Assessment of the Contralesional Corticospinal Tract in Early-Onset Pediatric Hemiplegia: Preliminary Findings

Rachel L. Hawe-*IEEE Student Member* and Jules P.A. Dewald- *IEEE Member*

Abstract— **While pediatric hemiplegia results from a unilateral lesion, the immature state of the brain at the time of injury increases the likelihood of observing changes in the non-lesioned hemisphere as well. The purpose of this preliminary study was to use diffusion tensor imaging to evaluate the contralesional corticospinal tracts in individuals with early-onset pediatric hemiplegia. Twelve individuals with pediatric hemiplegia and ten age-matched controls underwent diffusion tensor imaging (DTI). Corticospinal projections were reconstructed using probabilistic tractography for both the lesioned and contralesional side in pediatric hemiplegia as well as the dominant and non-dominant sides in control subjects. The contralesional tract was found to have decreased white matter integrity relative to control subjects. Compared to controls, the contralesional tract also showed increased tract volume. The increase in volume suggests the presence of ipsilateral corticospinal projections from the contralesional hemisphere that are maintained during development to control the paretic extremities. Decreases in integrity may be explained by diffuse damage or incomplete maturation. The findings of this study support the notion of bilateral motor involvement in pediatric hemiplegia, and the need to address bilateral neural changes as well as motor deficits in this population.**

I. INTRODUCTION

Early-onset pediatric hemiplegia describes primarily unilateral motor deficits that result from a unilateral lesion occurring in the prenatal or perinatal periods. Prior imaging studies in this population have attempted to characterize damage to the lesioned motor pathways and link this with motor deficits [1-3]. However, since the lesion occurs early in development, it is possible that the effects of the lesion and potential reorganization may take place contralesionally as well [4-6].

This research was supported by NIH Grant RO1 NS058667; NIH Grant T32 EB009406; and a NSF Graduate Research Fellowship.

R. L. Hawe is with the departments of Biomedical Engineering and Physical Therapy and Human Movement Sciences at Northwestern University, Chicago, IL, 60640, USA (phone: 312-503-1653; fax: 312-908-0741; e-mail: rhawe@u.northwestern.edu).

J. P. A. Dewald is with the departments of Physical Therapy and Human Movement Sciences, Physical Medicine and Rehabilitation, and Biomedical Engineering at Northwestern University, Chicago, IL 60611, USA (e-mail: j-dewald@northwestern.edu).

The contralesional motor pathways are of interest for several reasons. First, at the time of early lesions, the developing brain is extremely susceptible to damage [7]. However, this damage may be more diffuse and not visible on structural MRI images. Second, the developing brain has a large capacity for reorganization, much of which can occur through using contralesional neural resources [4]. Lastly, there have been reports of motor deficits not only on the hemiparetic side, but also in the "unaffected" or "less affected" upper extremity, as well as bimanual coordination deficits [8-10]. These clinical findings suggest that changes may exist contralesionally.

In typical development, corticospinal axons originate from both motor cortices. Following competition between ipsilateral and contralateral projections for motor neurons, the ipsilateral projections are typically withdrawn while the contralateral projections are strengthened [5]. Previous studies have shown that in early-onset lesions (prenatal and perinatal), direct ipsilateral corticospinal projections from the non-lesioned hemisphere to the paretic upper extremity can be maintained [4-5, 11-12].

The objective of this study was to use diffusion tensor imaging to assess the contralesional corticospinal tracts in pediatric hemiplegia to further our understanding of the neural mechanisms underlying motor deficits in this population. Additionally, we provide a comparison between prenatal and perinatal lesions to demonstrate the important role injury timing has on damage, reorganization, and resulting motor deficits.

II. METHODS

A. Participants

Twelve children and young adults with pediatric hemiplegia (age: 12.8 ± 8.7 years) participated in this study. Within this group, 6 had prenatal injuries and 6 had perinatal injuries. Injury timing was confirmed by review of medical records. Participants were between levels I and III on the Manual Ability Classification System (Level I: n=3; Level 2: n=7; Level III: n=2) with no significant differences in function between prenatal and perinatal groups. Ten typically-developing children (age 12.3 ± 3.9 years) were also recruited to serve as age-matched controls. All participants and guardians when appropriate provided written consent. The experiment was approved by the Northwestern University Institutional Review Board.

B. Imaging

All participants underwent structural and diffusion tensor imaging on a 3 T Siemens TIM Trio scanner with a 32-

channel receive-only head coil at Northwestern University's Center for Translational Imaging (CTI). An MP-RAGE sequence was used to obtain a T1-weighted structural image to determine lesion location. The following acquisition parameters were used: TR= 2.3 s, TE= 3 ms, TI= 900 ms, matrix= 256x256 and FOV= 256x256 mm^2 for a scanning time of 10 minutes. DTI images were acquired using an echo-planar based diffusion imaging sequence with diffusion weighting of 1000 s/mm^2 in 60 diffusion directions, as well as a total of 8 scans without diffusion weighting. The scan parameters used were: TR=5s, TE=85ms, matrix=128x128, FOV=256x256 mm^2, averages=1, 72 slices with thickness of 2 mm without gaps to cover the entire brain and scanning time of 11 minutes. Images were visually inspected and repeated if necessary due to movement artifacts.

C. Image Processing

Images were processed, visualized, and analyzed using the FMRIB Software Library. Brains were skull-stripped and affine registered to correct for eddy current distortions. Diffusion gradient vectors were re-aligned to the original reference system after eddy current correction. Using FMRIB's Diffusion Toolbox (FDT), a diffusion tensor model was fit at each voxel and voxel-wise values for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were derived.

In order to run probabilistic tractography, we first ran the BEDPOSTX algorithm of the FDT toolbox, which uses Markov Chain Monte Carlo sampling to build distributions for diffusion parameters for each voxel [13-14]. Seed masks were then hand-drawn for each participant to capture the corticopsinal tract at two different levels on both the lesioned and contralesional side. The first seed mask was drawn at the cerebral peduncles, with the second seed mask drawn at the posterior limb of the internal capsule. Additionally, an exclusion mask was drawn midsagitally to prevent fibers from crossing the midline. Probabilistic tractography was conducted from each seed mask, maintaining only the tracts that passed through both masks. Tractography results were then thresholded at 10% of total number of tracts generated to remove unlikely projections. Volume of the tracts were calculated as total number of voxels included in the resulting tract. FA, MD, AD, and RD were calculated as the average values within the resulting tract.

D. Statistical Analysis

All statistics were performed with SPSS v.22.0. ANOVAs were run for each metric between the lesioned, non-lesioned (pediatric hemiplegia group), dominant and non-dominant (control group) tracts. When appropriate, each metric was compared between the contralesional tract and dominant tract in control subjects using Fisher's LSD t-tests to correct for multiple comparisons. Additional comparisons were made between prenatal, perinatal, and control participants using ANOVAs and post-hoc LSD t-tests.

III. Results

Fig 1. Displays an example DTI image with corticospinal tracts reconstructed for a participant in the perinatal group. Fig. 2 shows the DTI metrics for the corticospinal tracts for

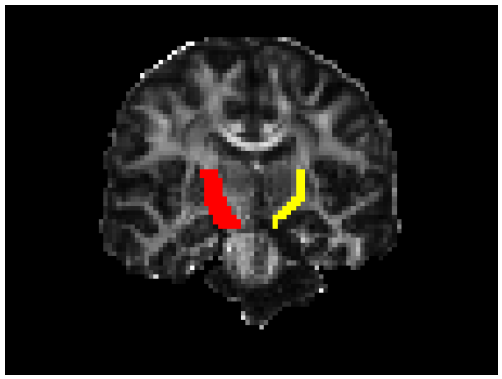

Figure 1. Example DTI Image. *Red indicates nonlesioned corticospinal tract, yellow indicates lesioned corticospinal tract, with volume loss.*

all individuals in the pediatric hemiplegia group as well as all pediatric control participants. Significant losses in integrity were found, reflected by decreased FA (p=0.03), increased MD (p = 0.02), and increased RD (p=0.03). Fig. 3 shows the volume differences between the lesioned, non-lesioned, and control (both dominant and non-dominant) corticospinal tracts. Volume was significantly increased in the non-lesioned tracts compared to control participants (p= 0.016).

In comparing prenatal and perinatal participants, the integrity of the white matter in the lesioned corticospinal tract was decreased compared to controls for both prenatal and perinatal injuries with regards to FA (prenatal: p=0.034; perinatal: p=0.001), and additionally in perinatal injuries for MD (p<0.001) and RD (p<0.001). Comparisons between the prenatal and perinatal groups showed greater damage in the perinatal group for all integrity measures on the lesioned side (FA: p<0.001; MD: p<0.001; AD: p=0.032; RD: p<0.001).

On the contralesional side, both prenatal and perinatal tracts showed decreased integrity compared to controls (*prenatal:* FA: p=0.034; MD: p=0.040; RD: p<0.001; *perinatal:* FA: p=0.001; MD: p=0.003; RD: p<0.001), though no significant differences were found between the prenatal and perinatal groups. Neither prenatal or perinatal injuries demonstrated decreases in tract volume compared to controls, however, perinatal injuries showed significantly greater volume on the nonlesioned side relative to controls (p=0.004).

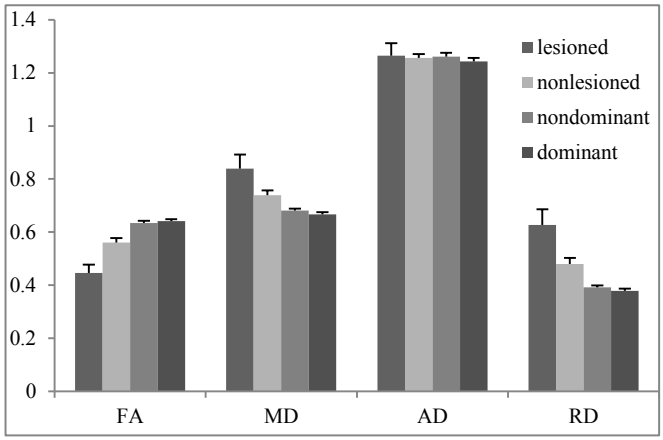

Figure 2. DTI Integrity Metrics for All Participants. *Note that MD, AD, and RD shown in 10^{-3} mm^2/s. Error bars show standard error. Significant differences between nonlesioned tract and controls for FA and RD.*

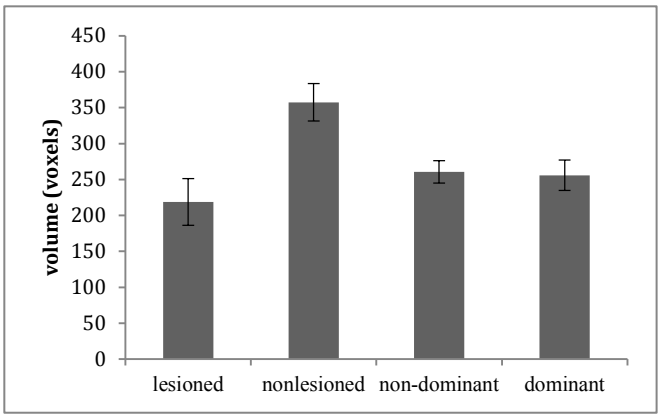

Figure 3. Tract Volume for All Participants. *Error bars represent standard error. Nonlesioned tract shows significant increase in volume compared to control subjects.*

IV. Discussion

The main finding from this study was that the contralesional corticospinal tract is not equivalent to age-matched controls. The differences consist both of decreased white matter integrity and increased tract volume compared to controls. While pediatric hemiplegia is traditionally thought of as unilateral motor deficits due to a unilateral lesion, these findings suggest that changes occur on both sides of the brain, potentially affecting both sides of the body.

There are several possible explanations for the decreased integrity metrics on the contralesional side. First, this could be due to diffuse effects of the initial injury. While all participants in this study had a unilateral lesion visible on a structural MRI, the etiologies of the lesions may cause more widespread damage that is not visible with traditional imaging. For instance, many of the participants, especially in the prenatal group, were born extremely premature (24-28 weeks gestation) with very low birthweights. Previous studies have shown reduced FA in such individuals, even when there is not a visible lesion or motor deficits [7]. Individuals in the perinatal group may also have had complications during birth causing more widespread damage.

An additional explanation is that the contralesional tracts are not damaged, however, fail to fully mature. As discussed above, the contralesional tracts quantified in this study may consist of both crossing corticospinal fibers to the nonparetic extremities, as well as ipsilateral projections to the paretic extremities. Ipsilateral corticospinal projections may not mature to the extent that crossed corticospinal projections due, in terms of characteristics such as myelination and fiber density. This would be reflected in the decreased integrity we found with DTI for the contralesional pathways. Failure of the ipsilateral corticospinal tract to fully mature could explain a previous finding that "normal" hand function is achieved only in children with contralateral projections (as determined by TMS) to their paretic hand [4].

Lastly, it is possible that even the crossed corticospinal projections to the non-paretic upper extremity do not mature to the extent of those in age-matched controls. Previous studies have shown that skilled motor tasks, such as playing an instrument or juggling, can change integrity measures of the corticospinal tracts in healthy adults[15-16]. While children with pediatric hemiplegia are thought to have predominantly unilateral motor deficits, their overall participation in fine motor tasks with either hand may be decreased due to difficulty with using their paretic upper extremity. A lack of skilled fine motor activity may prevent complete maturation of the corticospinal tract.

The increase in volume of the corticospinal tract on the contralesional side relative to controls is consistent with the hypothesis that early unilateral lesions can result in the maintenance of direct ipsilateral corticospinal projections from the contralesional hemisphere that would otherwise be withdrawn during typical development [4, 17-18]. In terms of differences between prenatal and perinatal injuries, we found greater contralesional volume increases in the perinatal group. The difference between groups may be due to the nature of the lesions. Prenatal injuries are typically periventricular, while perinatal injuries are cortical or subcortical lesions. In the case of the prenatal injury, it may be possible for the lesioned corticospinal tract to be displaced around the lesion rather than completely interrupted. The territory and size of the perinatal lesions, however, may cause them to completely intercept the corticospinal tract. Therefore in the prenatal condition, the lesioned corticospinal tract may still be highly functional, whereas the extent of damage in the perinatal conditional necessitate using ipsilateral projections from the contralesional hemisphere.

Our finding of decreased integrity in the contralesional corticospinal tract necesitates the implementation of more in depth quantitative measurments of possible motor impairments in the non-paretic upper limb compared to typically developing children. From a clinical perspective, it is therefore important to assess and address the possibility of bilateral deficits in children with hemiplegia.

An additional implication of this study is that imaging studies should use extreme caution when using the contralesional side for comparison. Changes in the contralesional side, as shown here, may mask or enhance changes observed in the lesioned hemisphere. We therefore advocate for the use of age-matched controls rather than within subject comparisons.

A limitation to our methods is that we cannot be certain we are restricting our tractography to the corticospinal projections alone, and may be including corticobulbar projections as well. However, our choice of seed masks increases our certainty of capturing primarily the corticospinal projections. Additionally, on the contralesional side we cannot delineate between contralateral and ipsilateral corticospinal projections.

Future work will expand this study to a larger number of participants as well as include a post-natal injury timing group to further our understanding of the effects of injury timing on motor pathways integrity and volume. Additionally, we plan to correlate DTI measures with highly quantitative assessments of motor impairments to improve our understanding of the neural mechanisms underlying motor impairments in pediatric hemiplegia.

ACKNOWLEDGMENT

The authors would like to acknowledge Todd Parrish, PhD for his technical expertise, and Theresa Sukal Moulton, PT, PhD for assistance with data collection.

REFERENCES

[1] A. H. Hoon, E. E. Stashinko, L. M. Nagae, D. D. M. Lin, J. Keller, A. Bastian, M. L. Campbell, E. Levey, S. Mori, and M. V. Johnston, "Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways," *Developmental Medicine & Child Neurology*, vol. 51, no. 9, pp. 697–704, Sep. 2009.

[2] S. M. Scheck, R. N. Boyd, and S. E. Rose, "New insights into the pathology of white matter tracts in cerebral palsy from diffusion magnetic resonance imaging: a systematic review.," *Developmental Medicine & Child Neurology*, vol. 54, no. 8, pp. 684–696, Aug. 2012.

[3] O. A. Glenn, N. A. Ludeman, J. I. Berman, Y. W. Wu, Y. Lu, A. I. Bartha, D. B. Vigneron, S. W. Chung, D. M. Ferriero, A. J. Barkovich, and R. G. Henry, "Diffusion tensor MR imaging tractography of the pyramidal tracts correlates with clinical motor function in children with congenital hemiparesis," *AJNR American journal of neuroradiology*, vol. 28, no. 9, pp. 1796–1802, Oct. 2007.

[4] M. Staudt, C. Gerloff, W. Grodd, H. Holthausen, G. Niemann, and I. Krägeloh-Mann, "Reorganization in congenital hemiparesis acquired at different gestational ages," *Ann Neurol*, vol. 56, no. 6, pp. 854–863, Dec. 2004.

[5] J. A. Eyre, "Corticospinal tract development and its plasticity after perinatal injury," *Neuroscience and biobehavioral reviews*, vol. 31, no. 8, pp. 1136–1149, 2007.

[6] M. Staudt, "Brain plasticity following early life brain injury: insights from neuroimaging," *Semin Perinatol*, vol. 34, no. 1, pp. 87–92, Feb. 2010.

[7] L. Eikenes, G. C. Løhaugen, A.-M. Brubakk, J. Skranes, and A. K. Håberg, "Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI," *Neuroimage*, vol. 54, no. 3, pp. 1774–1785, Feb. 2011.

[8] J. Duque, J.-L. Thonnard, Y. Vandermeeren, G. Sébire, G. Cosnard, and E. Olivier, "Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia.," *Brain*, vol. 126, no. 3, pp. 732–747, Mar. 2003.

[9] B. Steenbergen and R. G. J. Meulenbroek, "Deviations in upper-limb function of the less-affected side in congenital hemiparesis," *Neuropsychologia*, vol. 44, no. 12, pp. 2296–2307, 2006.

[10] T. Sukal-Moulton, T. M. Murray, and J. P. A. Dewald, "Loss of independent limb control in childhood hemiparesis is related to time of brain injury onset.," *Exp Brain Res*, vol. 225, no. 3, pp. 455–463, Mar. 2013.

[11] M. Staudt, W. Grodd, C. Gerloff, M. Erb, J. Stitz, and I. Krägeloh-Mann, "Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study," *Brain*, vol. 125, no. 10, pp. 2222–2237, Oct. 2002.

[12] L. J. Carr, L. M. Harrison, A. L. Evans, and J. A. Stephens, "Patterns of central motor reorganization in hemiplegic cerebral palsy," *Brain*, vol. 116, pp. 1223–1247, Oct. 1993.

[13] T. E. J. Behrens, M. W. Woolrich, M. Jenkinson, H. Johansen-Berg, R. G. Nunes, S. Clare, P. M. Matthews, J. M. Brady, and S. M. Smith, "Characterization and propagation of uncertainty in diffusion-weighted MR imaging," *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, vol. 50, no. 5, pp. 1077–1088, Nov. 2003.

[14] T. E. J. Behrens, H. J. Berg, S. Jbabdi, M. F. S. Rushworth, and M. W. Woolrich, "Probabilistic diffusion tractography with multiple fibre orientations: What can we gain?," *Neuroimage*, vol. 34, no. 1, pp. 144–155, Jan. 2007.

[15] A. Imfeld, M. S. Oechslin, M. Meyer, T. Loenneker, and L. Jancke, "White matter plasticity in the corticospinal tract of musicians: a diffusion tensor imaging study," *Neuroimage*, vol. 46, no. 3, pp. 600–607, Jul. 2009.

[16] J. Scholz, M. C. Klein, T. E. J. Behrens, and H. Johansen-Berg, "Training induces changes in white-matter architecture," *Nat Neurosci*, vol. 12, no. 11, pp. 1370–1371, Nov. 2009.

[17] J. A. Eyre, M. Smith, L. Dabydeen, G. J. Clowry, E. Petacchi, R. Battini, A. Guzzetta, and G. Cioni, "Is hemiplegic cerebral palsy equivalent to amblyopia of the corticospinal system?," *Ann Neurol*, vol. 62, no. 5, pp. 493–503, Nov. 2007.

[18] J. A. Eyre, "Development and Plasticity of the Corticospinal System in Man," *Neural Plast*, vol. 10, no. 1, pp. 93–106, 2003.