Published in final edited form as:

Neuropediatrics. 2016 October ; 47(5): 336–340. doi:10.1055/s-0036-1584938.

Changes of White Matter Diffusion Anisotropy in Response to a 6-week iPad Application-based Occupational Therapy Intervention in Children with Surgically Treated Hydrocephalus: a Pilot Study

Weihong Yuan^{1,5}, Karen Harpster², Blaise V. Jones³, Joshua S. Shimony⁹, Robert C. McKinstry⁹, Nicole Weckherlin¹⁰, Stephanie S. Powell^{11,12}, Holly Barnard^{4,8}, Jack Engsborg¹³, Darren S. Kadis^{1,5,8}, Jonathan Dodd^{11,12}, Mekibib Altaye^{6,8}, David D. Limbrick¹⁴, Scott K. Holland^{1,5}, Sarah M. Simpson¹, Sarah Bidwell¹, and Francesco T. Mangano^{7,8}

¹Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

²Division of Occupational Therapy and Physical Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

³Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁴Division of Developmental and Behavioral Pediatrics – Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁵Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁶Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁷Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁸University of Cincinnati College of Medicine, Cincinnati, OH

⁹Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

¹⁰Cerebral Palsy Center, St. Louis Children's Hospital, St. Louis, MO

¹¹Department of Neurology, Washington University School of Medicine, St. Louis, MO

¹²Department of Psychology, St. Louis Children's Hospital, St. Louis, MO

¹³Program in Occupational Therapy, Washington University School of Medicine, St. Louis, MO

¹⁴Dept. of Neurological Surgery, Washington University School of Medicine, St. Louis, MO

Correspondence should be addressed to Weihong Yuan, PhD, Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 5033, Cincinnati, OH 45229, United States, Phone: 1-513-636-2862; Fax: (513) 636-3754; Weihong.Yuan@cchmc.org.

Conflict of Interest/Disclosures No competing financial interest exists for any of the authors.

Informed Consent Statement All procedures followed were in accordance with the ethical standards of the IRB on human experimentation and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consents were obtained from participants' legal guardians at the enrollment.

Abstract

Our aims were (1) to test whether diffusion tensor imaging (DTI) could detect underlying white matter (WM) changes after a 6-week iPad application-based occupational therapy (OT) intervention in children with surgically treated hydrocephalus (HCP); and (2) to explore the association between WM changes and performance outcomes. Five children (age 6.05-9.10 yrs) with surgically treated HCP completed an intensive iPad-based OT intervention targeting common domains of long-term deficits in children with HCP. The intervention included 6 weekly sessions in an OT clinic supplementing home-based program (1 hour/day, 4 days/week). DTI and neuropsychological assessments were performed before and after the intervention. After the therapy, significant increases in fractional anisotropy (FA) and/or decreases in radial diffusivity (RD) were found in extensive WM areas. All participants demonstrated an increased Perceptual Reasoning Index (PRI, Wechsler Abbreviated Scale of Intelligence - Second Edition, PRI gains = 14.20 ± 7.56 , $p=0.014$). A significant positive correlation was found between PRI increase and the increase of FA in the right posterior limb of the internal capsule and the right external capsule (both $p<0.05$). This study provides initial evidence of DTI's sensitivity to detect subtle WM changes associated with performance improvements in response to a 6-week OT intervention in children with HCP.

Keywords

DTI; iPad Application; occupational therapy; pediatric hydrocephalus

INTRODUCTION

Long term neuropsychological deficits have been consistently documented in children with hydrocephalus (HCP) even after successful surgical treatment, particularly in the areas of efficiency in visual-spatial perception/reasoning, visual-motor coordination, and visual-attention.¹⁻⁴ However, many children who are neurologically asymptomatic but exhibiting subtle difficulties are not treated until the underlying difficulty manifests as an overt problem.

Data from both human and animal research have suggested that the enlarged ventricles and increased intracranial pressure in HCP result in damage to white matter (WM) connecting functionally important cortical and subcortical regions in the brain.^{1,5} DTI is an advanced MRI technique that uses the diffusion of water molecules to probe and examine tissue structure, revealing microscopic organizational characteristics.⁶ Accumulating evidence has shown that DTI can differentiate abnormal WM in HCP⁷⁻⁹ and can potentially offer insights about injury and recovery mechanisms as well as neuropsychological outcome of HCP.

In this study we present the preliminary results of a DTI investigation of WM integrity in school age children with surgically treated HCP before and after a newly developed 6-week iPad application-based OT intervention targeting visual-spatial performance, visual-motor coordination, and visual-attention. Initial data showed that this therapy protocol led to performance improvement in visual-perceptual¹⁰ as measured by the Perceptual Reasoning Index (PRI) of the Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II).

In the present study, we tested whether this intervention led to associated WM changes with the working hypothesis that the anisotropic diffusion properties based on DTI would change significantly in WM as a response to the therapy, underpinning the neuroanatomical changes in rehabilitation.

METHODS

Participants

The study group of the present study is a subsample of a longitudinal study that investigated the effectiveness of iPad application-based OT intervention in children with surgically treated HCP. The present study included five participants (age 6.05-9.10 yrs, 2F/3M) that underwent MRI scans and neuropsychological testing both before and after therapy. The time interval between the two scans was 53.4 ± 11.4 days. The interval between the two neuropsychological tests was 55.8 ± 9.1 days (See Table S1 in the Supplemental Material for detailed demographic and timing information).

iPad Application-based OT Intervention

The intervention was comprised of 6 weekly treatment sessions with an occupational therapist who assigned 3–4 iPad applications from each functional category (visual-motor, visual-attention, and visual-spatial processing) each week, selected at an appropriate level of challenge for each participant.¹⁰ The participants were then asked to complete 1 hour/day (20 minutes per functional domain), 4 days/week of the iPad intervention. Compliance was recorded via paper documentation and/or verbal report. All participants successfully completed at least 80% of the intervention each week. No significant correlation was found between the time and the magnitude of the PRI improvement or between the time and the change in any of the WM structures investigated. None of the five children received other occupational therapy during their participation of the study.

MRI Data Acquisition, Processing, and Analysis

MRI data were acquired on a 1.5 Tesla Phillips Ingenia MR scanner (Phillips Medical Systems, Best, The Netherlands) at Cincinnati Children's Hospital. DTI was acquired using a 15-direction single-shot EPI sequence (2.5 mm isotropic). A high resolution 3D T1-weighted image (1mm isotropic) was acquired for registration.

DTI data were processed using the FSL software (the FMRIB Software Library) following standard procedure which included the correction of head motion and eddy current artifact, the registration with the high resolution T1-w images and the brain template in MNI space (Montreal Neurological Institute 152), the reconstruction of diffusion tensor and calculation of DTI maps (including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)), and WM segmentation. The ICBM-DTI-81 WM labels atlas from Johns Hopkins University was used in the WM segmentation. The atlas included 48 major WM regions from which DTI values were extracted for the subsequent statistical analysis. See Supplemental Material for additional details.

Statistical Analysis

The four DTI measures were used to quantify structural integrity based on the WM atlas. The primary neuropsychological outcome measure was the PRI of the WASI-II. The pre- and post-therapy changes of DTI and PRI were tested with two-tailed paired t-test. Pearson correlation was used to explore the association between the changes in DTI and PRI. No multiple comparison correction was performed due to the small sample size in this study.

RESULTS

Change of DTI Measures after Intervention

Seven WM regions (some bilateral) showed statistically significant ($p < 0.05$) increases in FA after the intervention (Table 1). Among these, RD decreased significantly in three regions (Table 1). No significant change was found in MD or AD in any WM regions after the training. Fig 1A shows gCC, PLIC, and external capsule (EC) overlaid on T1-w brain template.

Changes in Neuropsychological Assessment after Intervention

The 5 participants scored 62, 95, 98, 77, and 76, respectively, on the WASI-II PRI (79.60 ± 16.41) at baseline. All 5 participants earned higher PRI scores after the training (75, 102, 119, 84, 89, respectively, an average increase in magnitude of 14.20 ± 7.56 , $p = 0.014$).

Correlation between Changes in DTI and Change in PRI

Significant positive correlations were found between the increase in PRI score and the increase of FA in the right PLIC ($r = 0.890$, $p = 0.043$, Fig 1B) and in the right external capsule (EC, $r = 0.888$, $p = 0.044$, Fig 1C).

DISCUSSION

This pilot study focused on short term DTI changes in response to a 6-week iPad application-based OT therapy in children with surgically treated HCP. A key motivator was to determine whether DTI sensitivity would be sufficient to link the effectiveness of the interventions to underlying neural mechanisms. Doing so enables us to use the approach on a wider basis to quickly assess and track the neurobiological impact of new treatments, and improve the targeting of such interventions at specific neural pathways and cognitive domains. Our results showed that a series of major WM structures had significantly increased FA and decreased RD after the intervention, providing initial support for DTI as a non-invasive imaging biomarker. In addition, the correlation between DTI change and the improvement in PRI score suggests an association between performance change and microstructural alterations in this cohort.

DTI has been found to be sensitive to WM alterations associated with outcome improvement after cognitive training with training length varying from 2–8 weeks^{11–13} to 3–6 months.^{14–15}, suggesting that short-term training is often practical and effective in triggering brain structural re-organization either acutely or a long time after the initial insult. In the present study, the length of training was 5–6 weeks with an average of 24 hours with the OT

intervention and it was administered an average of over 5 years after the last surgery for HCP. Consistent with our hypotheses, anisotropic diffusion properties changed significantly after the training, suggesting that the OT intervention effectively altered the WM microstructure.

Seven WM structures (some bilateral, Table 1) demonstrated significant DTI change after the intervention. Four of these WM regions, gCC, PLIC, PTR, and uncinate fasciculus (UF), have been reported to have abnormal DTI measures in HCP.^{7–9} The correlations between PLIC and EC's FA change and the improvement in PRI scores are interesting findings. The PLIC contains both pyramidal tracts (including cortical spinal tract and corticobulbar fiber) and some sensory fibers. EC contains association fibers that are responsible for connecting various functional regions throughout the cortex. Some studies have shown significant correlation between the WM abnormality in these regions based on DTI and deficits in visual-motor, visual-perceptual, and visual-attention in other study cohorts (See Supplemental Material for additional references relevant to the current section). The correlation between the PRI change and the DTI change in the present study may be explained by the contribution from all these targeted domains of the intervention. Although the sample size did not allow us to pinpoint precisely the WM tracts related directly to the outcome measures, our results encourage further investigation aimed at establishing a causal relationship for WM structures responsible for the outcome changes in this patient cohort.

Caution should be taken in the interpretation of our results due to the small sample size, which prevented us from conducting multiple comparison correction in the statistical analysis. This limits the generalizability of our findings before they are validated in a larger study with sufficient statistical power. The lack of a control group to account for test-retest effect was another limitation. However, all 5 participants presented consistent gains in PRI at or above approximately half standard deviation (all ≥ 7 points), which is a level that we consider to be clinically relevant, warranting further large-scale investigation to allow for more rigorous statistical analysis.

Conclusion

We documented subtle but statistically significant DTI changes in WM regions in response to a 6-week iPad application-based OT intervention in school age children with HCP. In some WM regions, the DTI changes were highly correlated with improvement in neurocognitive outcomes. These initial findings suggest that DTI is a sensitive tool that can provide important neurobiological information regarding the effect of treatment in response to occupational therapy in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This study is supported in part by the Robert L. McLaurin, MD, Faculty Development Scholarship in Neurosurgery at Cincinnati Children's Hospital Medical Center (PIs: Yuan, W. & Mangano F. T.) and the NIH/NINDS (R01 NS066932, PIs: Yuan W. & Mangano F. T.). Support was also provided by the Eunice Kennedy Shriver National

Institute Of Child Health & Human Development of the NIH (U54 HD087011) to the Intellectual and Developmental Disabilities Research Center at Washington University.

REFERENCES

1. Mataró M, Junqué C, Poca MA, et al. Neuropsychological findings in congenital and acquired childhood hydrocephalus. *Neuropsychol Rev.* 2001; 11:169–178. [PubMed: 11883667]
2. Frank SV, Lazarus T, Nathoo N. Visuospatial deficits in children 3–7 years old with shunted hydrocephalus. *S Afr Med J.* 2003; 93:865–868. [PubMed: 14677514]
3. Gupta N, Park J, Solomon C, et al. Long-term outcomes in patients with treated childhood hydrocephalus. *J Neurosurg.* 2007; 106:334–339. [PubMed: 17566197]
4. Bakar EE, Bakar B, Taner YI, et al. Evaluation of the intellectual skill problems of hydrocephalic children: a clinical study. *Turk Neurosurg.* 2009; 19:29–35. [PubMed: 19263350]
5. Del Bigio MR. Neuropathology and structural changes in hydrocephalus. *Dev Disabil Res Rev.* 2010; 16:16–22. [PubMed: 20419767]
6. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed.* 2002; 15:435–455. [PubMed: 12489094]
7. Assaf Y, Ben-Sira L, Constantini S, et al. Diffusion tensor imaging in hydrocephalus: initial experience. *AJNR Am J Neuroradiol.* 2006; 27:1717–1724. [PubMed: 16971621]
8. Scheel M, Diekhoff T, Sprung C, Hoffmann KT. Diffusion tensor imaging in hydrocephalus--findings before and after shunt surgery. *Acta Neurochirurgica (Wien).* 2012; 154:1699–1706.
9. Yuan W, McKinstry RC, Shimony JS, et al. Diffusion tensor imaging properties and neurobehavioral outcomes in children with hydrocephalus. *AJNR Am J Neuroradiol.* 2013; 34:439–445. [PubMed: 22899790]
10. Harpster, K.; Weckherlin, N.; Yuan, W., et al. Tablet-Based Occupational Therapy Intervention for Children with Hydrocephalus; American Occupational Therapy Association Annual Conference; 2016. Accepted
11. Strangman GE, O'Neil-Pirozzi TM, Supelana C, et al. Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic brain injury. *NeuroRehabilitation.* 2012; 31:295–310. [PubMed: 23093456]
12. Engvig A, Fjell AM, Westlye LT, et al. Memory training impacts short-term changes in aging white matter: a longitudinal diffusion tensor imaging study. *Hum Brain Mapp.* 2012; 33:2390–2406. [PubMed: 21823209]
13. Gebauer D, Fink A, Filippini N, et al. Differences in integrity of white matter and changes with training in spelling impaired children: a diffusion tensor imaging study. *Brain Struct Funct.* 2012; 217:747–760. [PubMed: 22198594]
14. Mackey AP, Whitaker KJ, Bunge SA. Experience-dependent plasticity in white matter microstructure: reasoning training alters structural connectivity. *Front Neuroanat.* 2012; 22(6):32. [PubMed: 22936899]
15. Prosperini L, Fortuna D, Giannì C, et al. Home-based balance training using the Wii balance board: a randomized, crossover pilot study in multiple sclerosis. *Neurorehabil Neural Repair.* 2013; 27:516–525. [PubMed: 23478168]

Figure 1.

A. White matter regions of interests segmented based on JHU WM atlas overlaid on a T1w brain image. Only regions with significant change or trend of change in FA are displayed. Abbreviation: gCC = genu of callosum; EC: external capsule; PLIC=posterior limb of internal capsule; **B.** Correlation between change in WASI PRI score and change of FA in right posterior Limb of internal capsule, $p < 0.05$; **C.** Correlation between change in WASI PRI score and change of FA in right external capsule $p < 0.05$.

Table 1

Statistics of DTI measures (FA and RD) in white matter areas with statistically significant increase or with trend level increase, (p value based on paired t-test; MD and AD values are not included because no change was observed in these two measures)

		Pre-			Post-			P
		Minimum	Median	Maximum	Minimum	Median	Maximum	
gCC	FA	0.308	0.433	0.499	0.315	0.4497	0.548	0.040
	RD	0.619	0.714	0.823	0.552	0.732	0.811	NS
ML (left)	FA	0.291	0.359	0.493	0.339	0.360	0.521	0.035
	RD	0.595	0.742	1.158	0.579	0.728	1.074	NS
CP (right)	FA	0.325	0.440	0.459	0.357	0.462	0.488	0.008
	RD	0.676	0.843	1.254	0.649	0.782	1.192	0.012
PLIC (left)	FA	0.336	0.410	0.488	0.353	0.468	0.515	0.018
	RD	0.515	0.564	0.658	0.500	0.547	0.639	0.004
PLIC (right)	FA	0.312	0.446	0.505	0.332	0.479	0.515	0.027
	RD	0.509	0.544	0.933	0.501	0.536	0.861	NS
PTR (Right)	FA	0.272	0.329	0.426	0.281	0.335	0.449	0.017
	RD	0.683	0.697	0.735	0.682	0.695	0.758	NS
EC (right)	FA	0.236	0.247	0.330	0.266	0.286	0.338	0.010
	RD	0.675	0.723	0.775	0.655	0.722	0.739	NS
UF (left)	FA	0.195	0.213	0.338	0.231	0.245	0.403	0.004
	RD	0.770	0.834	0.992	0.660	0.776	0.817	0.010
UF (right)	FA	0.272	0.278	0.320	0.287	0.316	0.378	0.026
	RD	0.779	0.836	0.895	0.669	0.779	0.835	NS

gCC = genu of corpus callosum; ML = medial lemniscus; CP = cerebral peduncle; PLIC = posterior limb of internal capsule; PTR = posterior thalamic radiation; EC = external capsule;; UF = uncinated fasciculus. NS = not significant.