Widespread Reductions in Cortical Thickness Following Severe Early-Life Deprivation: A Neurodevelopmental Pathway to Attention-Deficit/ Hyperactivity Disorder

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Background: Children exposed to early-life psychosocial deprivation associated with institutional rearing are at markedly elevated risk of developing attention-deficit/hyperactivity disorder (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 subcortical 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 control subjects ($n = 22$). Magnetic resonance imaging data were acquired when children were aged 8 to 10 years, and ADHD symptoms were assessed using the Health and Behavior Questionnaire.

Results: Children reared in institutions exhibited widespread reductions in cortical thickness across prefrontal, parietal, and temporal regions relative to community control subjects. No group differences were found in the volume of subcortical 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.

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

Key Words: Attention-deficit/hyperactivity disorder (ADHD), brain development, childhood adversity, cortical development, deprivation, institutionalization

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 functional magnetic resonance imaging 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 hypoactivation in left hemisphere frontal-parietal-cerebellar circuits during timing tasks (10,11).

Attention-deficit/hyperactivity disorder is also associated with atypical neural structure, including smaller volume of the PFC and basal ganglia (12–14) and reductions in cortical thickness across prefrontal, parietal, and temporal cortex (15,16). Children with ADHD experience 2- to 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 to 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 gray matter volumes have been observed in institutionally reared children (24,25), as well as white

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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 with 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 subcortical 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 subcortical volume in these regions would be associated with ADHD pathology. Finally, we investigated whether disrupted cortical and subcortical development is a mechanism explaining the association between early psychosocial deprivation and ADHD.

Methods and Materials

Sample

The Bucharest Early Intervention Project is a longitudinal study of early institutionalization of young children in Bucharest, Romania (31). A sample of 136 children (age range 6–30 months, mean [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 the 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 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 magnetic resonance imaging assessments, 80 were included in analysis: 31 CAUG children (15 female participants), 27 FCG children (13 female participants), and 22 NIG children (12 female participants). 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, $t_{51} = .46$, $p = .646$, or impulsivity, $t_{51} = .69$, $p = .497$, or in cortical thickness or subcortical volume were observed at age 8 to 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 analyses. No differences in gender distribution or age were observed for EIG and NIG children, although differences in IQ, birth weight, and cerebral and cortical gray 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 (Siemens, Munich, Germany). Images were obtained using a transverse magnetization-prepared rapid gradient-echo three-dimensional sequence (echo time = 2.98 msec, inversion time = 1000 msec, flip angle = 8°, 176 slices with 1 × 1 × 1 mm isometric voxels) with a 16-channel head coil. The repetition time (TR) for this sequence was 1710 milliseconds for most participants ($n = 59$) and varied between 1650 milliseconds and 1910 milliseconds 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 analyses.

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/cerebrospinal fluid (CSF) boundaries are constructed using spatial intensity gradients across tissue classes. A segmentation process

Table 1. Sociodemographic and Developmental Characteristics Among Children Reared in Institutions and Community Control Subjects 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. (%)	$n = 28$ (48.3%)		$n = 12$ (54.5%)		$\chi^2_1 = .25$	.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)	.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[a]	.040
Head Circumference at Birth (cm)	46.07	(2.61)	46.5	(2.08)	.04	.843
Full-Scale IQ	72.0	(15.8)	107.9	(14.67)	96.49[a]	.001
Intracranial Volume	1,456,490	(132,948)	1,499,091	(109,367)	1.79	.184
Cerebral Gray Matter	790,429	(71,160)	833,849	(62,887)	6.31[a]	.014
Cortical Gray Matter	577,432	(57,120)	613,899	(48,391)	7.04[a]	.010

HBQ, MacArthur Health and Behavior Questionnaire; MRI, magnetic resonance imaging.
[a]Significant at the $p < .05$ level, two-sided test.