Bachelor of Science in Medicine Degree Program
End of Term Final Report

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Project Title: Changes in cortical thickness in pediatric sports-related concussion: a pilot study

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Summary (250 words max single spaced):

Background: Preliminary studies suggest that traumatic brain injury is associated with alterations in cortical thickness. Here, we use advanced magnetic resonance imaging (MRI) techniques to examine group and individual differences in cortical thickness among adolescent sub-acute sports-related concussion (SRC) patients compared to an institutional atlas of healthy normal control subjects.
Methods: Fifteen SRC patients (mean age=16.3, range 14-20 years) and 27 healthy control subjects (mean age=17.6, range 13-21 years) underwent anatomical MRI imaging. Vertex-by-vertex group and individual differences in regional cortical thickness were examined using Freesurfer software: cortical thickness cluster maps were generated; three different statistical methods were applied to the cluster map; sum of areas of brain regions with increased and decreased cortical thickness were calculated. Then, leave-one-out receiver operating characteristic curve (ROC) method was used to determine whether brain cortical thickness difference biomarkers correctly discriminate between SRC patients and healthy control subjects.
Results: All studies were tolerated with no complications. Group comparisons revealed clusters of increased cortical thickness localized to the right lateral-occipital region of brain. Leave-one-out ROC curve analysis using neuroimaging biomarkers reflective of cortical thickness revealed area under the curve (AUC) values for the method 1 and 2 and thinned and thickened clusters of 0.467, 0.638, 0.389, 0.567.
Conclusions: Preliminary results of this pilot study suggest that adolescent SRC is not associated with

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Changes in cortical thickness in pediatric sports-related concussion: a pilot study

Introduction & Background

Concussion is a complex pathophysiological process whereby abnormal biomechanical forces are transmitted to the brain either via a direct blow to the head or indirectly through forces transferred to the head from another part of the body. Concussion may cause neurological disturbances that manifest as a wide variety of signs and symptoms[1]**.** Participation in full contact sports such as football or hockey that involve frequent blows to head are associated with an elevated risk of concussion.

Expert consensus has historically viewed sports-related concussion (SRC) as an injury resulting in clinical features that arise from transient disturbances in brain functioning occurring in the absence of structural brain injury[2]. Although clinical neuroimaging studies including conventional magnetic resonance imaging (MRI) may reveal evidence of structural injury in patients with mild traumatic brain injury (mTBI) including microhemorrhages, white matter hyper densities, focal encephalomalacia or brain atrophy[3] , these studies are typically normal in patients with SRC[4]. For this reason, recent studies have aimed to apply even more sophisticated neuroimaging techniques to this condition including magnetoencephalography, diffusion tensor imaging (DTI), and task-based functional magnetic resonance imaging[5]. Despite detecting changes between groups of concussion patients and healthy controls, none of these techniques have emerged as useful clinical tools that contribute to the management of acute SRC patients.

In recent years there has been increased media and research attention aimed at the effect of SRC and repetitive sub-concussive head injuries on neurodegeneration in youth and adult athletes[6]. Preliminary studies suggest that athletes including retired professional football players with a history of repetitive head trauma may be at an elevated risk of mild cognitive impairment, neurodegenerative diseases such as Alzheimer's and Parkinson's Disease and chronic traumatic encephalopathy (CTE) which are associated with diffuse brain atrophy[7–10]. Although preliminary studies have suggested that pediatric moderate and severe TBI is associated with reductions in grey matter volume and cortical thickness, few studies have investigated the effect of SRC on these characteristics and neuroimaging biomarkers among youth athletes.

In this pilot study, we examine group and individual differences in cortical thickness among adolescent sub-acute SRC patients compared to an institutional atlas of healthy normal control subjects. Using a leave-one-out receiver operating characteristic (ROC) analysis we examined whether quantitative biomarkers reflective of cortical thickness can be reliably used to distinguish between subjects with and without sub-acute SRC in group and individual comparisons to the normal atlas.

Material & Methods

Ethics:

Informed patient, and where applicable, parental consent were obtained for all participants prior to participating in the study. The following study has been approved by the Biomedical Research Ethics Board (BREB) at the University of Manitoba.

Research Design & Clinical Assessment:

We conducted a case-control study of adolescent SRC patients that were compared to an institutional atlas of healthy control subjects that includes subjects used in previous studies conducted by our group[11,12]. Adolescent SRC patients were recruited from the Pan Am Concussion Program, a multi-disciplinary pediatric concussion clinic that accepts referrals for children and adolescents with sports- and non-sports-related TBI in Winnipeg, Manitoba, Canada.

All adolescent SRC patients included in the study underwent a clinical assessment by a single neurosurgeon. Patient inclusion criteria for this study included: 1) physician diagnosis of SRC according to the definition of the International Consensus on Concussion in Sport guidelines[2]; 2) age 13-21 years; 3) patients had to be symptomatic at rest or during exercise at the time of neuroimaging assessment.

All healthy control subjects underwent a clinical interview to collect demographic, past medical history, and past concussion history data. Healthy control subject inclusion criteria for the study included: 1) age 13-21 years. Exclusion criteria for control subjects included: 1) the presence of a symptomatic concussion; 2) diagnosis of prior moderate or severe TBI or neurological condition resulting in structural brain abnormality detected on prior neuroimaging; 3) contra-indication to MRI (i.e dental braces, claustrophobia); 4) diagnosis of a neurological condition requiring prescription medication.

In general, SRC patients were deemed clinically recovered when they were asymptomatic at rest, were back to full-time school, had a normal neurological examination and successfully completed the International Consensus on Concussion in Sport return-to-play guidelines where applicable[2]. Some patients underwent graded aerobic treadmill testing as part of their clinical management to help classify patients into post- concussion clinical sub-types and inform the design of multi-disciplinary rehabilitation strategies. Patients were diagnosed with autonomic/physiological post-concussion disorder (PCD) if they demonstrated a symptom-limited threshold on graded aerobic treadmill testing as previously described[13,14].

On the day of neuroimaging all subjects completed the Post-Concussion Symptom Scale (PCSS), a concussion symptom inventory consisting of 22 symptoms that are rated on a 7-point (0-6) Likert scale with a maximum score of (6 × 22) = 132[15].

MRI Assessment:

Neuroimaging assessment in this study consisted of 1) anatomical imaging; 2) BOLD CVR mapping; and 3) global resting CBF measurement. Prior to neuroimaging

assessment, all study subjects were exposed to a short trial of the breathing sequence to familiarize them with the changes in breathing that would occur while in the MRI scanner. During MRI assessment, subjects underwent non-invasive heart rate, pulse oximetry, and blood pressure (BP) monitoring. Subjects were also given a hand-held call button that allowed them to voluntary terminate the test at any time.

Imaging acquisition:

Images were acquired using a Siemens Verio 3.0T MR scanner with a 12-channel phased-array head coil. Anatomical imaging was acquired without manipulation of end-tidal gases using a sagittal 3D T1 MPRAGE (whole brain coverage; matrix: 256×256; slice thickness: 2.2 mm; no interslice gap; voxel size 2×2×2 mm) and axial gradient recalled echo planar (GRE) sequences to screen for cerebral micro-hemorrhages.

Image Processing and Statistical Analysis:

Prior to data processing, subject head motion artifact and end-tidal CO_2 targeting was examined. Study subjects were excluded if motion over the course of the imaging acquisition was greater than 3 mm in any plane or if inadequate end-tidal CO_2 targeting was identified during BOLD MRI acquisition. The analysis and results for CVR and resting cerebral blood flow imaging are reported elsewhere.

Cortical thickness analysis was undertaken using the T1-weighted MRI images and FreeSurfer software (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) using a multi-step process. First, representations of the gray and white matter boundary were reconstructed for each subject using both intensity and continuity information from the T1 weighted MRI images. This data was analyzed by uploading our anatomical MRI T1 weighted *nifti* files onto the CBrain server (http://mcin-cnim.ca/technology/cbrain/) to be processed by supercomputer.

Second, we manually reviewed all of the FreeSurfer processed outputs to troubleshoot any automatically generated errors in the data[11,16]. In summary, reviewing steps include removal of nonbrain tissue, automated Talairach transformation, segmentation of subcortical white and gray matter structures, nonparametric nonuniform intensity normalization, tessellation of the gray matter white matter boundary, topology correction, and surface deformation following intensity gradients to place optimally the gray/white and gray/cerebrospinal fluid borders.

Subsequently, to match cortical geometry across subjects to make them ready for between subject comparison, data underwent registration to a spherical atlas (fsavarage, provided by Freesurfer) using individual cortical folding patterns. Then, epresentations of cerebral cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface, were generated for each subject[17].

Finally, thickness data were smoothed using a 10-mm (full width at half maximum) Gaussian kernel to increase signal-to-noise. Using the general linear model (GLM)[18], local cerebral cortical thickness was regressed against the concussion history, discrete 2

class variable (class 0: Control; class 1: Concussed) to explain the data at each vertex and generate cortical thickness difference clusters (CTDC) maps both for the groups comparisons as well as for comparison of individual subject with the institutional atlas of 27 healthy controls. These CTDCs were evaluated in 3 different ways that is illustrated in Figure 1:

1- *Method 1:* Generating clusters based on the vertices with $p_{value} < 0.005$; Adding up the areas of statistically significant clusters for each individual subject in both left and right hemispheres; generating a table of features for each subject from the sum of thinned and thickened areas (Table 2).

2- *Method 2:* Generating clusters based on the vertices with False Discovery Rate (FDR = 0.05)[19] ; Adding up the areas of statistically significant clusters for each individual subject in both left and right hemispheres ; generating a table of features for each subject from the sum of thinned and thickened areas (Table 2).

3- *Method 3:* Generating clusters based on the vertices with $p_{value} < 0.05$, applying Monte-Carlo cluster correction algorithm[20] ($p_{value} < 0.05$) to the statistically significant clusters; Adding up the areas of statistically significant clusters for each individual subject in both left and right hemispheres; generating a table of features for each subject from the sum of thinned and thickened areas (Table 2).

In addition, we used a leave-one-out ROC curve analysis to evaluate whether the quantitative cortical thickness biomarkers (sum of the areas of CTDCs for each subject for the thinned and thickened clusters) could be used to reliably distinguish between SRC patients and health controls. Figure 1 shows simplified steps of our analysis.

Results

Participants:

A total of 55 subjects were enrolled in the study including 37 healthy control subjects and 18 SRC patients however, subject data for 7 controls and 3 SRC patients were excluded due to excessive motion and data for 3 controls was excluded due to poor end-tidal CO_2 targeting. Therefore, 27 healthy control subjects (13 males, 14 females, mean age=17.6, SD=2.6, range 13-21) and 15 SRC patients (9 male, 6 female, mean age=16.3, SD=1.6, range 14-20 years) were included in the final analysis.

Normal control subject past medical history was significant for previous concussion in 5/27 (19%) and migraine headaches 1/27 (4%). Past medical history among SRC patients included previous concussion in 12/15 (80%) and pre-injury migraine headaches in 2/15 (13%). The mean PCSS score among healthy controls at the time of neuroimaging assessment was 1 (range 0-7, 1 subject had missing data). The mean PCSS score among SRC patients at the time of neuroimaging assessment was 42 (range 1-82). The mean time from injury to neuroimaging assessment for the SRC patients was 16 days (range 3-32 days). Sports played by the patients at the time of injury included hockey (6 patients), football (4 patients) and basketball (1 patient), rugby (1 patient), volleyball (1 patient), soccer (1 patient), and ringette (1 patient). Additional clinical data are summarized in Table 1.

Anatomical Imaging:

Anatomical imaging was reviewed and reported by a board-certified neuro-radiologist. Anatomical imaging studies were normal in 26/27 (96%) of healthy control subjects with 1 patient found to have a developmental right frontal venous anomaly. Anatomical imaging studies were normal in 11/15 (73%) of SRC patients. Abnormalities found among SRC patients included a developmental left frontal venous anomaly (1 patient), pineal cyst (1 patient), non-functioning pituitary microadenoma (1 patient), and a traumatic micro-hemorrhage located in the splenium of the corpus callosum that was identified on imaging obtained following a previous concussion (1 patient).

Analysis:

The statistically significant clusters after applying Monte Carlo cluster wise correction between the atlas of controls (instituted from 27 control subjects) and the average brain of concussed subjects (generated from 15 concussed subjects) is shown in Figure 2-A; Overall, group comparison between the SRC patients and healthy control subjects showed a cluster of increased cortical thickness located in the right lateral-occipital region. No other group differences were detected. Figure 2-B, shows the maximum normalized thickness values for each subject in the lateral-occipital region cluster.

Table 2 shows the sum of the increased and decreased clusters' area for each individual subject calculated with the three different mentioned methods. ROC curve analysis using the cortical thickness biomarkers to distinguish concussed patients from the healthy controls revealed area under the curve (AUC) values for the method 1 and 2 and thinned and thickened clusters of 0.467, 0.638, 0.389, 0.567, respectively. These results suggest

that quantitative neuroimaging biomarkers of cortical thickness do not reliably distinguish between subjects with and without sub-acute SRC. Figure 3 shows the leave-one-out ROC curve for voxels manifesting a greater or less change in cortical thickness for increased change of thickness methods 1 and 2. The AUC for the method 3 thinned cluster was not calculatable, as there is only one control subject in this group with; the AUC for the method 3 thickened clusters was 0.68 which does not provide considerable statistical power for correct subject based on this feature classification as well.

Discussion

In this study, we examined group and individual differences in cortical thickness between adolescent sub-acute SRC patients and healthy normal control subjects. Overall, group comparisons using Method 3 with both vertex and cluster values at $p<0.05$ revealed clusters of increased cortical thickness within the right lateral-occipital region among adolescent SRC patients compared to normal control subjects.

However, by analyzing at the extracted features (Table 2), no significant trends can be seen, distinguishing control from concussed patients. For example, there is more areas of increased cortical thickness using all 3 methods, and the area of thickens/thinned are comparable among control and concussed individual; mean of thinned area and thickened area for the control group (using method 1) is 259 mm^2, and 1045 mm^2 and for the concussed group is 325 mm^2, and 1171 mm^2, respectively. These results and that of our leave-one-out ROC curve analysis suggest that quantitative biomarkers derived from cortical thickness neuroimaging data does not reliably distinguish between group of subjects with and without sub-acute SRC.

Moreover, the results of our individual and leave-one-out ROC curve analysis suggests that quantitative biomarkers derived from cortical thickness neuroimaging data do not reliably distinguish between subjects with and without sub-acute SRC.

In comparison to adults, generalized cerebral atrophy and neurodegenerative change following TBI remains understudied in the pediatric population. Available studies that have included pediatric patients with TBI of all severities suggest that TBI may be associated with neurodegenerative changes including atrophy within selected brain regions including the hippocampus, amygdala, globus pallidus, thalamus, periventricular white matter, cerebellum, and brain stem as well as overall decreased whole brain volume and increased CSF and ventricular space[21]. Some of these studies looked at white matter vulnerability among TBI patients using diffusion tensor imaging (DTI)[22–24], while some other looked at volumetric and cortical thickness changes[16,25,26]. To date, most studies available studies have focused on changes that have occurred in patients in the more chronic phase of injury.

For example, Wilde et al[27] examined cortical thickness changes in pediatric moderate and severe TBI patients and orthopedic injured controls at 3 months and 18 months post-injury using Cortical reconstruction was performed with the FreeSurfer image analysis suite version 4.5.0 for cortical thickness reconstruction. At 3 months post-injury, TBI patients demonstrated decreased cortical thickness bilaterally in aspects of the superior frontal, dorsolateral frontal, orbital frontal, and anterior cingulate regions compared to controls. At 18 months, some of the regions of cortical thinning evident at 3 months post-injury in the TBI group remained significantly decreased while others were attenuated. Interestingly at 18 months post-injury, several regions of cortical thinning were also observed among the control subjects. Moreover, several areas of cortical thickening were observed among TBI patients at 18 months which the authors attributed to either compensatory hypertrophy or random effects.

In another study, Merkley et al.[25] assessed changes in cortical thickness using Freesurfer (version v4.0.4) among pediatric moderate and severe TBI patients and demographically matched controls. This study demonstrated global significant cortical thinning in the TBI group compared to the cohort of control subjects that correlated to deficits in working memory evaluated using the Behavior Rating Inventory of Executive Function (BRIEF)[28].

Among the studies that focused on volumetric and cortical thickness changes in patients with SRC, Albaugh et al. investigated the association of cortical morphology and concussion history and post-concussive symptoms among 29 male hockey players (mean age-17.8 years) using neuroimaging and baseline Immediate post-concussion Assessment and Cognitive Testing (ImPACT). Cortical thickness was regressed against ImPACT Total Symptom Score (TSS), concussion history, as well as baseline measures of psychopathology. They used FreeSurfer (version 5.3.0) to reconstruct the brain surfaces and used Monte-Carlo algorithm to correct cluster errors. They showed that while ImPACT TSS was inversely associated with local cortical thickness in widespread brain areas, specifically in frontal and bilateral temporoparietal cortices, concussion history was not associated with cortical thickness. However, given recent consensus agreement that computerized neurocognitive tests such as ImpACT do not meet reliability standards for clinical use, the findings of this study are difficult to interpret[29].

Taken together, the results of these preliminary studies suggest that moderate and severe pediatric TBI may be associated with longitudinal changes in cortical thickness and grey and white matter volumes but that orthopedically injured and control subjects can also show inter-subject variability that can contribute to changes in these measures.

The preliminary results of our pilot study do not suggest that adolescent SRC is associated with any neuroimaging evidence of early brain atrophy or neurodegeneration and that quantitative biomarkers reflective of cortical thickness are not clinically to aid in the diagnosis of sub-acute SRC. Indeed, further research is needed to evaluate the short and long-term effect of pediatric SRC and repetitive head injury on cortical thickness and grey and white matter volumes. and should take into consideration the effect of age-related changes in brain compartment volumes that are expected across different stages of neurodevelopment.

The results of the present study must be considered in light of several important limitations. First, the sample size is relatively small and included adolescent patients that were recruited from a multi-disciplinary pediatric concussion program. Patients evaluated at tertiary concussion programs are more likely to have sustained more severe injuries that take longer to recover compared patients recruited from emergency room or other ambulatory care populations. Therefore, this population may not be reflective of the general adolescent SRC patient population. Future studies would benefit from the inclusion of child and adolescent patients who present with a wide spectrum of symptom burdens and reflect the heterogeneous natural history of this condition.

Second, the patient population examined in this study included those with a significant history of previous concussions. Although approximately 50% of patients that present to our multi-disciplinary pediatric concussion program have a history of previous

concussion[30], the lifetime burden of concussions among the SRC patient in this study was higher than what would be expected among a general population of adolescent SRC patients.

Third, the SRC patients in this study were imaged at non-uniform time-points following injury, thus limiting direct comparisons between individual subjects. This time period may have been too early in the injury process to detect any evidence of brain atrophy or neurodegeneration. As such, future prospective longitudinal studies incorporating larger samples of adolescents without a history of previous concussion who are imaged at uniform time-points are needed to evaluate the impact of individual concussions on volumetric grey and white matter and cortical thickness changes during the acute and clinically recovered stages of injury.

Fourth, there are numerous techniques that can be used to investigate surface and volume based brain morphometry such as Freesurfer, FSL, SPM and CAT12[31]. Finding a consistent MRI imaging markers and processing method for brain disorders is important as low statistical power of neuroimaging and neuroscience studies, differences in the demographics of data, image acquisition settings, assumptions made on data and algorithms used will affect the result. In this study, we used Freesurfer, and could not find a statistically significant biomarker between the SRC patients and healthy controls. However, using other algorithms may result in different findings. Future studies should consider the use of different processing methods examining cortical thickness and grey and white matter volumes and compare results between techniques in order to properly assess the diagnostic and prognostic value of quantitative biomarkers derived from these analyses. Indeed, previous studies have found discrepancies in brain volume estimates using different techniques within the same patient population[31].

Taking these limitations into consideration, the preliminary results of this pilot study suggest that adolescent SRC is not associated with any neuroimaging evidence of early brain atrophy or neurodegeneration and that quantitative biomarkers reflective of cortical thickness do not reliably distinguish between subjects with and without sub-acute SRC. Future prospective studies including a larger sample of subjects are needed to further evaluate the association between adolescent SRC and repetitive head injury exposure and morphological changes in brain structure including cortical thickness and grey and white matter volumes.

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Figures, Figure Legends, and Tables

Figure Legends:

Table 1: Summary of demographic, clinical features, and outcomes in sports-related concussion patients.

Table 2: Sum of the clusters area in the left and right hemispheres for each subject for 3 different analysis; 1) Vertices $p_{value} < 0.005$; 2) FDR = 0.05; 3) Monte Carlo clustering.

Figure 1: Analysis algorithm flowchart.

Figure 2-A: Group differences in cortical thickness clusters between SRC patients and normal healthy control subjects.
Figure 2-B: Maximum normalized thickness values for each subject in the lateral-occipital region cluster.

Figure 3. A: Receiver operating characteristic curve analysis of cortical thickness biomarkers using Method 2 (FDR = 0.05); greater than thickness.
Figure 3. B: Receiver operating characteristic curve analysis of cortical thickness biomarkers using Method 1 (Vertex $p_{value} < 0.005$); greater than thickness.

Tables:

Table 1: Summary of demographic, clinical features, and outcomes in sports-related concussion patients.

Subject	Past medical history	Time from injury to imaging assessment (days)	Clinical outcomes
1	3 previous concussions	29	- Autonomic/ Physiological PTD - Required medication for post-traumatic headaches - Remained symptomatic at last follow-up (154 days)
2	1 previous concussion	13	- Clinically recovered (41 days post-injury)
3	2 previous concussions	3	- Clinically recovered (9 days post-injury)
4	1 previous concussion	27	- Autonomic/ Physiological PTD - Remained symptomatic at last follow-up (90 days post-injury)

5	1 previous concussion	7	- Clinically recovered (34 days post-injury)
6	2 previous concussions, migraine headaches	6	- Autonomic/ Physiological PTD - Remained symptomatic at last follow-up (40 days post-injury)
7	2 previous concussions	7	- Autonomic/ Physiological PTD - Clinically recovered (140 days post-injury)
8	None	22	- Autonomic/ Physiological PTD - Clinically recovered (211 days post-injury)
9	3 previous concussions, depression	4	- Remains in treatment - Abnormal formal neuropsychological testing (196 days post-injury)
10	2 previous concussions	12	- Autonomic/ Physiological PTD - Remained symptomatic at last follow-up (60 days post-injury)
11	1 previous concussion	8	- Clinically recovered (21 days post-injury)
12	None	27	-Autonomic/ Physiological PTD - Clinically recovered (84 days post-injury)
13	None	25	- Autonomic/ Physiological PTD - Clinically recovered (39 days post-injury)
14	1 previous concussion	32	- Autonomic/ Physiological PTD - Clinically recovered (101 days post-injury)
15	3 previous concussions, migraine headaches	18	- Autonomic/ Physiological PTD - BPPV - Clinically recovered (55 days post-injury)

Table 2: Sum of the clusters area in the left and right hemispheres for each subject for 3 different analysis; 1) Vertices $p_{value} < 0.005$; 2) FDR = 0.05; 3) Monte Carlo clustering.

	Clusters with vertices ($p_{value} < 0.05$) – Method 1		**Clusters after applying FDR (0.05) – Method 2**		**Monte-Carlo Clustering – Method 3**	
	Thinned area (mm^2)	**Thickened area (mm^2)**	**Thinned area (mm^2)**	**Thickened area (mm^2)**	**Thinned area (mm^2)**	**Thickened area (mm^2)**
Healthy Controls						
Subj_1	124.86	225.27	0	0	0	0
Subj_2	325.05	0	0	0	0	0
Subj_3	543.15	12924.48	87	9257	0	31118.15
Subj_4	260.62	246.63	0	0	0	0
Subj_5	0	767.99	0	0	0	0
Subj_6	1144.34	146.3	0	0	2934.13	0
Subj_7	164.42	178.42	0	0	0	0
Subj_8	454.6	45.17	0	0	0	0
Subj_9	219.72	383.38	0	0	0	0
Subj_10	261.64	44.19	0	0	0	0
Subj_11	14.22	610.48	0	0	0	0
Subj_12	0	840.52	63	2344	0	989.28
Subj_13	466.13	5044.75	0	32	0	3179.43
Subj_14	507.29	503.06	0	0	0	00
Subj_15	188.44	473.54	0	0	0	0
Subj_16	192.26	97.22	0	0	0	0
Subj_17	213.08	3.44	0	0	0	0
Subj_18	31.43	186.9	0	0	0	0
Subj_19	82.98	685.76	0	0	0	0
Subj_20	152.66	118.14	0	0	0	0
Subj_21	204.37	682.05	0	0	0	0
Subj_22	517.05	792.74	0	21.43	0	0
Subj_23	308.21	463.56	0	109	0	0
Subj_24	8.12	918.97	0	0	0	0
Subj_25	94.39	381.86	0	0	0	0
Subj_26	62.39	94.43	0	0	0	0
Subj_27	463.2	1361.21	0	0	0	1769.41
Concussed Patients						
Subj_1	163.05	178.44	0	0	0	0
Subj_2	0	1571.89	0	0	0	0
Subj_3	77.47	1377.58	0	0	0	2199.26
Subj_4	422.21	98.74	101	0	0	0
Subj_5	72.78	891.29	0	0	0	0
Subj_6	1185.56	464.14	207	0	1156.6	
Subj_7	102.47	183.12	0	0	0	0
Subj_8	40.41	6671.87	0	2350	0	9024.92
Subj_9	220.9	346.75	53	0	0	0

Subj_10	1911.84	1599.73	1042	321	2748.87	830.43
Subj_11	28.25	92.57	0	0	0	0
Subj_12	121.86	920.04	0	0	0	0
Subj_13	287.71	608.7	0	107	0	0
Subj_14	112.9	2228.62	0	0	0	0
Subj_15	124.76	324.37	0	0	0	0

Figures:

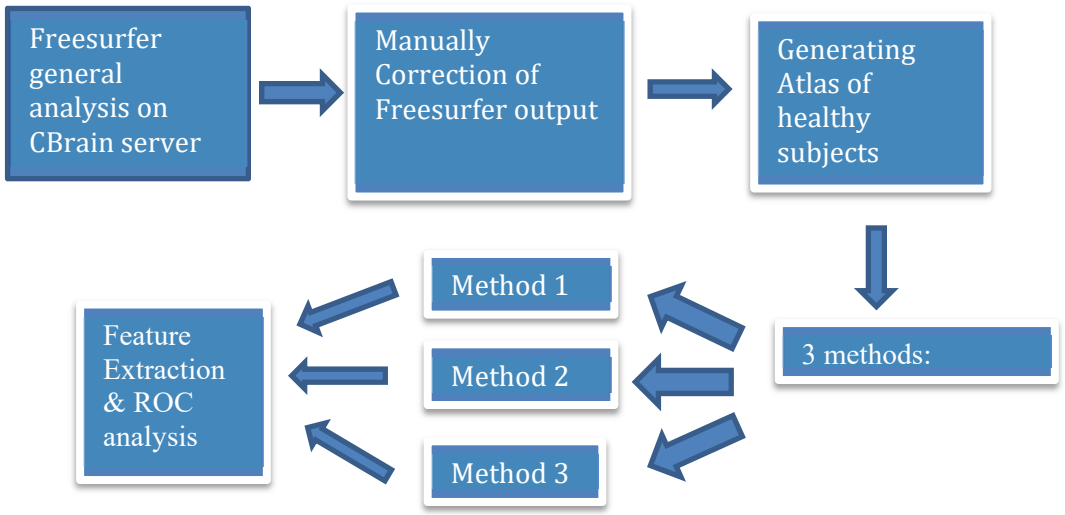

Figure 1: Analysis algorithm flowchart.

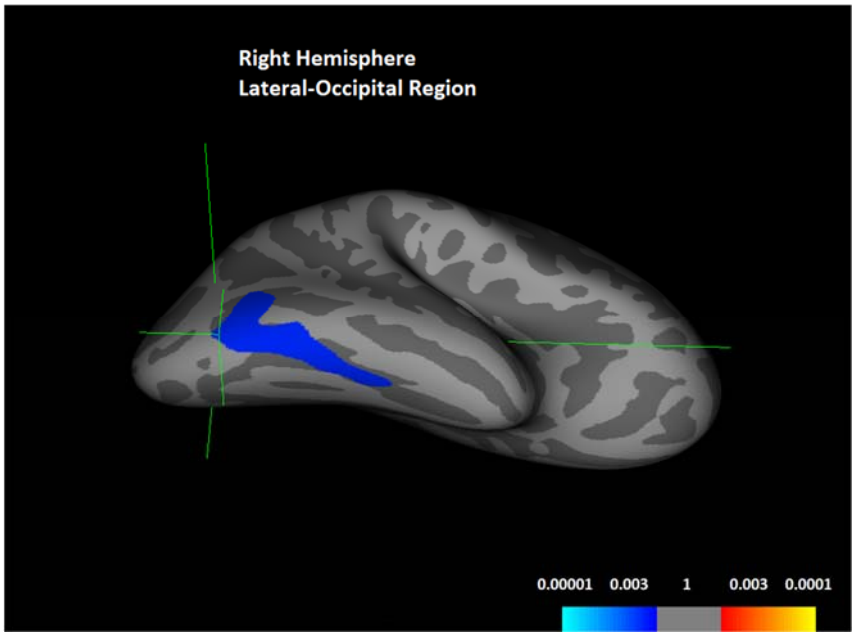

Figure 2-A: Group differences in cortical thickness clusters between SRC patients and normal healthy control subjects. Overall, group comparison between the SRC patients and healthy control subjects showed a cluster of increased cortical thickness (blue hues) located in the right lateral-occipital region. No other group differences were detected. This cluster was statistically significant after applying vertex and Monte-Carlo cluster wise correction of $p_{value} < 0.05$. The color map shows the associated p-values with the color; cold and warm hues indicate increased and decreased thickness, respectively.

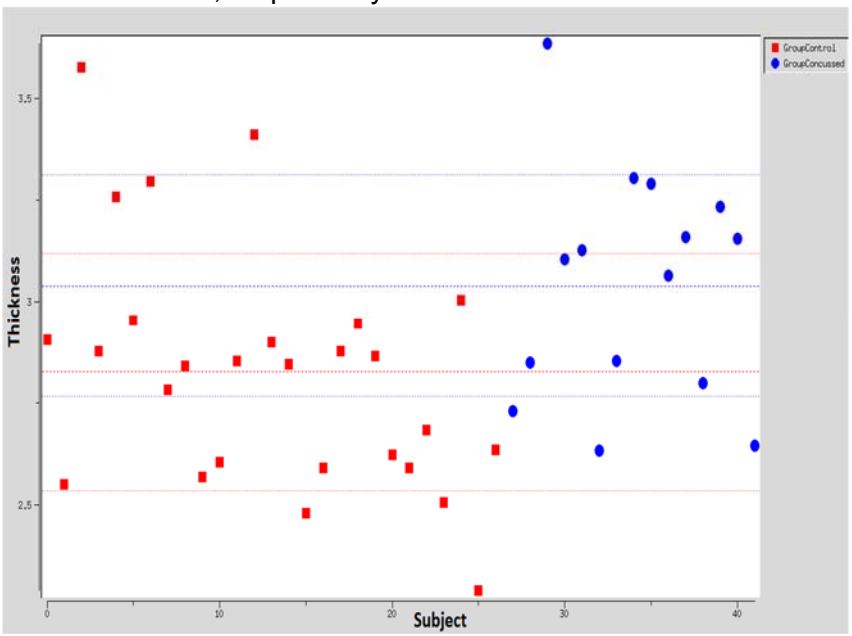

Figure 2-B: Maximum normalized thickness values for each subject in the lateral-occipital region cluster. This plot shows the maximum thickness value for each subject in that cluster in fig. 1-A. Blue circles represent concussed patients and red circle represent healthy controls.

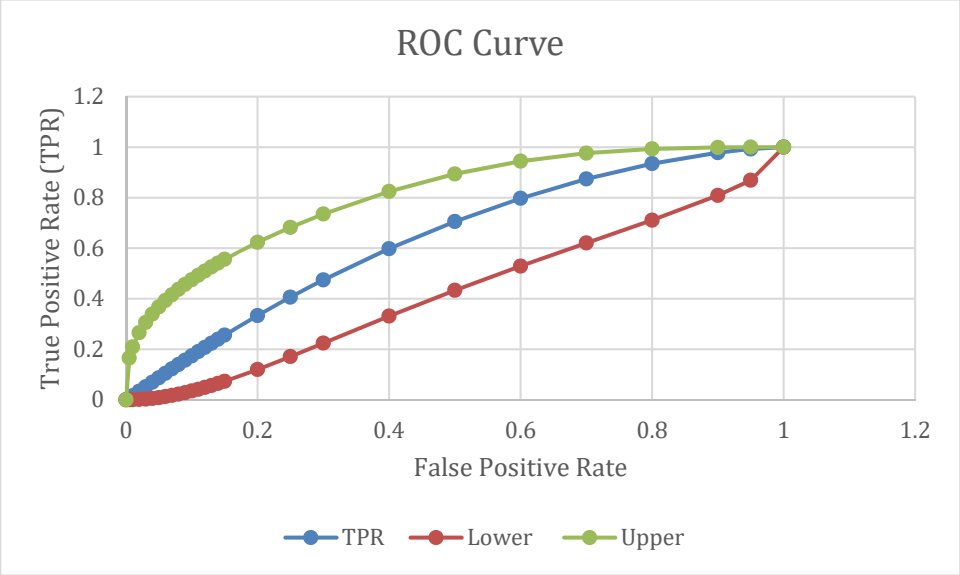

Figure 3. A: Receiver operating characteristic curve analysis of cortical thickness biomarkers using Method 2 (FDR = 0.05); greater than thickness. Blue line show the fitted ROC curve. Red and green lines show 95% confidence interval of the fitted ROC curve.

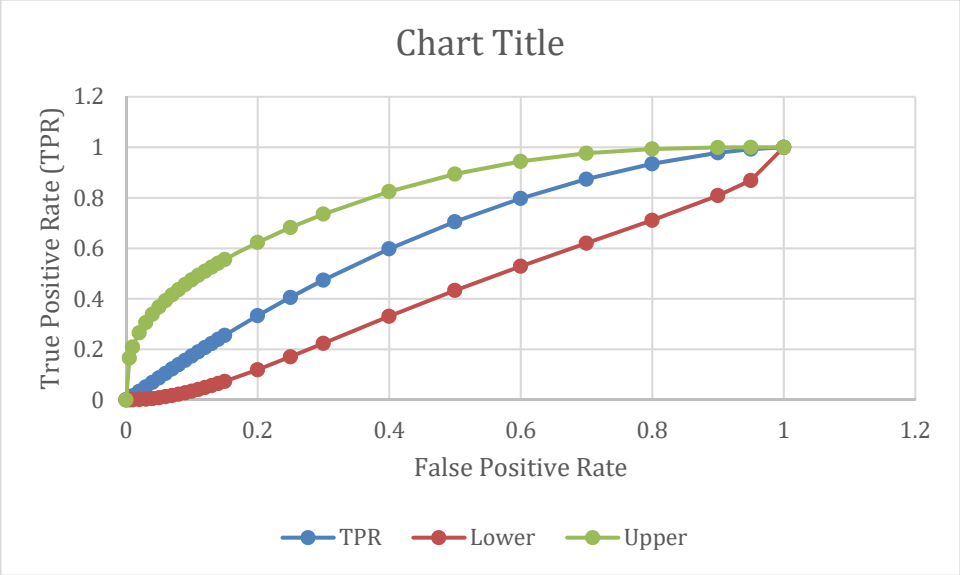

Figure 3. B: Receiver operating characteristic curve analysis of cortical thickness biomarkers using Method 1 (Vertex $p_{value} < 0.005$); reater than thickness. Blue line show the fitted ROC curve. Red and green lines show 95% confidence interval of the fitted ROC curve