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A Randomized Clinical Trial of Foster Care as an Intervention for Early Institutionalization: Long Term Improvements in White Matter Microstructure

Johanna Bick, Ph.D.,
Boston Children's Hospital, Harvard Medical School, Boston, MA, 02115

Tong Zhu, Ph.D,
Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan, 48109

Catherine Stamoulis, Ph.D.,
Department of Radiology, Boston Children's Hospital, Harvard Medical School Boston, MA 02115

Nathan A. Fox, Ph.D.,
Department of Human Development University of Maryland, College Park, MD 20742

Charles Zeanah, M.D., and
Tulane University Health Science Center, New Orleans, LA, 70112

Charles A. Nelson, Ph.D.
Boston Children's Hospital, Harvard Medical School, Harvard Graduate School of Education, Cambridge, MA 02115

Johanna Bick: Johanna.bick@childrens.harvard.edu; Tong Zhu: ztong@med.umich.edu; Catherine Stamoulis: catherine.stamoulis@childrens.harvard.edu; Nathan A. Fox: fox@umd.edu; Charles Zeanah: czeanah@tulane.edu; Charles A. Nelson: Charles_nelson@harvard.edu

Abstract

Importance—Severe early life neglect is associated with compromises in brain development and associated behavioral functioning. Although early intervention has been shown to support more normative trajectories of brain development, specific improvements in white matter pathways that underlie emotional and cognitive development are unknown.

Objective—To examine associations between early life neglect, early intervention, and microstructural integrity of white matter pathways in middle childhood.

Design, setting, and participants—The Bucharest Early Intervention Project is a randomized clinical trial of high quality foster care as an intervention for institutionally reared children in Bucharest, Romania. During infancy, children were randomly selected to remain in an institution or to be placed into foster care. Developmental trajectories of these children were compared to a group of socio-demographically matched children reared in biological families at baseline and several points throughout development. At around eight years of age, 69 of the original 136 children underwent structural MRI scans.

Correspondence to: Charles A. Nelson, Charles_nelson@harvard.edu.

The authors declare no conflicts of interest.

Intervention(s) for Clinical Trials—Institutionally reared children were randomized into high quality foster homes in Bucharest, Romania.

Main Outcome Measure(s)—Four estimates of white matter integrity (Fractional Anisotropy, and Mean, Radial, and Axial Diffusivity) for 48 white matter tracts throughout the brain were obtained through Diffusion Tensor Imaging.

Results—Significant associations emerged between early life neglect and microstructural integrity of the body of the corpus callosum and tracts involved in limbic circuitry (fornix crus, cingulum), fronto-striatal circuitry (anterior and superior corona radiata, external capsule) and sensory processing (medial lemniscus, retrolenticular internal capsule). Follow up analyses revealed that early intervention promoted more normative white matter development among previously neglected children who entered foster care.

Conclusions and Relevance—Results suggest that removal from conditions of severe early life neglect and entry into a high quality family environment can support more normative trajectories of white matter growth. Findings have implications for public health and policy efforts designed to promote normative brain development among vulnerable children.

Trial Registration—clinicaltrials.gov Identifier: NCT00747396

Many aspects of postnatal brain development depend heavily on experience. Consequently, serious violations of the so-called “expectable environment” (i.e., experiences that all members of our species should expect to encounter) can lead to profound changes in neural development[1]. Institutional rearing represents a profound violation of the expectable environment in that children typically experience high child to caregiver ratios, limited access to language and cognitive stimulation, and insufficient caregiving. Not surprisingly, institutionally-reared children often show compromises in brain development and associated behavioral functioning[2–4].

Recent investigations using diffusion tensor imaging (DTI) have demonstrated significant associations between institutional neglect and microstructural alterations in white matter. Alterations are wide-spread and have included limbic and paralimbic pathways[5–7], fronto-striatal circuitry[7–9], and sensory processing pathways[7]. Although findings are compelling, these studies share a methodological weakness associated with the potential for sample biases; institutionalized children selected for international adoption may differ developmentally from those not selected. One potential example is that IQs of internationally adopted children often fall within the normal range, whereas IQs of comparably-aged children who remain in institutions often fall 2–3 standard deviations (SD) below average[6,10,11].

Randomized clinical trials involving early intervention can overcome this methodological issue and uncover associations not confounded by selection biases. Improved total white matter content during middle childhood has recently been demonstrated in children randomly assigned to enter into a responsive family setting relative to those who remained in the institution[12]. However, the microstructural changes that underlie these global white matter improvements have not yet been elucidated.

The current study investigated white matter integrity of three groups of children who participated in the Bucharest Early Intervention Project (BEIP), a randomized clinical trial of Romanian infants reared in institutional settings. During infancy, children were randomly assigned to either remain in the institution or be removed from the institution and placed in high quality foster care. Developmental trajectories were compared to a group of demographically-matched children reared in biological families. We hypothesized that institutionally reared children would show abnormalities in white matter integrity throughout the brain, specifically in regions supporting cognitive and emotional regulation. We expected that white matter compromises would be most severe for children who remained in the institution. We also hypothesized that institutionally-reared children placed into foster care would show evidence for remediation in specific fiber tracts as a result of early intervention.

Materials and Methods

Procedure

BEIP is the first-ever randomized controlled trial of foster care as an intervention for early institutionalization. At around 2 years of age, 136 children who had spent more than half of their lives in institutions in Bucharest were recruited and assessed (see eMethods in the supplement for additional information). Half of this cohort was then randomly selected to be placed into foster care (the “foster care group”). The other half received care as usual in the institutional setting (the “care as usual group”). A third group of age- and gender-matched children reared in their biological families in Bucharest (the “never institutionalized group”) was used as a comparison group[13]. Institutional Review Boards from the University of Maryland, Boston Children’s Hospital, and Tulane University approved all procedures, as did an institutional review board established in Romania. In addition, informed written consent was obtained from each of the six local Commissions for Child Protection in Bucharest and/or the biological parents when possible.

Participants

DTI data from 69 participants (ages 8–11 years) were selected for the Tract Based Spatial Statistics (TBSS) analysis in order to investigate potential white matter abnormalities due to institutional rearing during early development. Participants included children randomized out of the institution who were placed into foster care (n=23, mean age=9.87, SD=0.63 years), children randomly assigned to remain in institutional care (n=26, mean age=9.69 years, SD=0.93 years), and children who had never been in institutional care (n=20, mean age=9.80, SD=0.52 years). There were no statistically significant differences in children’s ages (p=0.69), or gender (p=0.35) across groups at the MRI assessment.

DTI Scan Protocol and Image Pre-processing

DTI scans were performed on a Siemens 1.5T scanner using a single-shot EPI sequence with twice-refocused spin echoes. The scanning parameters for DTI acquisitions were: TR/TE=8600/100ms, slice thickness=2.3 mm with no gap and a total of 55 slices for a whole brain coverage, data matrix=208×208, FOV=240mm×240mm. Diffusion weighted images

were acquired along 30 non-collinear and non-coplanar directions with b=1000 s/mm^2 along with two b=0 s/mm^2 images.

DTI Image Pre-processing

Tensor and tensor-derived parametric maps, for Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AD), were first estimated using the DTIFIT tool in FSL package (FMRIB Analysis Group, Oxford, UK). Maps were then fed into the TBSS tool to generate a white matter skeleton[14]. Considering the ages of participants in the BEIP, a study-specific template in the standard space, instead of FMRIB_FA_58 adult brain template, was created in a two-step approach[15] for the TBSS analysis in this study.

Spatial Classifications of DTI Changes Using DTI Atlases

The DTI atlas from the Laboratory of Brain Anatomical MRI at John Hopkins University included in the FSL package, the ICBM-DTI-81 White Matter Atlas (referred as the WM Atlas henceforth), was chosen as a template to facilitate identification of major WM structures. Forty-eight tracts from the WM atlas were identified for analyses in the current study (see Table 4 for a complete list of tracts) using nomenclature and names established by Mori[16]. Average FA, MD, RD, and AD values across all voxels for each of the 48 tracts as defined by the WM Atlas were calculated. An individual mean DTI index for each tract was extracted per subject using the FSL package.

Statistical Analysis

All statistical analyses were conducted using the software R (www.r-project.org). DTI data were compared between groups primarily using linear regression models. Analyses examined group differences with children categorized as falling in their originally assigned care as usual or foster care groups. However, over the years, some children originally assigned to the care as usual or foster care groups underwent changes in living arrangements (for details see[17]). Therefore, analyses provide a conservative estimate of the impact of early intervention on white matter microstructure.

Linear regression models were first developed to investigate correlations between white matter structural alterations (the outcome) and histories of institutional rearing or subject group (the independent variable; categorized as care as usual group=1, foster care group=2, and never institutionalized group=3). Individual models were developed for each tract and each DTI parameter. The relatively small samples limited the development of larger models. As this analysis aimed to assess the sensitivity of *individual* tracts and DTI parameters, the issue of multiple comparisons was not of concern and associations were considered significant at $p<.05$. Multinomial regression models were also developed to compare pairs of tracts across groups. These models used the never institutionalized group as the reference group and compared the care are usual and foster care groups to it. The significance level was adjusted for these two comparisons in the models.

Results

Four tracts in which FA was statistically distinct in the three groups were identified: the body of the corpus callosum, left external capsule, right external capsule, and right retrolenticular internal capsule. Also, four tracts were identified in which RD was statistically distinct in the three groups: the body of the corpus callosum, right cingulum, left external capsule, and right retrolenticular internal capsule. AD of four tracts was statistically distinct in the three groups: the right anterior corona radiata, right fornix crura, right medial lemniscus, and left superior corona radiata. Finally, MD in six tracts was statistically distinct in the three groups: the body of the corpus callosum, right cingulum, left external capsule, right medial lemniscus, right retrolenticular internal capsule, and the left superior corona radiata (see Table 1).

Next, separate linear regression models examined whether associations between each of these 18 DTI values (four FA, four RD, four AD, and six MD values) continued to be associated with group when controlling for covariates (age, birth weight, and intracranial volume). Identified tracks and corresponding DTI parameters continued to be statistically distinct in the three groups even when covariates were included in the model. Overall, these covariates were not significantly associated with the DTI parameters except for birth weight, which was positively associated with FA for the body of the corpus callosum. However, the positive association between group and FA of the body of the corpus callosum remained significant even when controlling for birth weight.

Next, we tested whether combinations of tracts were more strongly associated with group when compared with each tract as an independent predictor. Pairs of uncorrelated tracts were tested in multinomial logistic regression models with group as the outcome and DTI parameters as predictors (see Table 2 for pairs of tracts that were not significantly correlated with each other for each DTI parameter). Results of the multinomial logistic regressions revealed that there were no tract pairs that were combinatorially distinct in the three groups. This could potentially be due to the small sample size, but in the absence of a larger sample to verify the lack of combinatorial tract correlations with group, our results suggest that associations between each DTI parameter for each tract and group occurred independently, rather than in combination with other tracts

Intervention effects

Several multinomial regression models showed that in some cases, values for certain tracts were statistically significantly associated with the log odds of belonging to the care as usual group relative to the never institutionalized group, but were not significantly associated with the log odds of belonging to the foster care group relative to the never institutionalized group, suggesting an intervention effect. This evidence for remediation in the foster care group but not the care as usual group was observed for FA values in the left external capsule, FA values in the right external capsule, FA, MD, and RD values in the retrolenticular internal capsule, MD and RD values in the right cingulum, AD values in the right anterior corona radiata, AD values in the left superior corona radiata, MD and AD values in the medial lemniscus, and (at a trend level) AD values in the right fornix crura (see Table 3).

Intervention Timing

Finally, we examined whether variations in the timing of the intervention (i.e. entry into foster care) predicted white matter integrity during middle childhood. As age of placement into foster care was associated with age at the MRI scan ($r = .89$, $p < .001$), child age was entered as a covariate in analyses. There were no significant associations between intervention timing and white matter integrity, when accounting for effects of child age at the time of the scan.

Discussion

This is the first investigation to examine effects of severe early life neglect on white matter microstructural organization within the context of a randomized controlled trial of foster care as an intervention for early institutionalization. The randomized design is a critical strength of this investigation as it allows for the control of potential selection biases encountered in previous investigations involving internationally adopted youth. Results from this study extend prior knowledge by further delineating white matter tracts affected by extreme early life neglect. They also suggest that removal from conditions of severe early life neglect and entry into a high quality family environment may support more normative trajectories of white matter growth in the long term.

Our results revealed that early life neglect was associated with alterations in white matter microstructure throughout the brain, specifically involving the body of the corpus callosum, cingulum, fornix, anterior and superior corona radiata, external capsule, retrolenticular internal capsule, and medial lemniscus. The FCG did not significantly differ from the NIG in parameters of these tracts, with the exception of the body of the corpus callosum and superior corona radiata. These findings suggest a potential for remediation of specific white matter pathways for children removed from institution and placed in responsive families early in life.

The BEIP intervention focused on facilitating high quality parent/child attachment relationships between the institutionally reared children and their foster care providers. As part of the program, foster parents were encouraged to develop responsive, committed relationships with their child, were educated on the child's specialized cognitive and emotional needs, and were provided guidance on behavioral management strategies to support the child's optimal development. Previously, we demonstrated evidence for intervention-associated improvements in total white matter volume among institutionally reared children placed into foster care[12]. Results here delineate the specific white matter tracts that may contribute to the global improvements in white matter changes. Prior work has also demonstrated that caregiving-based early intervention programs can support more normalized white matter development among children who are exposed to prenatal risk[18,19]. Our results suggest a similar potential for recovery in children exposed to extreme early adverse conditions post-natally.

Evidence presented in this study introduces several questions for future research. First, assessments of white matter microstructure occurred approximately six years after children were randomized into responsive family settings. Therefore, the specific timing and rate of

white matter improvements among foster care children is unknown. White matter increases linearly across development, and both experience-expectant and experience-dependent processes drive its growth and organization[20]. Potential improvements in white matter integrity could have occurred from appropriate, experience-expectant, caregiving input at sensitive periods of brain development in early childhood and/or from ongoing exposure to enriching, experience-dependent experiences throughout the course of development.

The specific neural changes that contribute to these quantitative estimates of microstructural improvements are also unknown. Early life alterations in neural pruning and axonal organization may have contributed to these long-term white matter patterns. However, changes in the overall rates of myelination that occurs across the course of development may also contribute the group differences observed in this study. Future investigations involving longitudinal assessments of neural development will be critical for identifying the specific neural properties that subserve our observed long-term changes. Understanding these specific trajectories of white matter changes may have important public health implications regarding timing, duration, and format of the early intervention delivered to at risk children.

In terms of the specific white matter tracts, children in both the care as usual and foster care groups showed reduced integrity (decreased FA, increased RD and MD) in the body of the corpus callosum when compared with children reared in family settings. Alterations in this region are consistent with prior work demonstrating smaller corpus callosum volume[21,22], and reduced microstructural integrity[22,23,24] among individuals exposed to maltreatment in family settings. The corpus callosum is the largest myelinated fiber tract in the brain and supports inter-hemispheric transmission of neural information. Abnormalities in the corpus callosum have been associated with psychiatric and developmental disorders including attention deficit hyperactivity disorder (ADHD)[25], and cognitive and language delays[26]. ADHD-related symptoms in children exposed to deprivation seem especially persistent, even in children assigned to the foster care intervention[27]. Long term reductions in the integrity of the body of the corpus callosum for children the care as usual and foster care groups may subserve these pervasive patterns of neurocognitive risk.

Two white matter tracts involved in limbic circuitry were significantly associated with institutional rearing in this study. The cingulum, a collection of white matter fibers that runs along the cingulate gyrus and projects to the entorhinal cortex, supports communication between frontal and limbic regions of the brain[28,29]. The fornix crus, a flat band of efferent fibers in the posterior portion of the fornix, project to dorsal regions of the hippocampus. Reduced integrity of these regions, manifesting specifically as increased RD and MD for the cingulum and reduced AD in the body of the fornix, has been observed among individuals exposed to adverse early rearing conditions in several prior investigations[6,7,30]. Integrity of these regions have also been linked with increased externalizing[6,31] internalizing[30,32], inattention[33], and spatial planning difficulties[7]. A remaining question is whether these white matter disruptions underpin similar difficulties observed previously in the institutionally reared children in the current sample[27,34,35].

Histories of institutionalization were also associated with compromised integrity of tracts involved in fronto-striatal circuitry, specifically manifesting as decreased AD in the right

anterior corona radiata, decreased AD and MD in the left superior corona radiate, decreased FA in the left and right external capsule, and increased RD and MD in the right external capsule. The corona radiata is a bundle of white matter fibers that connect the cortex with the thalamus, basal ganglia, and spinal cord. The anterior portion connects the anterior cingulate cortex with the striatum, and disruptions to this portion of the corona radiata are consistent with a prior investigation involving institutionally reared children[7]. Functionally, this tract has been implicated in cognitive, emotional, and behavioral regulation[36,37]. More specifically, poorer integrity in this tract has been associated with spatial planning difficulties among institutionally reared children[7]. The external capsule is a series of white matter tracts that connect the cortex to the striatum. Although the specific function of the external capsule is largely unknown, reduced integrity has been associated with risk for addiction and substance abuse, compromised regulatory skills, and poor cognitive control[38]. Understanding the functional correlates of the reduced integrity of these tracts for children in the current sample will be an important direction for future work.

Finally, early life neglect was also associated with alterations in two white matter tracts implicated in basic sensory processing. These tracts included the right retrolenticular portion of the internal capsule and the right medial lemniscus. The retrolenticular portion of the internal capsule contains fibers involved in the visual system. Unexpectedly, histories of institutional neglect were associated with higher FA and lower MD and RD. The medial lemniscus is a major afferent pathway that carries sensory information from the brainstem to the thalamus. Results revealed positive associations between early life neglect and MD and AD values in this region. Reduced integrity in the medial lemniscus may result from insufficient sensory input experienced at critical points in neural development and may be associated with lower level difficulties in sensory processing.

The inclusion of multiple DTI parameters in the analytical approach is a strength of this study as the examination of MD, RD, and AD parameters may yield a more comprehensive understanding of specific white matter properties[39]. We observed microstructural alterations of white matter tracts across all four parameters, suggesting that early life neglect may be associated with a variety of alterations in white matter development involving fiber density, membrane structure, myelination, axonal organization, and projection.

In conclusion, results from this study contribute to growing evidence that severe early life neglect affects the structural integrity of white matter throughout the brain, and that early intervention may support long term remediation in specific fiber tracts involved in limbic and frontal-striatal circuitry, and sensory processes. Our findings have important public health implications related to early prevention and intervention for children reared in conditions of severe neglect, or adverse contexts more generally. Understanding links between these white matter profiles and neurocognitive or psychiatric functioning will be an important aim for future work, and will shed light on mechanisms underlying risk and resiliency among children exposed to adverse early rearing conditions.

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Nathan Fox, Charles Zeanah, and Charles Nelson designed and carried out the study. Johanna Bick, Tong Zhu, and Catherine Stamoulis processed and analyzed the data. Johanna Bick, Nathan Fox, Charles Zeanah, Charles Nelson, and Catherine Stamoulis wrote the paper. Johanna Bick had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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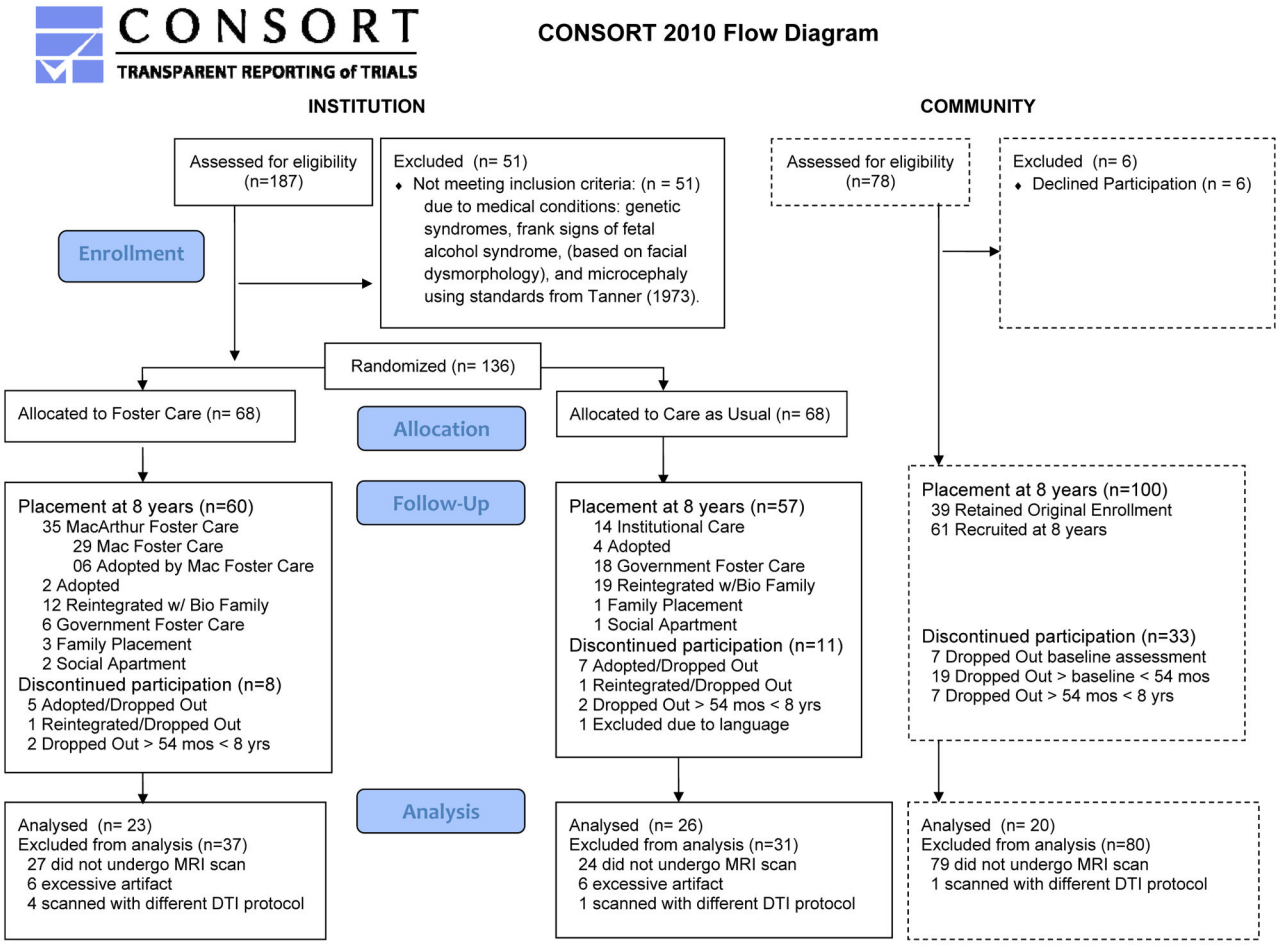

Figure.
CONSORT Flow Diagram

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Table 1

List of Tracts

White Matter Structures (JHU White Matter Atlas)	DTI Parameter	Intercept				Institutional Neglect (Care as usual = 1, Foster care = 2, Never institutionalized = 3)				Full Model			
		Coeff	S.E.	t	p	Coeff	S.E.	t	p	F	p	R^2	Adj R^2
ACR R	FA	0.52	0.01	67.74	1.9E-63	−0.01	0.00	−1.38	0.173	1.90	0.173	0.03	0.01
	RD	0.53	0.01	56.14	4.5E-58	0.00	0.00	0.19	0.851	0.04	0.851	0.00	−0.01
	AD	**1.29**	**0.01**	**100.99**	**6.0E-75**	**−0.01**	**0.01**	**−2.42**	**0.018**	**5.88**	**0.018**	**0.08**	**0.07**
	MD	0.78	0.01	89.81	1.5E-71	0.00	0.00	−1.05	0.297	1.10	0.297	0.02	0.00
BCC	FA	**0.69**	**0.01**	**85.96**	**2.7E-70**	**0.01**	**0.00**	**2.65**	**0.010**	**7.02**	**0.010**	**0.09**	**0.08**
	RD	**0.44**	**0.01**	**38.80**	**1.2E-47**	**−0.02**	**0.01**	**−2.90**	**0.005**	**8.40**	**0.005**	**0.11**	**0.10**
	AD	1.66	0.01	130.10	2.8E-82	0.00	0.01	−0.07	0.941	0.01	0.941	0.00	−0.01
	MD	**0.84**	**0.01**	**90.13**	**1.2E-71**	**−0.01**	**0.00**	**−2.35**	**0.022**	**5.52**	**0.022**	**0.08**	**0.06**
CC R	FA	0.52	0.01	48.67	5.2E-54	0.01	0.01	1.76	0.083	3.09	0.083	0.04	0.03
	RD	**0.53**	**0.01**	**48.50**	**6.5E-54**	**−0.01**	**0.01**	**−2.32**	**0.023**	**5.37**	**0.023**	**0.07**	**0.06**
	AD	1.28	0.02	71.66	4.7E-65	0.00	0.01	−0.55	0.587	0.30	0.587	0.00	−0.01
	MD	**0.78**	**0.01**	**77.61**	**2.4E-67**	**−0.01**	**0.00**	**−2.01**	**0.049**	**4.03**	**0.049**	**0.06**	**0.04**
EC L	FA	**0.44**	**0.01**	**59.55**	**9.4E-60**	**0.01**	**0.00**	**2.29**	**0.025**	**5.23**	**0.025**	**0.07**	**0.06**
	RD	**0.60**	**0.01**	**84.55**	**8.1E-70**	**−0.01**	**0.00**	**−2.55**	**0.013**	**6.50**	**0.013**	**0.09**	**0.07**
	AD	1.22	0.01	142.00	8.1E-85	0.00	0.00	0.54	0.591	0.29	0.591	0.00	−0.01
	MD	**0.81**	**0.00**	**170.07**	**4.7E-90**	**−0.01**	**0.00**	**−2.22**	**0.030**	**4.91**	**0.030**	**0.07**	**0.05**
EC R	FA	**0.44**	**0.01**	**68.49**	**9.3E-64**	**0.01**	**0.00**	**2.24**	**0.028**	**5.01**	**0.028**	**0.07**	**0.06**
	RD	0.60	0.01	85.48	3.9E-70	−0.01	0.00	−1.99	0.051	3.95	0.051	0.06	0.04
	AD	1.21	0.01	173.82	1.1E-90	0.00	0.00	0.87	0.389	0.75	0.389	0.01	0.00
	MD	0.80	0.01	153.63	4.2E-87	0.00	0.00	−1.39	0.169	1.93	0.169	0.03	0.01
FC R	FA	0.56	0.01	52.03	6.6E-56	0.00	0.01	0.40	0.692	0.16	0.692	0.00	−0.01
	RD	0.55	0.01	42.46	3.7E-50	0.00	0.01	0.24	0.814	0.06	0.814	0.00	−0.01

White Matter Structures (JHU White Matter Atlas)	DTI Parameter	Intercept				Institutional Neglect (Care as usual = 1, Foster care = 2, Never institutionalized = 3)				Full Model			
		Coeff	S.E.	t	p	Coeff	S.E.	t	p	F	p	R^2	Adj R^2
	AD	**1.43**	**0.02**	**89.95**	**1.3E-71**	**0.02**	**0.01**	**2.03**	**0.046**	**4.13**	**0.046**	**0.06**	**0.04**
	MD	0.84	0.01	86.92	1.3E-70	0.01	0.00	1.32	0.192	1.74	0.192	0.03	0.01
ML R	FA	0.62	0.01	73.92	6.0E-66	0.00	0.00	0.14	0.887	0.02	0.887	0.00	−0.01
	RD	0.43	0.01	48.52	6.3E-54	0.00	0.00	−1.08	0.284	1.17	0.284	0.02	0.00
	AD	**1.37**	**0.02**	**85.57**	**3.7E-70**	**−0.02**	**0.01**	**−2.04**	**0.045**	**4.18**	**0.045**	**0.06**	**0.04**
	MD	**0.74**	**0.01**	**90.06**	**1.2E-71**	**−0.01**	**0.00**	**−2.10**	**0.040**	**4.39**	**0.040**	**0.06**	**0.05**
RIC R	FA	**0.62**	**0.01**	**79.37**	**5.4E-68**	**−0.01**	**0.00**	**−3.27**	**0.002**	**10.69**	**0.002**	**0.14**	**0.12**
	RD	**0.47**	**0.01**	**47.31**	**3.3E-53**	**0.01**	**0.00**	**3.07**	**0.003**	**9.45**	**0.003**	**0.12**	**0.11**
	AD	1.43	0.01	106.69	1.6E-76	0.00	0.01	−0.24	0.809	0.06	0.809	0.00	−0.01
	MD	**0.79**	**0.01**	**86.51**	**1.8E-70**	**0.01**	**0.00**	**2.11**	**0.038**	**4.46**	**0.038**	**0.06**	**0.05**
SCR L	FA	0.54	0.01	81.39	1.0E-68	0.00	0.00	−0.91	0.368	0.82	0.368	0.01	0.00
	RD	0.49	0.01	78.48	1.1E-67	0.00	0.00	−1.01	0.315	1.03	0.315	0.02	0.00
	AD	**1.25**	**0.01**	**91.25**	**5.1E-72**	**−0.02**	**0.01**	**−2.41**	**0.019**	**5.79**	**0.019**	**0.08**	**0.07**
	MD	**0.75**	**0.01**	**109.71**	**2.4E-77**	**−0.01**	**0.00**	**−2.24**	**0.028**	**5.03**	**0.028**	**0.07**	**0.06**

Each FA, RD, AD, and MD value of the 48 available tracts was regressed separately on institutional rearing status (1=care as usual group, 2=foster care group, 3=never institutionalized group). Only significant associations are displayed. Abbreviations: FA: fractional anisotropy, RD: radial diffusivity, AD: axial diffusivity, MD: mean diffusivity; L: left hemisphere; R: right hemisphere; Anterior corona radiata = ACR; Body of the corpus callosum = BCC; Cingulum cingulate = CC; External capsule = EC; Fornix crus (stria terminalis) = FC; Medial lemniscus = ML; Retrolenticular internal capsule = RIC; Superior corona radiata = SCR

Table 2

Between-Group Comparisons of White Matter Tracts

DTI Parameter	Pairs of White Matter Tracts	Spearman Rho	*p* value	95% CI
FA	BCC and RIC R	.099	.420	−.136 – .322
	EC L and RIC R	.171	.161	−.063 – .377
	EC R and RIC R	.221	.068	−.014 – .433
RD	BCC and RIC R	.185	.128	−.045 – .403
	CC R and RIC R	.374	.002	.166 – .542
	EC L and RIC R	.253	.036	−.002 – .468
AD	ACR R and FC R	.006	.959	−.230 – .250
	ACR R and ML R	.229	.058	.004 – .422
	FC R and ML R	.097	.428	−.144 – .334
	FC R and SCR L	.233	.054	.021 – .418
	ML R and SCR L	.194	.110	−.039 – .426
MD	BCC and ML R	.101	.411	−.136 – .333
	BCC and RIC R	.358	.003	.141 – .546
	CC R and ML R	.170	.163	−.097 – .403
	EC L and ML R	.338	.005	.100 – .544
	EC L and RIC R	.325	.006	−.104 – .528
	ML R and RIC R	.236	.051	.000 – .467
	ML R and SCR L	.274	.023	.053 – .468

Pairs of tracts that emerged as significantly associated with rearing status were correlated with each other. Abbreviations: FA: fractional anisotropy, RD: radial diffusivity, AD: axial diffusivity, MD: mean diffusivity; L: left hemisphere; R: right hemisphere; Anterior corona radiata = ACR; Body of the corpus callosum = BCC; Cingulum cingulate = CC; External capsule = EC; Fornix crus = FC; Medial lemniscus = ML; Retrolenticular internal capsule = RIC; Superior corona radiata = SCR

Table 3

Correlation of Pairs of Tracts That Emerged as Significantly Associations with Rearing Status

White Matter Structures (JHU White Matter Atlas)	DTI Parameter	Care as usual v Never institutionalized group*(				Foster care v Never institutionalized group*			
		B	*se*	*Wald*	*p*	*B*	*se*	*Wald*	*p*
ACR R	AD	17.79	7.89	5.07	.024	8.42	7.70	1.19	.274
BCC	FA	−34.97	13.47	6.73	.009	−35.36	13.76	6.59	.010
	RD	29.55	10.61	7.74	.005	28.25	10.73	6.98	.008
	MD	28.71	12.23	5.50	.019	27.35	12.41	4.85	.028
CC R	RD	20.89	9.23	5.12	.024	17.43	9.31	3.50	.061
	MD	19.84	9.90	4.01	.045	17.64	10.05	3.07	.079
EC L	FA	−30.17	13.55	4.95	.026	−25.07	13.64	3.37	.066
	RD	28.83	14.23	4.10	.043	33.64	14.85	5.12	.024
	MD	55.06	23.31	5.57	.018	81.36	25.57	10.12	.001
EC R	FA	−34.16	15.65	4.76	.029	−29.41	15.7	3.47	.062
FC R	AD	−12.34	6.57	3.52	.060	6.98	6.29	1.22	.268
ML R	AD	11.99	6.14	3.80	.051	7.12	5.90	1.45	.228
	MD	23.80	11.96	3.95	.047	12.26	11.32	1.17	.279
RIC R	FA	36.97	13.13	7.92	.005	4.81	12.71	.145	.703
	RD	−27.99	10.33	7.34	.007	−2.22	9.66	.053	.818
	MD	−21.09	10.755	3.84	.050	.24	10.44	.001	.981
SCR L	AD	17.32	7.56	5.24	.022	12.13	7.55	2.57	.108
	MD	34.24	15.19	5.08	.024	25.63	15.58	5.23	.022

*Never Institutionalized Group is the reference category for all analyses. Abbreviations: FA: fractional anisotropy, RD: radial diffusivity, AD: axial diffusivity, MD: mean diffusivity; L: left hemisphere; R: right hemisphere; Anterior corona radiata = ACR; Body of the corpus callosum = BCC; Cingulum cingulate = CC; External capsule = EC; Fornix crus = FC; Medial lemniscus = ML; Retrolenticular internal capsule = RIC; Superior corona radiata = SCR

Table 4

Multinomial Regression Models Examining Effects of Intervention

Abbreviation	Name of WM Structure According to JHU WM Atlas)
ACR L	Anterior corona radiata (left)
ACR R	Anterior corona radiata (right)
ALIC L	Anterior corona radiata (left)
ALIC R	Anterior corona radiata (right)
BCC	Body of the corpus callosum
CP L	Cerebral peduncle (left)
CP R	Cerebral peduncle (right)
CC L	Cingulum cingulate (left)
CC R	Cingulum cingulate (right)
CH L	Cingulum hippocampus (left)
CH R	Cingulum hippocampus
CS L	Corticospinal tract (left)
CS R	Corticospinal tract (right)
EC L	External capsule (left)
EC R	External capsule (right)
FC L	Fornix crus (stria terminalis; left)
FC R	Fornix crus (stria terminalis; right)
FOR	Fornix (body)
GCC	Genu of the corpus callosum
ICP L	Inferior cerebellar peduncle (left)
ICP R	Inferior cerebellar peduncle (right)
ILF/IFOF L	Inferior longitudinal fasciculus/Inferior fronto-occipital fasciculus (left)
ILF/IFOF R	Inferior longitudinal fasciculus/Inferior fronto-occipital fasciculus (right)
ML L	Medial lemniscus (left)
ML R	Medial lemniscus (right)
MCP	Middle cerebellar peduncle
PC	Pontine crossing
PCR L	Posterior corona radiata (left)
PCR R	Posterior corona radiata (right)
PLIC L	Posterior limb of the internal capsule (left)
PLIC R	Posterior limb of the internal capsule (right)
PTR L	Posterior thalamic radiation (left)
PTR R	Posterior thalamic radiation (right)
RIC L	Retrolenticular internal capsule (left)
RIC R	Retrolenticular internal capsule (right)
SCC	Splenium of the corpus callosum
SCP L	Superior cerebellar peduncle (left)

Abbreviation	Name of WM Structure According to JHU WM Atlas)
SCP R	Superior cerebellar peduncle (right)
SCR L	Superior corona radiata (left)
SCR R	Superior corona radiata (right)
SFOF L	Superior fronto-occipital fasciculus (left)
SFOF R	Superior fronto-occipital fasciculus (right)
SLF L	Superior longitudinal fasciculus (left)
SLF R	Superior longitudinal fasciculus (right)
TAP L	Tapetum (left)
TAP R	Tapetum (right)
UCF L	Uncinate fasciculus (left)
UCF R	Uncinate fasciculus (right)