus accumbens, amygdala, hippocampus, thalamus, and cerebellum. FDR correction was applied to correct for multiple comparisons.

Third, the mediator must be associated with the outcome. Here, we examined the associations of cortical thickness and sub-cortical volume with ADHD symptoms using linear regression. We examined the association of cortical thickness in each cluster that differed between children raised in institutions versus the community after FDR correction with ADHD symptoms. To do so, we created a region of interest (ROI) for each FDR-corrected cluster that was significantly different between groups. This normalized ROI was mapped back to each participant (using deformation tools in FreeSurfer) to generate a mean thickness value for that ROI for each participant. Gender, age, total brain volume, and TR were included as covariates.

Finally, we tested the significance of the indirect effect using a bootstrapping approach that provides bias-corrected confidence intervals and is appropriate for use in small samples. (50) Confidence intervals that do not include zero indicate significant mediation. We required that a brain region differed in thickness or volume as a function of institutionalization and be associated with ADHD symptoms at the FDR-corrected threshold to be included in the mediation analysis.

Results

Institutionalization and ADHD

ADHD symptoms varied as a function of institutionalization for inattention, $F(1,70) = 29.48$, $p < .001$, and impulsivity, $F(1,69) = 17.94$, $p < .001$. Children with histories of institutional rearing (EIG) exhibited higher levels of inattention ($M = 6.46$, $SD = 2.86$) and impulsivity ($M = 8.73$, $SD = 5.53$) than community-reared children (inattention $M = 1.90$, $SD = 2.86$; impulsivity $M = 3.14$, $SD = 4.33$).

Institutionalization and Cortical Thickness

Results from the left hemisphere GLM revealed 34 clusters that differed significantly in thickness as a function of institutionalization. Institutionally-reared children had reduced thickness compared to never-institutionalized children in all 34 clusters. Table 2 provides the Montreal Neurologic Institute (MNI) coordinates and peak of each cluster, and Figure 1

displays results. Significant differences in cortical thickness were observed in multiple clusters and were most pronounced in the superior and inferior parietal cortex (5 and 4 clusters, respectively), precuneus (4 clusters), superior temporal gyrus and sulcus (3 clusters), precentral gyrus (2 clusters), and posterior cingulate (2 clusters). Significant differences were also present in the superior frontal gyrus, middle frontal gyrus (MFG), fusiform gyrus, supramarginal gyrus, lateral orbitofrontal cortex (OFC), lateral occipital cortex, and insula.

The right hemisphere GLM revealed 27 clusters that differed significantly between groups, with institutionally-reared children exhibiting reduced cortical thickness than controls in all clusters (Table 3, Figure 2). Findings mirrored those from the left hemisphere, with the exception of greater differences in the MFG. Areas with multiple significant clusters and the largest group differences were the MFG (2 clusters), superior and inferior parietal cortex (3 and 4 clusters, respectively), precuneus (4 clusters), supramarginal gyrus (2 clusters), and superior temporal gyrus and sulcus (2 clusters). Additional regions differing in thickness included the superior frontal gyrus, inferior temporal gyrus, frontal pole, lateral OFC, lateral occipital cortex, fusiform gyrus, lingual gyrus, and insula.

We also examined the association of duration of institutionalization with cortical thickness in institutionally-reared children. Similar regions in the prefrontal, parietal, and temporal cortex that emerged in the between-groups analysis were associated with duration of institutionalization; however, none of these associations survived FDR correction.

Institutionalization and Sub-Cortical and Cerebellar Volume

Consistent with a previous report, (25) no differences in the volume of the striatum (including the caudate, putamen, globus pallidus, and nucleus accumbens), amygdala, hippocampus, thalamus, or cerebellum were observed as a function of institutionalization (Table 4).

Cortical Thickness and ADHD

Cortical thickness was significantly associated with inattention in 15 of the 34 left hemisphere regions and 13 of the 27 right hemisphere regions that differed in thickness between children with and without exposure to institutionalization, such that reduced thickness was associated with higher symptoms levels (Table 5). Reduced cortical thickness was associated with greater impulsivity in 10 of the 34 left hemisphere regions and 13 of the 27 right hemisphere regions that differed according to institutionalization. Cortical thickness was significantly associated with both inattention and impulsivity in the superior and inferior parietal cortex, MFG, superior temporal gyrus and sulcus, supramarginal gyrus, and precuneus. Additional regions associated with ADHD symptoms included the lateral OFC, frontal pole, postcentral gyrus, fusiform gyrus, inferior temporal gyrus, insula, and lingual gyrus.

Mediation Analysis

A significant indirect effect of institutionalization on inattention through cortical thickness was observed for the OFC (95% CI: 0.07, 1.54), insula (95% CI: 0.20, 1.57), inferior parietal

cortex (95% CI: 0.01, 2.44), supramaringal gyrus (95% CI: 0.05, 2.16), precuneus (95% CI: 0.43, 2.18), superior temporal cortex (95% CI: 0.86, 3.18), and lingual gyrus (95% CI: 0.07, 1.56). The total effect of institutionalization on inattention, $\beta = 0.54$, $p < .001$, was no longer significant when these regions were added to the model, $\beta = 0.19$, $p = .15$, and was reduced by 64.8% when cortical thickness in these regions was controlled.

A significant indirect effect of institutionalization on impulsivity through cortical thickness was observed for the OFC (95% CI: 0.11, 2.49), insula (95% CI: 0.13, 2.36), inferior parietal cortex (95% CI: 0.10, 3.61), precuneus (95% CI: 0.68, 3.30), superior temporal cortex (95% CI: 0.27, 4.08), fusiform gyrus (95% CI: 0.13, 2.53), and lingual gyrus (95% CI: 0.13, 2.33). The effect of institutionalization on impulsivity, $\beta = 0.43$, $p < .001$, was no longer significant when these regions are added to the model, $\beta = 0.08$, $p = .58$, and was reduced by 81.7% after accounting for cortical thickness in these regions.

Sensitivity Analysis

We conducted sensitivity analyses to determine whether other differences between the groups explained our findings, including birth weight, IQ, and medication status. We used a GLM to examine the association of cortical thickness with a) birth weight in the 66 participants (82.5%) that had this data available; and b) IQ in every vertex in the brain. After correction for FDR, no brain regions in either hemisphere were associated with birth weight or IQ, indicating that these factors were not plausible confounders of the association between institutionalization and neural structure. We also examined group differences in cortical thickness after excluding: a) the 4 participants on psychiatric medications at the time of scan; and b) the 5 participants acquired in a different orientation. Cortical regions that differed in thickness across groups were unchanged (Supplement: Tables S1–S4).

Discussion

ADHD is a common neurodevelopmental disorder. Institutional rearing is strongly associated with ADHD, which has generated questions about the neurodevelopmental pathways linking early-life psychosocial deprivation to ADHD. (21–23) We investigated this issue in a sample of children raised in deprived institutional settings to determine whether atypical neural structure was a mechanism linking institutional rearing to elevations in ADHD symptoms. Our findings provide novel evidence of widespread reductions in cortical thickness as a neurodevelopmental mechanism linking adverse psychosocial experience to the onset of ADHD. We found no evidence for a sub-cortical pathway linking institutionalization to ADHD.

This is the first study to document the effects of psychosocial deprivation on patterns of cortical thickness in children. Prior research indicates that a wide range of adverse early environments—including institutional rearing, abuse, and neglect—are associated with reduced cerebral and cortical volume. (24,25, 51–54) However, with one exception, (53) these studies have focused on global markers of cortical development and have not identified specific cortical regions associated with environmental adversity. Our findings indicate that institutional rearing is associated with pronounced reductions in cortical thickness in the PFC, including dorsolateral and OFC regions, throughout lateral and medial

parietal cortex, including superior and inferior regions, the supramarginal gyrus, precuneus, and posterior cingulate, and in the superior temporal gyrus and sulcus. This pattern of widespread reductions in cortical thickness is consistent with one previous study examining cortical structure in physically abused children, which found reductions in cortical volume in the OFC and in parietal and temporal regions. (53) These findings are also similar to the pattern of pervasive reductions in cortical thickness observed in children with ADHD. (15–17)

We provide novel evidence indicating that reduced cortical thickness is a neurodevelopmental mechanism linking institutionalization to ADHD symptoms. Reductions in cortical thickness associated with institutionalization might reflect either a developmental delay in reaching peak cortical thickness or accelerated cortical thinning in children exposed to psychosocial deprivation. Additional research is needed to adjudicate between these possibilities. In either case, our results suggest that these perturbations in cortical development are associated with the elevated rates of ADHD observed among children exposed to institutional rearing. Although reduced cortical thickness was present in children exposed to institutionalization across numerous regions, only a few areas significantly mediated the association of institutionalization with ADHD symptoms. Specifically, cortical thickness in lateral OFC, insula, inferior parietal cortex, precuneus, superior temporal gyrus and sulcus, and lingual gyrus mediated the association of institutionalization with inattention and impulsivity; supramarginal gyrus thickness additionally mediated the association with inattention and fusiform gyrus thickness additionally mediated the association with impulsivity. This pattern is largely consistent with findings from meta-analyses of fMRI studies, which document blunted activation in dorsolateral PFC, inferior parietal cortex, precuneus, and superior temporal cortex during attention tasks in ADHD. (11) These regions are integral to cognitive processes disrupted in ADHD including working memory storage, target detection, attentional orienting, and attention allocation. (55–59) Additionally, the precuneus and inferior parietal lobule are central nodes in the default mode network. (60, 61) Fluctuations in default mode network activation have been linked to attention lapses, (62) and some have hypothesized that this network underlies attention to external stimuli; (63) it is possible that atypical cortical structure in regions associated with the default mode network are related to the attentional deficits that underlie ADHD. This possibility warrants examination in future research. Finally, the OFC is involved in emotion regulation, social behavior, and decision making in situations involving reward or other emotionally salient cues. (64, 65) Children with ADHD exhibit impulsivity and problems in decision making, particularly in situations with high reward salience, (66) which may be related, in part, to abnormalities in the structure of the OFC.

In contrast, institutionalization was unrelated to the volume of sub-cortical structures, including the striatum, or to cerebellar volume. These findings are surprising for several reasons. First, institutional rearing has been associated with amygdala and cerebellum volume in previous studies. (24,29–30) Second, meta-analyses have identified the caudate and other divisions of the basal ganglia as regions that differ in structure among those with ADHD relative to controls. (13, 14) Third, previous research suggests important functional differences in the basal ganglia, particularly the caudate, among children with ADHD

compared to controls. (67–71) Abnormalities in fronto-striatal function are central to theoretical conceptualizations of cognitive deficits in ADHD, including working memory and response selection and inhibition. (9,72–73) Striatal contributions to ADHD symptomatology may reflect predominantly genetic and prenatal influences whereas cortical mechanisms reflect a combination of both pre- and postnatal influences. Future research is needed to evaluate this possibility empirically. It is important to acknowledge, however, that the lack of differences in striatal volume as a function of institutionalization may have resulted from measurement error given the optimization of FreeSurfer algorithms for cortical analysis.

Children exposed to institutionalization exhibited reductions in cortical thickness in numerous regions of the prefrontal, parietal and temporal cortex, and this atypical pattern of neurodevelopment was a mechanism linking institutionalization to ADHD. These findings have important implications for understanding the role of psychosocial experience in the developmental neurobiology of ADHD. Theoretical conceptualizations argue that ADHD involves fundamental deficits in the ability to generate accurate predictions about the type and timing of environmental events and to engage top-down control processes to alter behavior following experiences that violate predictions. (9) The deprived social environment of institutions may contribute to these deficits by affording children few opportunities to detect and learn environmental contingencies in order to facilitate accurate predictions about future events. Moreover, associative learning that occurs in the highly structured and atypical environment of institutions might impair prediction ability once children leave institutional care. In either case, children are provided limited experience engaging top-down control systems to regulate behavior in novel or unexpected circumstances. These experiences likely result in pervasive underutilization of multiple areas in association cortex, which may ultimately lead to the widespread reductions in cortical thickness observed here.

Identifying the specific aspects of psychosocial experience that predict disruptions in cortical development is an important goal for future research in order to elucidate mechanisms linking other types of adverse environments with ADHD. Executive functioning deficits and ADHD are common among children raised in families with low socio-economic status (74, 75) and those exposed to other types of psychosocial adversity. (76, 77) Determining whether the same cortical pathways are involved in these associations warrants examination in future studies. Conversely, other types of experience that lead to the pattern of cortical maturation observed here may also increase propensity for ADHD (e.g., preterm birth). Finally, the degree to which early intervention can mitigate the effects of adverse environmental experiences on cortical development is unknown.

The lack of intervention effect on ADHD and cortical structure among children randomized to foster care in this sample is surprising, given marked improvements resulting from the intervention in other cognitive and psychosocial domains. (21, 78) A previous study of children adopted out of Romanian institutions observed no elevations in ADHD among children placed before 6 months of age. (22, 23) No children were placed in foster care this early in the BEIP, suggesting that psychosocial experience very early in life might exert a lasting influence on cortical development that influences risk of ADHD and is not ameliorated by later intervention.

Several limitations are worth noting. First, ADHD symptoms were assessed using a teacher-report measure rather than a diagnostic interview. However, ADHD behaviors frequently manifest in the school setting, and in this sample teacher reports provide a more standardized method of reporting ADHD symptoms than caregiver reports, given variation across groups in the length and quality of caregiver relationships. Teachers have a unique perspective in having substantial amounts of time in which to observe children of a given age and to evaluate individual differences. Future research is nevertheless needed to replicate these findings in predicting ADHD diagnosis based on structured interviews. Second, the number of control participants was small relative to the number of children exposed to institutional rearing. Third, several previously-institutionalized children were on medications for ADHD at the time of scan. However, sensitivity analysis indicated no difference in results when these children were excluded. Fourth, group differences in ADHD may be related to factors other than postnatal rearing environments, such as prenatal malnutrition, exposure to alcohol or other toxins, or genetic factors. Though we cannot rule out genetic and prenatal differences between children with and without exposure to institutionalization, results were unchanged when we controlled for birth weight. Additionally, although meaningful IQ and birth weight differences exist across study groups, IQ and birth weight were unassociated with cortical thickness, indicating that they are not a plausible confounders of the observed associations with neural structure. Finally, differences in scan acquisition or motion may have contributed to our findings. However, neither differences in scan parameters nor rejection of scans due to artifact differed across groups, reducing concern about this possibility. Moreover, TR was included a covariate in all analysis and sensitivity analysis indicates that removing the five subjects acquired in a different orientation did not change the pattern of results.

We present novel evidence for a neurodevelopmental mechanism linking institutional rearing to ADHD symptomatology. Children reared in institutions exhibited widespread reductions in cortical thickness. Reductions in thickness in the prefrontal, parietal, and temporal cortex explained, at least in part, inattention and impulsivity observed in these children. Early-life psychosocial deprivation appears to disrupt cortical development, culminating in heightened risk of ADHD. Future research is needed to determine whether interventions targeted very early in the life course ameliorate these aberrant patterns of brain development and their behavioral consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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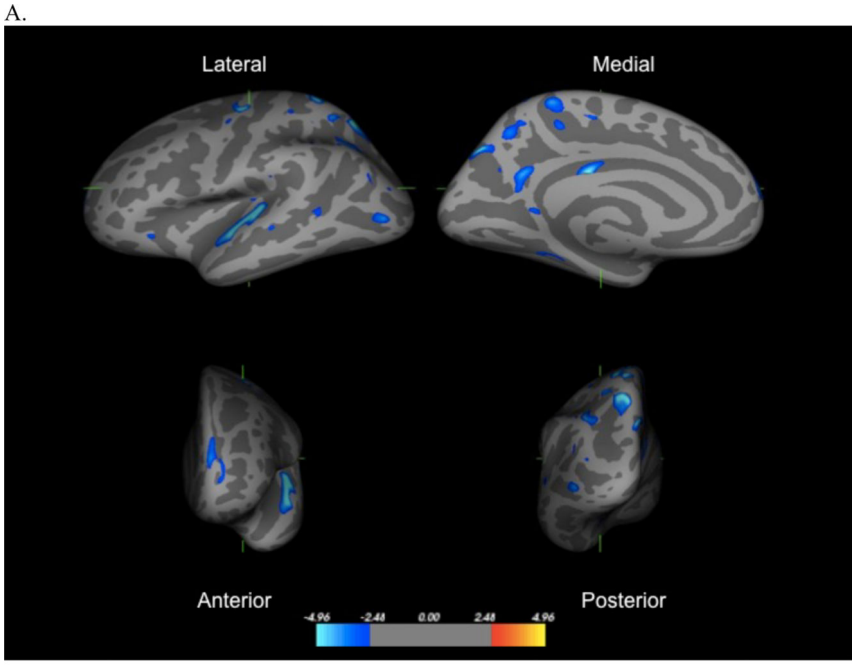
A.



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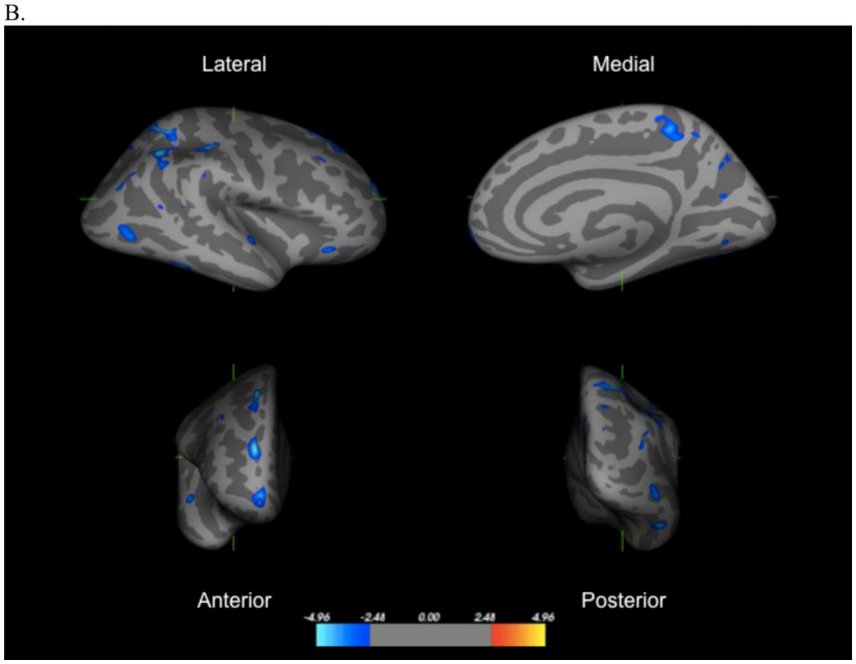

Figure 1.

Regions in left hemisphere (panel a) and right hemisphere (panel b) with significant reductions in thickness among children exposed to institutional rearing relative to controls, following FDR correction. Images represent (clockwise from top left), lateral, medial, posterior, and anterior views of the group average brain.

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Table 1

Socio-demographic and developmental characteristics among children reared in institutions and community controls in the Bucharest Early Intervention Project (n=80)

	Ever Institutionalized Group (n=58)		Never Institutionalized Group (n=22)		Group Difference	
	M	SD	M	SD	F	p-value
Female, No. (%)	48.3%		54.5%		$\chi^2_1 = 0.25$	.617
Age, (months)						
Age at Study Entry	17.7	(7.8)	20.0	(7.2)	1.21	.276
Age at MRI Scan	116.3	(9.0)	117.9	(10.6)	0.1	.816
Age at HBQ Assessment	103.2	(4.6)	101.4	(4.0)	2.49	.149
Birth Weight, (grams)	2780.0	(623.3)	3150.0	(411.8)	4.41*	.040
Head Circumference at birth (cm.)	46.07	(2.61)	46.5	(2.08)	0.04	.843
Full-scale IQ	72.0	(15.8)	107.9	(14.67)	96.49*	.001
Intracranial Volume[1]	1,456,490	(132,948)	1,499,091	(109,367)	1.79	.184
Cerebral Grey Matter[1]	790,429	(71,160)	833,849	(62,887)	6.31*	.014
Cortical Grey Matter	577,432	(57,120)	613,899	(48,391)	7.04*	.010

*Significant at the p<.05 level, 2-sided test

Table 2

Left hemisphere regions with significant differences in cortical thickness (mm) among children reared in institutions relative to community controls in the Bucharest Early Intervention Project (n=80)[1,2]

Brain Area	Cluster size (mm^2)	Peak within Cluster t	Approximate coordinates in MNI space (*x*, *y*, *z*) *x*	*y*	*z*
1. Superior Parietal Cortex	307.0	−6.65	−15.2	−66.1	50.1
2. Superior Temporal Gyrus	567.7	−6.65	−52.8	−10.3	−0.7
3. Precentral Gyrus	179.4	−6.02	−35.2	−14.6	64.7
4. Superior Parietal Cortex	337.4	−5.91	−16.8	−52.4	60.5
5. Superior Parietal Cortex	168.0	−5.24	−16.7	−74.2	37.6
6. Posterior Cingulate	67.7	−5.10	−3.9	−26.7	26.6
7. Inferior Parietal Cortex	251.9	−4.22	−36.2	−63.8	40.9
8. Precuneus	158.6	−4.16	−8.2	−57.5	22.4
9. Paracentral	130.8	−4.04	−15.4	−41.5	62.8
10. Lateral Occipital	121.6	−4.00	−43.9	−81.0	1.7
11. Superior Parietal Cortex	53.9	−3.96	−28.6	−56.2	56.7
12. Superior Frontal Gyrus	179.4	−3.92	−9.1	62.9	17.4
13. Precuneus	121.1	−3.74	−9.9	−59.9	45.2
14. Fusiform Gyrus	55.6	−3.49	−33.9	−47.4	−11.9
15. Paracentral	15.5	−3.48	−8.5	−25.9	51.1
16. Precuneus	30.3	−3.35	−18.3	−41.2	45.5
17. Posterior Cingulate	25.7	−3.29	−10.4	−48.3	3.5
18. Middle Frontal Gyrus	79.5	−3.20	−19.7	61.2	4.0
19. Lateral Orbitofrontal Cortex	32.8	−3.18	−35.8	28.4	−7.2
20. Superior Temporal Gyrus	20.3	−3.15	−49.9	−29.0	−2.9
21. Precentral Gyrus	22.3	−3.03	−41.6	−7.3	53.3
22. Inferior Parietal Cortex	12.3	−2.99	−40.6	−60.9	42.9
23. Postcentral Gyrus	22.8	−2.93	−32.7	−35.9	55.6
24. Inferior Parietal Cortex	21.0	−2.91	−44.2	−72.6	25.9
25. Supramarginal Gyrus	17.8	−2.89	−47.5	−48.2	42.7

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Brain Area	Cluster size (mm^2)	Peak within Cluster t	Approximate coordinates in MNI space (*x*, *y*, *z*) *x*	*y*	*z*
26. Insula	11.1	−2.89	−31.4	−29.7	13.4
27. Superior Temporal Sulcus	39.6	−2.87	−53.1	−51.5	3.4
28. Inferior Parietal Cortex	10.5	−2.85	−38.2	−84.3	14.5
29. Precuneus	6.5	−2.79	−13.0	−63.4	28.4
30. Supramarginal Gyrus	5.8	−2.76	−56.6	−29.4	18.9
31. Supramarginal Gyrus	0.4	−2.72	−44.5	−50.2	40.4
32. Superior Parietal Cortex	1.7	−2.72	−36.6	−48.6	51.5
33. Postcentral Gyrus	0.3	−2.71	−29.8	−32.3	68.2
34. Superior Frontal Gyrus	0.7	−2.71	−15.0	58.7	13.9

[1] Analyses control for age, gender, total brain volume, and TR.

[2] Significant group differences are shown at the p<.05 level, corrected for the false discovery rate (FDR). All significant group differences represent reduced cortical thickness in children reared in institutions relative to controls.

Table 3

Right hemisphere regions with significant differences in cortical thickness (mm) among children reared in institutions relative to community controls in the Bucharest Early Intervention Project (n=80)[1,2]

Brain Area	Cluster size (mm^2)	Peak within Cluster t	Approximate coordinates in MNI space (*x*, *y*, *z*) *x*	*y*	*z*
1. Middle Frontal Gyrus	197.7	−5.26	18.7	53.7	21.4
2. Inferior Parietal Cortex	353.6	−5.23	41.7	−55.9	41.1
3. Superior Frontal Gyrus	223.1	−5.10	20.6	23.4	55.1
4. Inferior Temporal Gyrus	136.5	−4.80	47.3	−45.1	−15.3
5. Supramarginal Gyrus	142.3	−4.76	40.7	−27.2	40.3
6. Superior Parietal Cortex	330.8	−4.71	26.7	−55.4	59.6
7. Frontal Pole	200.6	−4.47	10.0	64.0	−8.0
8. Precuneus	173.1	−4.33	16.2	−42.9	55.0
9. Superior Temporal Gyrus	73.0	−4.11	57.1	−4.8	−2.6
10. Lateral Orbitofrontal Cortex	62.9	−4.03	40.1	25.2	−13.7
11. Lateral Occipital Cortex	181.7	−4.02	40.6	−70.3	−1.9
12. Fusiform Gyrus	58.9	−3.83	29.3	−66.1	−13.8
13. Precuneus	22.0	−3.59	8.3	−54.7	52.1
14. Middle Frontal Gyrus	34.9	−3.51	36.9	26.8	43.4
15. Inferior Parietal Cortex	47.1	−3.49	42.2	−77.4	24.9
16. Insula	1.2	−3.29	31.0	13.6	−12.4
17. Inferior Parietal Cortex	24.1	−3.26	41.9	−71.0	35.0
18. Precuneus	27.6	−3.23	22.0	−67.3	15.1
19. Precuneus	26.6	−3.13	15.3	−69.8	39.0
20. Inferior Parietal Cortex	17.1	−3.11	51.7	−56.1	13.2
21. Lingual Gyrus	32.6	−3.11	15.7	−73.0	−5.8
22. Superior Parietal Cortex	26.0	−3.09	18.4	−66.3	46.8
23. Supramarginal Gyrus	8.9	−3.05	55.5	−34.5	35.2
24. Precuneus	19.9	−2.94	10.7	−66.1	34.9
25. Superior Temporal Sulcus	3.5	−2.93	49.8	−41.8	14.3

Brain Area	Cluster size (mm^2)	Peak within Cluster t	Approximate coordinates in MNI space (*x*, *y*, *z*) *x*	*y*	*z*
26. Superior Parietal Cortex	5.9	−2.92	24.1	−84.3	30.7
27. Insula	0.3	−2.92	29.6	13.4	−13.7

[1] Analyses control for age, gender, total brain volume, and TR.

[2] Significant group differences are shown at the p<.05 level, corrected for the false discovery rate (FDR). All significant group differences represent reduced cortical thickness in children reared in institutions relative to controls.

Table 4

Group differences in the volume of sub-cortical structures and the cerebellum among children reared in institutions and community controls in the Bucharest Early Intervention Project (n=80)[1]

	Ever Institutionalized Group (n=58)		Never Institutionalized Group (n=22)		Group Difference[1]	
	M	SD	M	SD	F	p-value
Striatum						
Caudate	8338.2	865.1	8693.7	878.1	1.03	.512
Putamen	11,742.7	1052.2	11,804.0	1058.4	0.31	.763
Globus Pallidus	4242.6	485.5	4417.8	484.2	1.00	.512
Nucleus Accumbens	1447.2	216.3	1389.5	187.7	3.68S	.472
Amygdala	3759.2	395.8	3893.8	336.4	1.43	.512
Hippocampus	9254.7	792.5	9382.8	749.7	0.00	.992
Thalamus	14,465.7	1459.8	15.046.2	1187.1	1.47	.512
Cerebellum	130,490.5	12,289.3	134,281.3	13,773.0	0.19	.763

[1] Analyses control for age, gender, total brain volume, and TR and p-values corrected for the false discovery rate (FDR).

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Table 5

Cortical regions significantly associated with symptoms of inattention and impulsivity in the Bucharest Early Intervention Project (n=74)[1]

		Inattention		Impulsivity	
		β	FDR corrected p-value	β	FDR corrected p-value
Brain Area	Region[2]				
	Left Hemisphere				
Superior Parietal Cortex	1	−.38	.013	−.29	.027
Superior Temporal Gyrus	2	−.45	.001	−.36	.009
Superior Parietal Cortex	5	−.27	.036	−.33	.013
Inferior Parietal Cortex	7	−.34	.013	−.27	.051
Superior Parietal Cortex	11	−.43	.001	−.34	.012
Precuneus	16	−.36	.007	−.35	.011
Posterior Cingulate	17	−.25	.040	−.20	.098
Middle Frontal Gyrus	18	−.34	.009	−.25	.053
Lateral Orbitofrontal	19	−.37	.009	−.31	.035
Inferior Parietal Cortex	22	−.32	.011	−.30	.018
Postcentral Gyrus	23	−.27	.036	−.19	.133
Supramarginal Gyrus	25	−.27	.036	−.24	.063
Superior Temporal Sulcus	27	−.43	.001	−.35	.009
Inferior Parietal Cortex	28	−.25	.049	−.15	.211
Superior Parietal Cortex	32	−.30	.018	−.12	.314
	Right Hemisphere				
Middle Frontal Gyrus	1	−.33	.008	−.31	.018
Inferior Parietal Cortex	2	−.43	.001	−.42	.002
Inferior Temporal Gyrus	4	−.33	.014	−.35	.013
Supramarginal Gyrus	5	−.36	.005	−.34	.011
Superior Parietal Cortex	6	−.43	.001	−.38	.009
Frontal Pole	7	−.36	.007	−.36	.012
Precuneus	8	−.45	.001	−.41	.002

		Inattention		Impulsivity	
		β	FDR corrected p-value	β	FDR corrected p-value
Superior Temporal Gyrus	9	−.40	.002	−.30	.023
Fusiform Gyrus	12	−.34	.008	−.36	.009
Insula	16	−.43	.001	−.37	.009
Lingual Gyrus	21	−.40	.002	−.36	.009
Superior Temporal Sulcus	25	−.41	.001	−.26	.045
Insula	27	−.40	.002	−.27	.039

*Significant at the .05 level, 2-sided test after correction for false discovery rate (FDR)

[1]Associations reported for symptoms of inattention and impulsivity are based on linear regression controlling for age, gender, total brain volume, and TR.

[2]Regions from analysis of group differences in cortical thickness presented in Tables 2–3, with region 1 having the most pronounced thickness difference as a function of institutionalization, region 2 having the second most pronounced thickness difference, and so on.