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Abnormal Fronto-striatal Connectivity in Children with Histories of Early Deprivation: A Diffusion Tensor Imaging Study

Michael E. Behen · Otto Muzik · Anita S. D. Saporta · Benjamin J. Wilson · Darshan Pai · Jing Hua · Harry T. Chugani

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Abstract An Inattentive/Overactive (I/O) behavioral phenotype has been reported in a significant percentage of children raised from birth in orphanages. While a number of studies have identified both functional and structural brain abnormalities in children raised from birth in orphanages, no published studies have evaluated potential neural correlates of the I/O phenotype. We applied diffusion tensor imaging (DTI) to 15 pre-teen children raised in orphanages in Eastern Europe or Asia and later adopted to the US. Fiber tracts were constructed from DTI data using probabilistic fiber tracking and the cortical fiber distribution of fibers originating from the head of the caudate was compared between the early deprivation (ED) group and 12 age-matched controls. The ED group showed a more diffuse connectivity pattern, especially in the right hemisphere, potentially related to incomplete neuronal pruning during development. These structural abnormalities may be associated with inattention and overactivity encountered in children with ED.

Keywords Orphan · Early deprivation · Fiber tracking · Fronto-striatal pathway

An Inattentive/Overactive (I/O) behavioral phenotype has been reported in a significant percentage of children raised from birth in orphanages (Stevens et al. 2008; Behen et al. 2008). While it is assumed that such findings are reflective of abnormal neurologic development resulting from early deprivation, the neural substrate(s) or brain regions most affected are poorly understood. A small number of studies of children raised from birth in orphanages have identified both functional and structural brain abnormalities as compared to typically developing non-adopted controls (Chugani et al. 2001; Eluvathingal et al. 2006). However, there are currently no studies that have evaluated potential neural correlates of the I/O phenotype in children with histories of early deprivation (ED).

Research on idiopathic or developmental attention deficit hyperactivity disorder (ADHD) has strongly implicated fronto-striatal brain regions and/or circuitry as involved in the disorder. Volumetric magnetic resonance imaging (MRI) studies have shown abnormal caudate and prefrontal grey matter volumes (Shaw et al. 2007; Giedd et al. 2001). Studies using diffusion tensor imaging (DTI) have identified reduced white matter integrity (decreased fractional anisotropy) in fronto-striatal circuitry in children with ADHD (Pavuluri et al. 2009). Therefore evaluation of this

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M. E. Behen · O. Muzik · A. S. D. Saporta · B. J. Wilson · H. T. Chugani
Departments of Pediatrics, Children's Hospital of Michigan,
Wayne State University School of Medicine,
Detroit, MI, USA

O. Muzik
Departments of Radiology, Children's Hospital of Michigan,
Wayne State University School of Medicine,
Detroit, MI, USA

M. E. Behen · O. Muzik · H. T. Chugani
Departments of Neurology, Children's Hospital of Michigan,
Wayne State University School of Medicine,
Detroit, MI, USA

D. Pai · J. Hua
Department of Computer Science, Wayne State University,
Detroit, MI, USA

O. Muzik (✉)
PET Center, Children's Hospital of Michigan,
3901 Beaubien Blvd,
Detroit, MI 48201, USA
e-mail: otto@pet.wayne.edu

neural substrate in children with the I/O phenotype appears warranted.

The objective of this paper was to apply probabilistic fiber tracking to fronto-striatal pathways and determine whether the connectivity pattern differs between children with histories of ED and normal controls. A secondary aim was to evaluate whether Inattentive-Overactive (I/O) behavioral characteristics are associated with patterns of fronto-striatal connectivity.

Materials and methods

Participants Fifteen children (age at testing=126.3, SD=30.9 months, range=87 to 191 months; six males/nine females) raised from birth in orphanages in Eastern Europe, Northern Asia, or South Asia, and later adopted in the US were included in the study. Mean duration of time spent in the orphanage was 35.5, SD=21.5 months; mean duration of time in the adoptive home was 89.4, SD=46.7 months. All of the participants were right-hand dominant, English-speaking, and attended school regularly. Inclusion/exclusion criteria are described in Behen et al. 2008. Written informed consent was obtained from all participants prior to enrollment in the study.

The normal control group consisted of 12 right-handed, typically developing, non-adopted children (seven males, five females; mean age=145.5, SD=36.7 months; age range 72–191 months). All the children underwent intellectual testing and social-historical interview to rule out any current and/or historical developmental, medical, or psychiatric conditions.

The demographic and neuropsychological profiles for the ED and NC groups are presented in Table 1. As can be seen, both groups are functioning within the average range (SS=85–115) in global intellectual functioning (FSIQ). While the controls are functioning well within normal limits in sustained attention and impulsivity the ED group was measured in the low average and borderline ranges for sustained attention and impulsivity respectively. Externalizing behavioral problems were reported to be in the "at-risk" (mean T-score=64; SD=12.7) range for the ED group, and within normal limits for controls.

Neuropsychological evaluation The specific battery of neuropsychological tests has been described elsewhere (Behen et al. 2008). The following scores were used to quantify global intellect (Fullscale IQ, Wechsler Intelligence Scales for Children—Fourth Edition, Wechsler, 1991) and functioning in two performance and one parent-reported domain: Sustained Attention (Gordon Diagnostic System, GDS, Vigilance Hits; Gordon and Mettelman 1988), Impulsivity (GDS, Vigilance false alarms); and parent-reported externalizing behavioral problems (Behavioral Assessment System for Children, Reynolds and Kamphaus 1992).

Data acquisition protocol MRI studies were performed on a GE 1.5T Signa unit (GE Medical Systems, Milwaukee, Wisconsin) using a protocol described previously (Govindan et al. 2008).

Integrative analysis of DTI and volumetric data In order to combine information from DTI and the T1-weighted images in native space, we previously developed an integrative framework (Zou et al. 2006, Muzik et al. 2007). Using this software, regions of interest (ROIs)

Table 1 Group demographic and neuropsychological profiles

	ED Group		NC Group	
	Mean	Std. deviation	Mean	Std. deviation
Age (months)	126.3	30.9	145.5	36.7
Body Mass Index kg/m^2	16.5	3.3	22.7	3.1
Gender	7 males/8 females		7 males/5 females	
Domain				
Full scale IQ[a]	98.3*	18.7	110.7	14.9
Sustained Attention[b]	85.4*	34.1	94.8	7.3
Impulsivity[c]	70.1*	38.5	99.3	10.9
Externalizing Behaviors[d]	64.5**	12.6	45.7	9.4

[a] Wechsler Intelligence Scales for Children-Third Edition

[b] Gordon Diagnostic System-Vigilance hits score

[c] Gordon Diagnostic System-Vigilance commission errors score

[d] Behavioral Assessment System for Children-Externalizing scale

*Standard Score (Mean=100, SD=15) Higher scores indicate better performance, **T-score (Mean=50, SD=10) Higher scores indicate worse performance representing the head of caudate were defined, by a rater blind to group, based on high-resolution T1-weighted image volumes. These 3D ROIs were then transformed into DTI space and subsequently used as seed regions for probabilistic tractography in native space. Finally, sets of finite elements representing the whole hemisphere, dorsolateral prefrontal cortex (DLPF) and the frontal pole (FP) were defined in both hemispheres and used as target regions for probabilistic fiber tracking.

Probabilistic fiber tracking Probabilistic fiber tracking was performed using a Bayesian framework (Friman et al. 2006) in which the local probability density function (PDF) in each voxel is based on the angular distribution of the primary eigenvectors in all neighboring voxels. Starting from a seed point in the basal ganglia regions, random samples were drawn from the PDF and fiber paths were created which terminated when the local FA decreased below a value of 0.15. For each seed point, 100 paths were created yielding a minimum of 100,000 paths originating from the source region. To quantitatively assess the connectivity between the defined source and target regions, we calculated for each individual fiber path i of length N_i connecting the source and target region, the average probability p_i (Eq. 1) where p_{ij} is the randomly sampled probability of voxel j ($j=1,..N_i$) calculated earlier. This value can be interpreted as the average probability along the path i. Because the number of fiber paths which connect the seed and target region is only a subset of all created fibers (M>N), all path probabilities p_i were subsequently normalized to the sampling space (total number of fiber paths $k=1,\ldots,M$) as p_i' (Eq. 2). Finally the normalized probability score of connection between two regions A and B was calculated as $P_{A\text{-}B}$ (Eq. 3) with the index l (L<M) representing all fiber paths connecting the two regions.

$$p_i = \sqrt[N_i]{\prod_{j=1}^{N_i} p_{ij}} \tag{1}$$

$$p_i' = \frac{p_i}{\sum_{k=1}^{M} p_k} \tag{2}$$

$$P_{A\to B} = \sum_{l=1}^{L} p_i' \tag{3}$$

The normalized probability score p_i' of each fiber tract was subsequently color coded from dark red (low p_i') to bright yellow (high p_i', see Fig. 1a).

For each seed region (L/R head of caudate) the normalized probability score $P_{A\text{-}B}$ was calculated for each of the 512 cortical elements and the cortical pattern was subsequently transformed into a two-dimensional cortical fiber distribution (CFD) map using the Mercator projection (Fig. 1b). To determine the normalized probability score between the seed region and target regions (hemisphere, DLPF, FP) in each hemisphere, the normalized probability score was summed over all finite elements comprising the target regions. This yielded for each subject the normalized probability score between the head of caudate and the hemisphere, FP, or DLPF, separately for the two hemispheres.

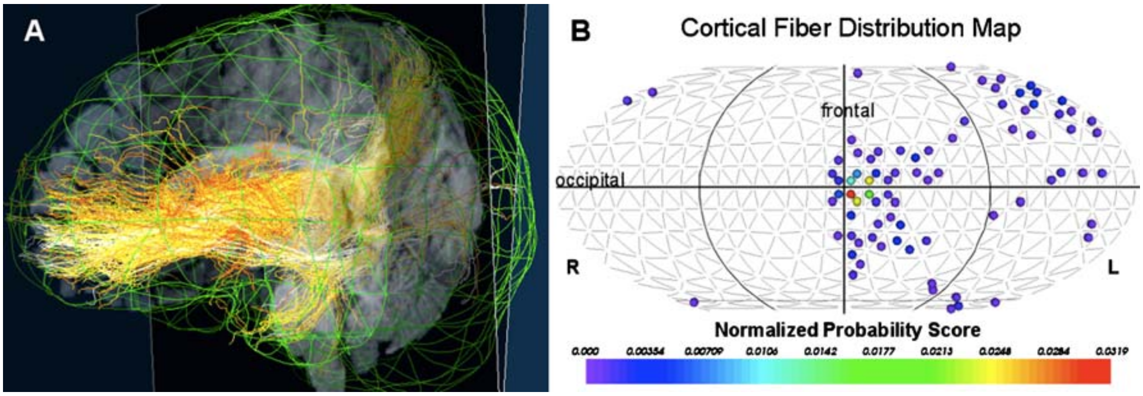

Fig. 1 Display of results obtained from probabilistic fiber tracking in native space (**a**) and in a two-dimensional display following a Mollweide projection of the cortex onto a plane (**b**). **a** Shown are fiber paths created using the left head of caudate as seed region. The normalized probability score for each fiber was calculated according to Eq. 3 and color-coded using a hot metal color table. **b** The cortical pattern of normalized probability scores displayed as a two-dimensional fiber distribution map. The eight quadrants of the brain are shown in the map with the frontal cortex being displayed in the center and the occipital cortex on the periphery. As each finite element corresponds spatially across subjects, the fiber distribution maps can be directly compared across the patient population

Statistical assessment Preliminary analyses involved between-group comparisons on demographic and neuropsychological variables. Tests for continuous variables (age, BMI, FSIQ) involved two-tailed t-tests; for gender chi-square analysis was used. Variables found to differ between groups were included in subsequent comparisons as covariates.

To determine whether there were group differences with respect to the probability of fibers originating from the L/R head of caudate to the target regions (hemisphere, FP and DLPF), a $2\times(2\times3)$ mixed-design ANOVA was applied, where the between-subjects factor was the group (ED, controls) and the two within-subjects factors were the side of the source region (L/R head of caudate) and the target region (hemisphere, FP and DLPF). Finally, in order to test the relationship between the neuropsychological variables (performance measures of sustained attention and impulsivity, and parent-reported externalizing behaviors) and the six normalized connectivity scores (head of caudate—L/R hemisphere; head of caudate—L/R FP, and head of caudate—L/R DLPF), six separate backwards stepwise multiple regressions were run, with covariates and the three neuropsychological variables entered as predictors and each of the connectivity scores as the outcome.

Results

Demographic variables Between-group comparisons of demographic variables showed significantly reduced BMI in the ED group (p=0.002). Although the control group was slightly older and included a slightly higher proportion of females, these differences were not statistically significant (age, p=0.11; gender, p=0.54); nor were there group differences on IQ. BMI was included as a covariate in subsequent between-group comparisons.

Cortical fiber distribution Pearson's correlation coefficients between two independent raters for connectivity scores ranged between 0.96 and 0.99, suggesting excellent reliability of the method. The overall mixed design ANCOVA, controlling for BMI revealed a significant 3-way (Group x side x region, $F_{2,23}$=6.527; p=0.006) interaction. Follow up simple effects tests revealed that the normalized probability scores between the head of the caudate and hemisphere were significantly increased in the ED group on both the right ($F_{1,24}$=12.76; p=0.002) and left ($F_{1,24}$=8.74; p=0.007) sides (see Fig. 1a); and also showed reduced probability of connection to the right FP in the ED group ($F_{1,24}$=6.58; p=0.017). No difference was found between the two groups in the left FP or the DLPF region.

Association between neuropsychological variables and connectivity scores Results of the six regression analyses resulted in significant models for left (R^2=.28; p=0.007) and right (R^2=.30; p=0.022) caudate-hemispheric connectivity and left caudate-FP connectivity (R^2=.17; p=0.048). Significant predictors for the models included externalizing behavior for left (partial r=.53; p=0.007) and right (partial r=.54; p=0.008) caudate-hemispheric connectivity; and BMI for left FP (partial r=−.31; p=0.007).

Discussion

The results of our study indicate aberrant connectivity in fronto-striatal projections in children with histories of ED. Specifically, the ED group had significantly increased probability of connection of striatal projections terminating in the cortex, however, with a concomitant reduced probability of connection to the frontal pole in the right hemisphere. Increased fronto-striatal connectivity was associated with increased externalizing behavioral problems. These findings represent the first to demonstrate structural abnormalities of the fronto-striatal circuit in children with ED, and suggest a plausible neural substrate for symptoms associated with the I/O behavioral phenotype often described in children with histories of ED (Stevens et al. 2008)

Importantly, one of the most prevalent characteristics of children with histories of ED is problems with inattentiveness and overactivity; up to one third of children with such histories demonstrate the I/O phenotype based both on parent-reported and performance measures of attention and impulsivity (Behen et al. 2008; Stevens et al. 2008). In the present sample, mean sustained attention and impulsivity were in the low average and borderline ranges, respectively; and 36% of the sample had absolute impairment in one of these two domains.

Stevens et al. (2008) presented functional support for similarities between the idiopathic ADHD phenotype and expression of I/O in children who had experienced ED. Given the findings from imaging studies of neural correlates of idiopathic ADHD which have demonstrated abnormalities in the fronto-striatal circuit (Shaw et al. 2007; Giedd et al. 2001), findings from the present study provide some structural support for similarities between the I/O phenotype and idiopathic ADHD. Shaw et al. (2007) speculated that the delayed pattern of heteromodal cortical maturation identified in idiopathic ADHD might reflect a lack of normal pruning. The findings of excessive fronto-striatal connectivity in the present study may also be consistent with an abnormal pruning process, perhaps associated with lack of experience-expectant stimulation (e.g., language stimulation, caregiver regulation of emotional states) during orphanage rearing. Chatterjee et al.

(2007), showed elevations in the number of neurons and supporting astroglial cells and reduced indices of functionality in cortical regions in rat pups subjected to maternal deprivation. Reduced functionality was associated with reduced neuronal pruning and apoptosis (Chatterjee et al. 2007).

Abnormalities in fronto-striatal connectivity observed in the children with ED may also be associated with the adverse effects of chronic stress. Prolonged stress has been documented in both animal and human studies to influence structure and function of the nervous system (Mirescu et al. 2004; Kaufman et al. 2000) Dysregulation of stress-response as a result of social deprivation has been demonstrated in post-institutionalized children (Gunnar et al. 2001).

It is important to note that findings in the present study could also be due to a host of additional factors, including perinatal insult, poor prenatal nutrition (Lozoff 2007), maternal stress during pregnancy (Coe et al. 2003; Van den Bergh et al. 2005), and/or prenatal exposure to alcohol (see Miller et al. 2007; Spadoni et al. 2007) all of which have been shown to affect both the structure and function of the brain. Importantly, alcohol exposure is associated with increased white matter volume, and hypothesized to be due to a lack of axonal pruning (Miller et al. 2007). Although the children included in the present study did not show any of the morphological characteristics of fetal alcohol syndrome (and children with elevated Miller criteria were excluded—see Behen et al. 2008), the effects of alcohol (or other substances) during the prenatal period cannot be definitively ruled out. The correlation between BMI and connectivity scores suggests postnatal malnutrition, which has been shown to be associated with structural brain changes (Cordero et al. 1993).

A number of methodological issues warrant discussion. Firstly, with regard to probabilistic tractography, even if sophisticated and advanced, the presently available models do not/cannot account for all uncertainties/complexities of fiber orientation in some parts of the brain. Further, accuracy of tractography results are restricted by limitations on spatial resolution, thermal and physiological noise, brain motion and image artifacts. Finally, these techniques are not completely validated; information about the relationship between tractography methods and anatomical data is still sparse. Also important to note is that although neither age nor region of adoption was associated with connectivity scores, given the small sample sizes, it cannot be ruled out that these factors contribute to findings. Given these issues, results should be interpreted cautiously and further validation of these findings in larger, more homogeneous samples and with alternative methods (i.e., deterministic fiber tracking) is warranted.

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