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Detection of hand and leg motor tract injury using novel diffusion tensor MRI tractography in children with central motor dysfunction

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ABSTRACT

Purpose: To examine whether an objective segmenation of corticospinal tract (CST) associated with hand and leg movements can be used to detect central motor weakness in the corresponding extremities in a pediatric population.
Material and Methods: This retrospective study included diffusion tensor imaging (DTI) of 25 children with central paresis affecting at least one limb (age: 9.0 ± 4.2 years, 15 boys, 5/13/7 children with left/right/both hemispheric lesions including ischemia, cyst, and gliosis), as well as 42 pediatric control subjects with no motor dysfunction (age: 9.0 ± 5.5 years, 21 boys, 31 healthy/11 non-lesional epilepsy children). Leg- and hand-related CST pathways were segmented using DTI-maximum *a posteriori* (DTI-MAP) classification. The resulting CST volumes were then divided by total supratentorial white matter volume, resulting in a marker called "normalized streamline volume ratio (NSVR)" to quantify the degree of axonal loss in separate CST pathways associated with leg and hand motor functions. A receiver operating characteristic curve was applied to measure the accuracy of this marker to identify extremities with motor weakness.
Results: NSVR values of hand/leg CST selectively achieved the following values of accuracy/sensitivity/specificity: 0.84/0.84/0.57, 0.82/0.81/0.55, 0.78/0.75/0.55, 0.79/0.81/0.54 at a cut-off of 0.03/0.03/0.03/0.02 for right hand CST, left hand CST, right leg CST, and left leg CST, respectively. Motor weakness of hand and leg was most likely present at the cut-off values of hand and leg NSVR (i.e., 0.029/0.028/0.025/0.020 for left-hand/right-hand/left-leg/right-leg). The control group showed a moderate age-related increase in absolute CST volumes and a biphasic age-related variation of the normalized CST volumes, which were lacking in the paretic children.
Conclusions: This study demonstrates that DTI-MAP classification may provide a new imaging tool to quantify axonal loss in children with central motor dysfunction. Using this technique, we found that early-life brain lesions affect the maturational trajectory of the primary motor pathway which may be used as an effective marker to facilitate evidence-based treatment of paretic children.

1. Introduction

Hemiparesis is defined as weakness of one vertical side of the body due to injury to the central nervous system. In most cases, the injury occurs to the side of the brain contralateral to the affected limbs. Its most severe form is known as hemiplegia, which entails full paralysis of the muscles in the affected side [1,2]. Bilateral paresis can develop if the primary motor cortex or motor pathways are injured bilaterally (tetraparesis). There is a wide range of injuries that can cause central paresis in children, such as peri- or postnatal stroke, brain trauma, or genetic/metabolic disorders [3]. In general, such injuries occur in 1 out of every 500 births, whereas the incidence highly increases with low birth weight and prematurity, but can also be acquired later in life [4]. Such injuries present significant challenges in the rehabilitation and education of the affected children; thus, there is a great demand for an imaging marker that could objectively assess severity of structural motor abnormalities, predict future development of motor function and monitor effects of therapy for these patients.

Diffusion tensor imaging (DTI) tractography is a well-established imaging technique that quantifies water diffusivity along the axons, enabling *in vivo* study of neural pathways including the corticospinal

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tract (CST) [5–10]. CST connects the motor cortex to the spinal cord enabling voluntary motor control over the limbs [11]. In previous DTI studies, CST was evaluated as a whole. This approach, while informative, does not account for possible discrepancies in the degree of injury to leg and hand related fibers, thus significantly masking the measures of DTI in the regions of interest. To overcome this critical problem, we recently developed a new method, independent component analysis combined with ball-stick model (ICA + BSM) allowing identification and isolation of crossing fibers related to control of the hands and legs [12–15]. Using this approach, it was found that in children with unilateral brain damage due to Sturge–Weber syndrome, hand-related (but not leg-related) CST volumes were consistently decreased in the affected hemisphere [16]. Follow-up showed that depending on the level of brain damage, varying degrees of compensation occurred as reflected by changes in CST volume [16]. Another study demonstrated that asymmetries also exist between the development of hand- and leg-related fibers of the CST in typically developing children [17]. In the present study, we postulated that DTI tractography may provide additional information about the development of CST in children with central motor weakness, and that the presence of DTI abnormalities would reflect the pattern of motor weakness in the affected hands and legs.

This study aims to investigate a new tool using DTI tractography, which can objectively evaluate axonal loss (and plasticity) of primary motor functions in children with paresis. A novel method called "diffusion tensor imaging maximum *a posteriori* probability" (DTI-MAP) classifier was utilized to identify two prominent subdivisions of the CST [14,15], which are associated with hand/arm and leg/trunk motor control. The volumes of resulting CST segments were analyzed with respect to the presence and distribution of motor weakness determined by clinical neurological examination. We postulated that paretic children would show significantly decreased CST fiber volumes in the affected hemisphere, when compared to corresponding CST volumes of age-matched non-paretic controls. Also, it was postulated that the decreased fiber volumes of the hand- and leg-related CST segments would correlate with the deficit in the corresponding limbs.

2. Materials and methods

2.1. Subjects

The present study is a retrospective observational on 25 children with motor weakness of central origin, either unilateral or bilateral in either the hands and/or legs (23 children also had increased muscle tone documented in the affected extremity; age: 1.5–16.5 years, mean age: 9.0 ± 4.2 years, 15 boys, 8/7/9/1 right/left/bi-handedness/unknown) and 42 control subjects (age: 1.8–19.0 years, mean age: 9.0 ± 5.5 years, 21 boys, 28/7/2/5 right/left/bi-handedness/unknown) including 31 children with typical development (mean age 11.2 ± 4.7 years) and 11 children with new onset epilepsy but having no structural abnormalities on MRI and no motor impairment (mean age: 2.7 ± 0.6 years). Age and gender did not differ between central motor deficit (MD) and control groups ($p = 0.39$ and 0.28, respectively).

The patients with MD were recruited through the pediatric neurology clinics at Children's Hospital of Michigan with the following criteria: 1) having motor weakness in at least one extremity. 2) having no known genetic disorders and 3) having no severe comorbidities (e.g., severe intellectual disability). Based on the above criteria, we included 5/13/7 children with left/right/both hemispheric lesions including ischemia, cyst, and gliosis confirmed by MRI. Among them 14 children had epilepsy, and 13 were developmentally delayed. MD children were categorized into 4 subgroups according to their distribution of motor weakness associated with each body part as listed in Table 1. Time interval between the initial diagnosis and MRI was 1.3 ± 1.7 years. None of the control subjects had motor weakness on neurological examination. The Human Investigations Committee (HIC) of Wayne State University granted permission for performing MRIs (without sedation) in children with typical development, and parents signed an informed consent form. We had also permission from the HIC to use clinically acquired MRI scans after deidentification. The 25 patients with MD and 11 patients with focal epilepsy were sedated for clinical MRI acquisition.

Table 1
Motor dysfunction (MD) subgroups classified by the presence and distribution of motor weakness.

Subgroup	Sample size (n)	Extremity			
		Left hand	Right hand	Left leg	Right leg
MD_1	10	Yes	Yes	Yes	Yes
MD_2	6	Yes	No	Yes	No
MD_3	4	No	Yes	No	Yes
MD_4	5	Yes	Yes	No	No

2.2. MRI acquisition

MR scans were performed using a 3 T GE-Signa scanner (GE Healthcare, Milwaukee, WI) equipped with an 8-channel head coil and ASSET. DTI was acquired with a multi-slice single shot diffusion weighted echo-planar-imaging (EPI) sequence at repetition time = 12,500 ms, echo time = 88.7 ms, field of view (FOV) = 240 mm, 128 × 128 acquisition matrix (nominal resolution = 1.89 mm), contiguous 3 mm thickness in order to cover entire axial slices of the whole brain using 55 isotropic gradient directions with $b = 1000 s/mm^2$, one $b = 0$ acquisition, and number of excitations = 1. Children with neurological conditions being scanned clinically were sedated, if needed, using pentobarbital (3 mg/kg) followed by fentanyl (1 μg/kg).

2.3. DTI-MAP classification

Whole brain tractography was performed using ICA + BSM to reconstruct streamlines of white matter fibers, as described and validated recently in various pediatric patient groups using functional MRI and invasive electrical stimulation mapping symptoms [12,13]. In brief, the orientations of up to three stick compartments were identified at each voxel using the ICA + BSM. The resulting orientations were interpolated to track ongoing fibers using deterministic streamline tractography parameterized at fractional ratio ≥ 0.1, deflection angle ≤ 60°, and step size = 0.5 voxel width. To identify the two segments of CST streamlines associated with primary motor pathways of the hand and leg, DTI-MAP classifier was applied, which can automatically classify individual streamlines into one of three segments, hand, leg, and face, based on their stereotactic atlases constructed from healthy children [14,15]. For each segment, a streamline visitation map was created by using the number of streamlines passing through each voxel. Voxels having at least 1 visit were assumed to belong to each motor pathway. Streamline volume was measured by the total volume of all voxels belonging to the segment. Finally, normalized streamline volume ratios (NSVR) of the hand and leg segments were obtained in each hemisphere by dividing the corresponding streamline volume to total white matter volume of both cerebral hemispheres (i.e., excluding cerebellum).

2.4. Statistical analysis

To investigate the group differences between controls and MD subgroups listed in Table 1, separate univariate analyses of variance (ANOVA) were applied for four NSVR values (i.e., hand and leg CST segments in both hemispheres). For these analyses, both age and gender were included as covariates. Receiver operating characteristic (ROC)