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Structural connectivity related to persistent symptoms after mild TBI in adolescents and response to aerobic training: preliminary investigation

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Abstract

OBJECTIVE—To quantify structural connectivity abnormalities in adolescents with mild traumatic brain injury (mTBI) and to investigate connectivity changes following aerobic training using graph theory and diffusion tensor imaging (DTI) tractography.

SETTING—Outpatient research setting.

PARTICIPANTS—Twenty two children (age: 15.83±1.77 years, 10 F) with 4–16 weeks of persistent symptoms after mTBI and a matched healthy comparison group.

DESIGN—Randomized clinical trial of aerobic training and stretching comparison combined with case-control comparison.

MAIN MEASURES—(1) Five global network measures: global efficiency (Eglob), mean local efficiency, modularity, normalized clustering coefficient (γ), normalized characteristic path length (λ), small-worldness (σ). (2) The self-reported Post-Concussion Symptom Inventory (PCSI) score.

RESULTS—At initial enrollment, adolescents with mTBI had significantly lower Eglob and higher γ , λ , and σ (all $p<0.05$) when compared to healthy peers. After the intervention, significant increased Eglob and decreased λ (both $p<0.05$) were found in the aerobic training group. Improvement in PCSI scores were significantly correlated with the Eglob increase and λ decrease in the aerobic training and λ decrease in the stretching comparison group (all $p<0.05$).

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CONCLUSION—This pilot study showed initial evidence that structural connectivity analysis was sensitive to brain network abnormalities and may serve as an imaging biomarker in children with persistent symptoms after mTBI.

Keywords

structural connectivity; aerobic training; graph theory; DTI tractography; mild traumatic brain injury; persistent symptom

Introduction

Mild traumatic brain injury (mTBI) is a leading cause of pediatric morbidity.¹ An estimated one-third of children with mTBI have persistent symptoms beyond one month.² There are no proven treatments to hasten recovery, reduce sequelae, or ameliorate long-term deficits in this population. Specifically, there is an incomplete understanding of how physical activity influences recovery. Common clinical practice is to recommend relative rest until symptom-free. However, clinical studies indicate that prolonged rest may be detrimental to recovery³ and that aerobic exercise may facilitate recovery.⁴ Although there appears to be clinical benefits of introducing aerobic activity after mTBI, biologic correlates related to this introduction and recovery are poorly understood. Further work is needed to understand the relationship of changes in brain connectivity with other markers of recovery or function.

In the present study, we investigated the structural connectivity of brain networks based on graph theoretical analysis and diffusion tensor imaging (DTI) tractography for the same cohort of individuals that completed our recently published randomized clinical trial on aerobic training in adolescents with persistent symptoms after mTBI.⁵ Structural connectivity analysis has emerged in recent years as a novel approach that quantifies brain connectivity based on the topological characteristics of the entire network.⁶ With this approach, the brain network is modelled as a system comprised of functionally associated but spatially segregated grey matter regions integrated by white matter tracts that transfer information critical for the normal functioning of the network. Several recent TBI studies successfully adopted this approach to examine abnormal structural connectivity features in TBI of various chronicities or to quantify associations between network connectivity measures and neurobehavioral outcomes.^{7,8} Most recently, a longitudinal cohort of adolescents with moderate to severe TBI showed that the structural connectivity analysis was sensitive to detect subtle but significant change in network measures in response to an intervention designed to improve attention deficits.⁹

The primary objectives of this study were to apply structural connectivity analysis to: (1) investigate abnormalities in structural connectivity in the brain network of children with persistent symptoms after mTBI and (2) investigate longitudinal changes in structural connectivity in response to an aerobic training intervention. We hypothesized that structural connectivity in our mTBI cohort would be abnormal at study enrollment compared to healthy peers, but would normalize after aerobic training. Further, we hypothesized that the improvement in structural connectivity metrics would be associated with improved symptoms.

Methods

Design

This was a cohort study of adolescents with persistent post-concussion symptoms who participated in a randomized clinical trial comparing aerobic training to a stretching protocol.⁵ An age and sex-matched historical cohort of healthy adolescents was also used as a comparison group.

Participants

Participants included 22 children (average age: 15.45 ± 1.72 years, 10F/12M) with 4–16 weeks of persistent symptoms after mTBI who participated in a prior randomized controlled trial and completed MRI/DTI scans.⁵ MRI and symptom burden assessments were acquired for all 22 children with mTBI at the initial study enrollment and again in 17 out of the 22 participants after intervention completion. Among the 17 patients tested at both time points, 8 (age: 15.04 ± 1.35 years, 4F/4M) completed the aerobic training intervention and 9 (age: 15.48 ± 2.08 years, 3F/6M) completed the stretching protocol. Twenty age- and sex-matched children (age: 16.28 ± 1.38 years, 7F/13M) were selected from an existing database collected through the pediatric functional neuroimaging research network (Cincinnati MR Imaging of NeuroDevelopment-CMIND) as a healthy control comparison. Families of participants gave written informed consent and children provided written assent.

MRI/DTI Data Acquisition and Processing

All MRI data were acquired on a 3 Tesla Phillips Achieva MRI scanner (Philips Medical Systems, Best, Netherlands). For the children with mTBI, DTI was acquired with a single-shot echo planar sequence with the following specifications: Repetition Time = 6565 msec; Echo time = 81 msec; field of view = 224 mm $\times$ 224 mm; acquisition matrix = 112 $\times$ 112; in-plane resolution = 2 mm $\times$ 2 mm; number of slices = 60; slice thickness = 2 mm; 61 non-collinear diffusion-weighted directions ($b=1000$ s/mm²); Seven volumes of images with no diffusion sensitization; SENSE factor = 2. Whole brain 3D T1-weighted anatomical images were acquired with 1 mm isotropic resolution for registration. The imaging data for the healthy controls were acquired on the same scanner. The DTI sequence differed only in the repetition and echo time: 6614 msec and 84 msec, respectively, with other specifications identical to those used in the mTBI group. The 3D T1 weighted sequence was identical in the two study groups.

DTI data were pre-processed in the Functional MRI of The Brain's (FMRIB, Oxford, UK) Diffusion Toolbox in the FSL software (the FMRIB Software Library). The procedure followed standard methods including head motion and eddy current artifact correction, image normalization and registration. The Automated Anatomical Labeling Atlas (AAL atlas) was used to parcellate the brain structures into 116 regions in MNI space. The 90 cortical and subcortical gray matter regions as defined by the AAL template were used in the whole brain tractography performed in Diffusion Toolkit/TrackVis.¹⁰ Tractography was performed based on a deterministic tracking algorithm with an angular threshold of 70° and a fiber length threshold of 20 mm.

Network Construction

Structural connectivity networks were constructed using the UCLA Multimodal Connectivity Package¹¹ for graph analysis. A 90×90 square connectivity matrix was constructed to represent the brain network comprised of 90 cortical and sub-cortical gray matter regions with white matter fibers connecting these regions. The matrix was calculated with the value in each entry equal to the number of streamlines connecting the corresponding pair of brain regions.

Graph Theoretical Analysis

Structural connectivity analysis based on graph theory and DTI tractography were performed following standard processes.^{6,10,11} This approach has been applied extensively in neuroscience research.¹² In the present study, both global and regional network connectivity measures were included in the analysis. The global connectivity measures included global efficiency (Eglob), mean local efficiency (mean Eloc), modularity (MOD), normalized clustering coefficient (γ), normalized characteristic path length (λ), and small-worldness (σ). The specific work flow has been described in our previous studies.^{8,9} A detailed description and the corresponding mathematical definition of the network measures can be found in Rubinov and Sporns' work in 2010.⁶

Symptom Burden

Symptom burden was measured using the self-ratings on the Post-Concussion Symptom Inventory (PCSI) for adolescents as described previously.¹³

Cognitive Assessments

The NIH® toolbox cognition batteries are a multidimensional set of measures used to assess cognitive function in individuals ages 3–85 years.^{14–16} The toolbox has been validated and normed in a broad sample of the U.S. population. We used the NIH toolbox measures to characterize baseline cognitive function in the study participants. Executive function, attention, working memory, and processing speed were assessed with the flanker inhibitory control and attention test, list sorting working memory test, dimensional change card sort test, and pattern comparison processing speed test. Age-corrected standard scores were used, for which the normative mean and standard deviation are 100 and 15, respectively.

Statistical Analysis

Descriptive statistics were used to characterize the sample. Two sample t-tests and Chi Square tests were used to compare baseline characteristics of the aerobic and stretching groups (Table 1). A two-sample t-test was used to compare the structural connectivity for children in the mTBI group at the initial enrollment and children in the healthy comparison group. We also performed an independent t-test to compare differences pre- and post-intervention between the aerobic training and stretching comparison groups. Associations between changes in network connectivity and PCSI symptom ratings post-intervention were explored using the Pearson correlation coefficient analysis. In this analysis, a *p*-value of .05 was used to define significance. Effect size and 95% confidence intervals were reported.

Results

Comparison of Global Network Measures

Cross-sectional comparison—At initial enrollment, 22 children with persistent symptoms after mTBI had significantly lower global efficiency, higher normalized clustering coefficient, higher normalized characteristic path length, and higher small-worldness (all $p < 0.05$) compared to 20 age and sex, matched controls (Table 2). Among the 17 children with mTBI who had imaging pre and post-intervention, no significant difference was found at the initial enrollment in any of the global network measures between the 8 children in the aerobic training group and the 9 children in the stretching comparison group.

Longitudinal comparison—Paired t-tests showed a significant increase in global efficiency (effect size = 1.92; 95% confidence interval: $-.04 - 3.88$) and a decrease in normalized characteristic path length (effect size = $-.85$; 95% confidence interval: $-2.81 - 1.11$) in the aerobic training group post program completion (both $p < 0.05$, Table 3). No other changes in global network measures were found in the aerobic training group. Paired t-tests did not reveal pre- to post-intervention differences in global network measures in the stretching comparison group. Independent t-tests comparing changes in global network measures between the aerobic training and stretching comparison groups did not demonstrate significant differences between groups.

Symptom Burden and Association with Changes in Network Measures

Significant correlation was found in the aerobic training group between the change in self-reported PCSI score and the change in global efficiency ($r = 0.715$, $p = 0.046$, 95% confidence interval: $0.021 - 0.944$, Figure 1A) and between the change in self-reported PCSI score and the change in normalized characteristic path length ($r = -0.725$, $p = 0.042$, 95% confidence interval: $-0.946 - -0.042$, Figure 1B). Significant correlation was also found in the stretching comparison group between the change in the self-reported PCSI score and the change in the normalized characteristic path length ($r = 0.725$, $p = 0.027$, 95% confidence interval: $0.118 - 0.937$, Figure 1C).

Discussion

This study provides preliminary support for the association of structural connectivity measurements in adolescents after mTBI who present with persistent symptoms as well as the recovery of these measures with symptom recovery. Further investigation is warranted to understand the association of structural connectivity with clinical recovery after mTBI. The comparison of adolescents with persistent symptoms at initial enrollment to healthy controls showed initial evidence of abnormality in global network connectivity measures. Within the group that received aerobic training, there were significant changes in structural connectivity associated with the intervention and reflective of more typical connectivity. However, differences between the aerobic training and stretching comparison groups were not detected. Correlations between changes in the global network measure and changes in self-reported PCSI score suggest that structural connectivity analysis may provide a sensitive

imaging tool for detecting network abnormalities that correspond to clinical symptom burden.

Findings from this study build on ours and others' prior work in the mTBI and more severe TBI populations. In a prior study of children and adolescents soon after mTBI, structural connectivity was found to be significantly associated with symptoms.⁸ Improved structural brain connectivity was found to be associated with better recovery of attention problems after a 10-week attention training intervention in children with more severe brain injury.⁹ Studies have also reported white matter changes and associated outcomes improvement following other cognitive or motor trainings of various lengths.^{17,18} In the present study, the aerobic training or stretching protocol lasted 6 to 8 weeks. As hypothesized, the structural connectivity indices of the brain network, which were derived from white matter diffusion properties, were sensitive to the white matter abnormality and improvement in symptoms post intervention suggesting that symptom improvement may be related to microstructural change. While it is difficult to speculate the exact physiological mechanisms that led to the changes observed in the study, we believe that aerobic exercise may alter the recovery process by improving cerebral blood flow, blood oxygen extraction, autonomic control pathway, and neuroplasticity that might affect structural organization of the brain.^{19–21}

The application of structural connectivity analysis based on graph theory and DTI fiber tracking is a novel but indirect approach to investigate the WM integrity in the brain network. There are a number of inherent limitations in its application, e.g., using DTI instead of HARDI sequence is insensitive to the crossing fibers and their impact to the overall network connectivity. The definition of network nodes using a parcellation scheme based on a certain anatomical template is subjective which may have variable sensitivity to the connectivity change in different patient populations. Finally, the graph theory metrics selected may not be optimal for the detection of underlying changes. This study was also limited by its small sample size, which prevented further, more rigorous statistical analysis. Our findings need to be replicated and validated with a larger scale study before reaching definitive conclusions. Additionally, the healthy controls did not receive an intervention and were only scanned once, precluding comparison of changes between injured and non-injured individuals in response to aerobic training. Future studies should be designed to evaluate whether changes found in the participants with TBI following an exercise intervention are also observed in healthy controls. Although the scan sequence in the patient group was only slightly different from the controls, it would be ideal to use identical sequences in future studies. Larger studies are needed to better elucidate how measures of brain connectivity correlate with outcomes after mTBI and their potential use as a marker of treatment response.

Conclusions

Structural connectivity analysis is potentially sensitive to brain network abnormalities associated with persistent symptoms in children after mTBI. The recovery of structural connectivity, as well as the correlation found between the recovery of network measures and the improvement in self-reported PCSI ratings suggests that this novel approach may serve as a diagnostic and monitoring tool capable of quantifying recovery and response to

rehabilitation interventions in this population. However, future larger studies are needed to verify this relationship and understand what other factors influence connectivity.

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Figure 1.

Significant correlation between total change in self-reported PCSI score and (A) change in global efficiency in aerobic training group; (B) change in normalized characteristic path length in aerobic training group; (C) change in normalized characteristic path in stretching comparison group.

Table 1

Comparison of baseline data between intervention and comparison groups

	Entire group (n=22)	Aerobic (n=8)	Stretching (n=9)	p-value*
Age at enrollment, mean (stdv) in years	15.45 (1.72)	15.04 (1.35)	15.48 (2.08)	.62
Time since injury, mean (stdv) in days	55.37 (23.98)	56.98 (24.24)	56.06 (25.04)	.94
Sex, number males	12	4	6	.49
Race, number non-white	4	1	2	.60
Primary caregiver education, number with bachelor degree or higher	12	5	4	.46
Income, number families with \$70,000 and above annual income	12	5	5	.77
Mechanism of injury, number sport-related	13	4	7	.23
Number reporting typical participation in an organized sport prior to injury	17	7	8	.93
History of 2 or more concussions, number including injury related to study	12	5	5	.77
Pre-injury Self-PCSI ratings, mean (std)	9.05 (8.94)	5.38 (7.23)	13.00 (10.62)	.11
Initial Baseline self-PCSI, mean (std)	39.59 (23.97)	28.38 (20.94)	42.00 (27.84)	.28
Pre-randomization self-PCSI, mean (std)	27.45 (17.56)	19.25 (11.32)	28.11 (22.24)	.33
Baseline cognitive assessment*				
Dimensional change card sort test, mean (std)	96.00 (12.70)	97.79 (12.28)	96.77 (13.41)	.87
Flanker inhibitory control and attention test, mean (stdv)	91.28 (14.44)	90.64 (12.85)	94.73 (14.91)	.56
List sorting working memory task, mean (std)	101.84 (14.05)	99.32 (13.42)	106.80 (15.06)	.30
Pattern comparison processing speed test, mean (std)	104.37 (25.26)	110.10 (24.89)	109.5 (24.35)	.96

* comparison between cycling and stretching groups

Table 2
Comparison of global network measures between the normal control group and the overall TBI group at baseline.

Global Network Measures	Healthy Controls n=20 (Mean±Std)	TBI n=22 (Mean±Std)	Effect Size			p
			Cohen's d	d lower limit	d upper limit	
E_{glob}	0.564±0.004	0.552±0.004	3.074	3.072	3.076	<0.0001
Mean E_{loc}	0.757±0.010	0.758±0.011	-0.097	-0.102	-0.093	NS
MOD	0.377±0.023	0.389±0.019	-0.586	-0.596	-0.578	NS
γ	2.117±0.122	2.222±0.113	-0.917	-0.970	-0.879	0.0059
λ	1.090±0.015	1.105±0.013	-1.099	-1.106	-1.094	0.0008
σ	1.942±0.092	2.010±0.084	-0.793	-0.833	-0.758	0.017

Note: γ = normalized clustering coefficient; λ = normalized characteristic path length; σ = small-worldness; E_{glob} = global efficiency; E_{loc} = local efficiency; MOD = modularity.

Table 3
Pre- to post-intervention difference in global network measures in the two studygroups.

		n	Pre-Training			Post-Training			t	df	p
			Minimum	Median	Maximum	Minimum	Median	Maximum			
Eglob	Aerobic	8	0.547	0.553	0.557	0.550	0.558	0.564	5.42	7	0.001
	Stretching	9	0.542	0.552	0.561	0.547	0.558	0.566	1.98	8	ns
Mean Eloc	Aerobic	8	0.740	0.757	0.766	0.735	0.763	0.772	0.97	7	ns
	Stretching	9	0.741	0.757	0.775	0.748	0.759	0.766	0.04	8	ns
MOD	Aerobic	8	0.360	0.386	0.413	0.328	0.389	0.414	0.45	7	ns
	Stretching	9	0.359	0.391	0.412	0.327	0.388	0.416	0.65	8	ns
γ	Aerobic	8	2.072	2.238	2.320	2.018	2.205	2.311	1.24	7	ns
	Stretching	9	2.029	2.177	2.418	1.975	2.159	2.354	1.79	8	ns
λ	Aerobic	8	1.087	1.105	1.127	1.081	1.097	1.128	2.41	7	0.047
	Stretching	9	1.077	1.105	1.118	1.064	1.101	1.115	0.79	8	ns
σ	Aerobic	8	1.906	2.005	2.067	1.848	2.016	2.052	0.65	7	ns
	Stretching	9	1.884	1.970	2.163	1.844	1.968	2.112	1.96	8	ns

Note: γ = normalized clustering coefficient; λ = normalized characteristic path length; σ = small-worldness; Eglob = global efficiency; Eloc = local efficiency; MOD = modularity.