NEUROTRAUMA RESEARCH LAB

2019 Accomplishments

*Congratulations to **Margaret Mahan PhD** who successfully defended her dissertation entitled* "Uncovering Disturbed Microstructure, Disrupted Microarchitecture, and Altered Network Topology in Traumatic Brain Injury" *and was awarded her PhD from the department of Bioinformatics and Computational Biology at the University of Minnesota in May of 2019. To see the abstract of dissertation flip to page #5 & 6.*

***Marcela Bravo** successfully presented her Master's capstone project, "An analysis of publication bias in clinical trials for traumatic brain injury" in December 2019.*

***Sam Naden** successfully presented his Master's capstone project, "The impact of cerebral atrophy and anticoagulant use on the development of subdural hemorrhage" in December 2019.*

Published Manuscripts

"Injury Rate in TackleBar Football."
Toninato J, Healy T, Samadani U, Christianson E. - **Orthopedic Journal of Sports Medicine [10/2019]** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6785918/

"Editorial: Lessons from the failure of diffusion tensor imaging to differentiate concussed from non-concussed NFL players."
Mahan MY, Samadani U. **- Journal of Neurosurgery [9/2019]**
https://doi.org/10.3171/2019.5.JNS19892

"Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury."
Darrow D, Balser D, Netoff TI, Krassioukov A, Phillips A, Parr A, Samadani U - **Journal of Neurotrauma [8/2019]** https://www.liebertpub.com/doi/10.1089/neu.2018.6006

"Discrepancy Between Internal and External Intracranial Pressure Transducers: Quantification of an Old Source of Error in EVDs?"
Darrow D, Lee-Norris A, Larson A, Samadani U, Netoff TI **- World Neurosurgery [8/2019]**
https://doi.org/10.1016/j.wneu.2019.07.213

"Glial Fibrillary Acidic Protein (GFAP) Outperforms S100 Calcium-Binding Protein B (S100B) and Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) as Predictor for Positive Computed Tomography of the Head in Trauma Subjects."

Mahan MY, Thorpe M, Ahmadi A, Abdallah T, Casey H, Sturtevant D, Judge-Yoakam S, Hoover C, Rafter D, Miner J, Richardson C, Samadani U- **World Neurosurgery [5/2019]** https://doi.org/10.1016/j.wneu.2019.04.170

"23.4% Hypertonic Saline and Intracranial Pressure in Severe Traumatic Brain Injury Among Children: A 10-Year Retrospective Analysis."

Wu AG, Samadani U, Slusher TM, Zhang L, Kiragu AW - **Pediatric Critical Care Medicine [5/2019]** https://insights.ovid.com/pubmed?pmid=30664588

"*Eye Tracking as a Biomarker for Concussion in Children.*"

Bin Zahid A, Hubbard ME, Lockyer J, Podolak O, Dammavalam VM, Grady M, Nance M, Scheiman M, Samadani U, Master CL - **Clinical Journal of Sport Medicine [9/2018]** https://insights.ovid.com/crossref?an=00042752-900000000-99145

"Traumatic brain injury reduction in athletes by neck strengthening (TRAIN)."

Toninato J, Casey H, Uppal M, Abdallah T, Bergman T, Eckner J, Samadani U - **Contemporary Clinical Trials Communication [6/2018]** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6037875/

"High prevalence of prior contact sports play and concussion among orthopedic and neurosurgical department chairs."

Sone JY, Courtney-Kay Lamb S, Techar K, Dammavalam V, Uppal M, Williams C, Bergman T, Tupper D, Ort P, Samadani U. - **Journal of Neurosurgery Pediatrics [7/2018]** https://doi.org/10.3171/2018.1.PEDS17640

"Increase in brain atrophy after subdural hematoma to rates greater than associated with dementia."

Bin Zahid A, Balser D, Thomas R, Mahan MY, Hubbard ME, Samadani U. **- Journal of Neurosurgery [12/2018]** https://doi.org/10.3171/2017.8.JNS17477

"Oxygen Therapy in Suspected Acute Myocardial Infarction."

Samadani U, Affana CK - **New England Journal of Medicine [1/2018]** https://doi.org/10.1056/NEJMc1714937

"Hyperbaric Oxygen Therapy in the Treatment of Acute Severe Traumatic Brain Injury: A Systematic Review."

Daly S, Thorpe M, Rockswold S, Hubbard M, Bergman T, Samadani U, Rockswold G **- Journal of Neurotrauma [2/2018]** https://doi.org/10.1089/neu.2017.5225

"Elevated intracranial pressure and reversible eye-tracking changes detected while viewing a film clip."

Kolecki R, Dammavalam V, Bin Zahid A, Hubbard M, Choudhry O, Reyes M, Han B, Wang T, Papas PV, Adem A, North E, Gilbertson DT, Kondziolka D, Huang JH, Huang PP, Samadani U. **- Journal of Neurosurgery [3/2018]** https://doi.org/10.3171/2016.12.JNS161265

"Assessment of acute head injury in an emergency department population using sport concussion assessment tool - 3rd edition."

Bin Zahid A, Hubbard ME, Dammavalam VM, Balser DY, Pierre G, Kim A, Kolecki R, Mehmood T, Wall SP, Frangos SG, Huang PP, Tupper DE, Barr W, Samadani U.

- Applied Neuropsychology Adult [3/2018] https://doi.org/10.1080/23279095.2016.1248765

Poster Presentations

"Potential Litigation Risks Associated with Adhering to Current Guidelines for Acute Spinal Cord Decompression."

Hurrelbrink, D., Vasedv, R., Rafter, D., Johnson, B., Samadani, U., Shen, F.

Congress of Neurological Surgeons 2019, Oct 19-23, San Francisco, CA.

"Decreased failure rates with 3D-printed calcium phosphate cranioplasty grafts when compared to autologous and traditional synthetic models."

Koller, M., Rafter, D., Samadani, U.

American Association of Neurological Surgeons 2019, 2018 April 15; San Diego, CA.

"Psychological Effects of Traumatic Brain Injury Measure after Objective, Diagnostic Assessment of Physiologic Disruption at Multiple Time Points."

Venkatesh, S., Thorpe, M., Samadani, U.

13th World Congress on Brain Injury 2019, March 13-16, Toronto Canada

"Injury Rates in Football and Football Alternatives."

Toninato, J., Samadani, U.

13th World Congress on Brain Injury 2019, March 13-16, Toronto Canada

"Systematic Review of Genetic Risk Factors for Traumatic Brain Injury."

Uppal, M., Hurrelbrink, D., Suek, T., Ahmadi, A., Edpuganti, R., Rafter, D., Samadani, U.

NeuroTrauma 2019, June 29 - July 3, Pittsburgh, PA

"Positive association between fractional anisotropy and memory deficits in mild acute traumatic brain injury patients."

Smith, C., Abdallah, T., Casey, H., Mahan, M., Samadani, U.

NeuroTrauma 2019, June 29 - July 3, Pittsburgh, PA

"Orthopedic and Neurosurgical Department Chairs Have a High Incidence of Prior Contact Sports Play Suggesting Complex Benefit from Sports."

Sone, J., Lamb, CK., Techar, K., Dammavalum, V., Uppal, M., Williams, C., Tupper, D., Ort, P., Samadani, U.

National Conference on Undergraduate Research 2019, April 11-19, Kennesaw, GA

"Improvement of cerebral autoregulation and autonomic cardiac control in humans with spinal cord injury: after epidural electrical stimulation."

Saleem, S., Darrow, D., Netoff, T.I., Tzeng, Y, Samadani, U., Krassioukov, A.V., Phillips, A.A.

Experimental Biology, 2019, April 6-9, Orlando, FL.

"Thoracoabdominal Crush Injury Causes Increased Intracranial Pressure Resulting in Traumatic Brain Injury Detectable with Eye Tracking Technology and Blood Based Biomarkers."
Rafter, D., Thorpe, M., Jaris, D. Mahan, M., Chettupally, T., Prasad, K., Samadani, U.
Congress of Neurological Surgeons 2018, Oct 6-10, Houston, TX.

"Differences in diffusion properties of white matter tracts in patients with acute traumatic brain injury."
Abdallah, T., Mahan, MY, Casey, H., Oswood, M., Truwit, C., Richardson, C., Samadani, U.
International Neurotrauma Society, Aug 10-13, 2018 Toronto, Canada.

"The Physiological Impact of ICP and CPP on Cranial Nerve Function as Demonstrated with Eye Tracking Technology."
Khan, A., Sturtevant, D., Edgupanti, R., Venkatesh, S., Thorpe, M., Ahmadi, A., Rafter, D. Samadani, U.
International Neurotrauma Society, Aug 10-13, 2018. Toronto, Canada.

"Vagus Nerve Stimulation to Treat Moderate Brain Injury."
Khan, A., Hubbard, M., Kroll, R., Bergman, T., Samadani, U.
International Neurotrauma Society, Aug 10-13, 2018. Toronto, Canada.

"An Improved Metric for Detecting Cerebrovascular Autoregulation: Performance and Comparison of the Granger Ratio against PRx."
Darrow, D., Lee-Norris, L., Samadani, U., Netoff, T.
International Neurotrauma Society, Aug 10-13, 2018. Toronto, Canada.

"Comparative Analysis of Continuous and Intermittent Intraventricular Pressure Monitoring."
Lee-Norris, A., Samadani, U., Netoff, T., Darrow, D.
International Neurotrauma Society, Aug 10-13, 2018. Toronto, Canada.

"Characterizing Spatial Attributes of Structural Networks in Acute Traumatic Brain Injury."
Mahan, M., Venkatesh, S., Thorpe, M., Abdallah, T., Casey, H., Ahmadi, A., Oswood, M., Truwit, C., Richardson, C., Samadani, U
BICB Bioinformatics Symposium UMN, Aug 17, 2018, Minneapolis, Minnesota.

"Validation of Natural Language Processing Algorithm for the Analysis of CT Reports."
Toninato, J., Mahan, M., Samadani, U.
BICB Bioinformatics Symposium UMN, Aug 17, 2018, Minneapolis, Minnesota.

"Describing Diffusion Properties in Mild to Moderate Traumatic Brain Injury Using Voxelwise Tract-Based Spatial Statistics."
Smith, C., Mahan, M., Venkatesh, S., Thorpe, M., Abdallah, T., Casey, H., Ahmadi, A., Oswood, M., Truwit, C., Richardson, C., Samadani, U.
BICB Bioinformatics Symposium UMN, Aug 17, 2018, Minneapolis, Minnesota.

"Characterizing Spatial Attributes of Structural Networks in Acute Traumatic Brain Injury."
Mahan, M., Venkatesh, S., Thorpe, M., Abdallah, T., Casey, H., Ahmadi, A., Oswood, M., Truwit, C., Richardson, C., Samadani, U.
27th Annual Computational Neuroscience Meeting CNS2018, July 13-18-2018. Seattle, Washington.

"Immediate Restoration of Voluntary Movement with Epidural Spinal Cord Stimulation in Two Patients with Paraplegia."
Darrow, D., Balser, D., Parr, A., Samadani, U.
International Neurotrauma Society, American Association of Neurological Surgeons 2018, 2018 April 30; New Orleans, LA.

"Automated Eye Tracking For Detection of Blast Brain Injury After a Natural Gas Explosion."
Bin Zahid, A., Thorpe, M., Smith, C., Hoover, C., Warren, E., Edpuganti, R., Venkatesh, S., Sturtevant, D., Ahmadi, A., Newgaard, O., Balser, D.Y., Kroll, R., Samadani, U.
American Association of Neurological Surgeons 2018, 2018 April 30; New Orleans, LA.

"Prospective Treatment of Traumatic Brain Injuries by Vagus Nerve Stimulation."
Casey, H and Abdallah, T., Samadani, U.
Minnesota Brain Injury Alliance, 2018, April 12, St. Paul, MN.

"Brain Injury Caused by Body Trauma: An Unrecognized Impact."
Chettupally, T., Prasad, K., Sindhu, G., Samadani, U.
Minnesota Brain Injury Alliance, 2018, April 12, St. Paul, MN.

Uncovering Disturbed Microstructure, Disrupted Microarchitecture, and Altered Network Topology in Traumatic Brain Injury

Mahan, Margaret Yvonne. University of Minnesota, ProQuest Dissertations Publishing, 2019. 13880563.

Abstract

Background. Traumatic Brain Injury (TBI) is a debilitating condition, with long-term sequelae, affecting a considerable portion of the population. Typically, TBI transpires from a direct impact to the head as well as from the onset of acceleration and deceleration forces following abrupt changes in head position. Both localized and diffuse damage generated after injury are subject to a cascade of events altering normal biological function, culminating in heterogeneous pathophysiology. Considerable attempts to tackle this heterogeneity have been made. However, this has lead to numerous TBI classifications primarily rooted in subjective measurements, such as the Glasgow Coma Scale score, loss of consciousness duration, and post-traumatic amnesia, each known to be poor indicators of TBI. Physical measures, such as clinical findings from Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans, are indispensable for assessing TBI, but they lack reliability and specificity in diagnosis and prognosis of TBI. Part of this deficiency arises from the reliance on subjective interpretation of these scans. A more significant issue arises as a result of inadequate methods that are unable to capture the extent and heterogeneity of damage.

Objective. To extensively capture the heterogeneous pathophysiology in TBI using objective and physical measurements to advance candidate neuroimaging biomarkers for TBI, which will aid in overcoming the critical barriers that currently exist in diagnosis and prognosis of TBI.

Contributions. For my first contribution, I developed and validated an algorithm that incorporates natural language processing methods to automate the extraction of TBI clinical findings from head CT scan radiology reports. The output of my algorithm is a structured summary of twenty-seven standardized TBI clinical findings with their respective status. My algorithm was validated using physician annotators as the gold standard and was found to be equivalent, sensitive, specific, and fast.

For my second contribution, I examined the shape of the diffusion tensor, explored microstructural disturbances using voxelwise tract-based spatial statistics, quantified the location of these disturbances, and established an ordered ranking of diffusion measurements using machine learning methods. I discovered widespread changes in diffusion measurements, often affecting long-range connections, indicating disturbances in microstructural integrity after TBI. Lastly, I reported that structural diffusion measurements were better able to differentiate TBI from control groups.

For my third contribution, I evaluated the construction of TBI structural networks using spectral graph theory and statistical network analysis to identify the most indicative diffusion measurements representing disrupted microarchitecture. I set out to uncover distinctions between diffusion measurements used in the construction of TBI structural networks, locate network disruptions, and discover preliminary network topologies. Using vastly different methodologies from my second contribution, I again found that structural diffusion measurements were better able to differentiate TBI from control groups. In addition, I discovered disrupted connections were primarily located in the parietal and temporal lobes, with geometric diffusion measurements more prevalent in these disruptions. These results indicate a dual representation of microarchitectural disruption in TBI structural networks.

For my fourth contribution, I assessed TBI structural and functional networks using graph theory. I examined five measures of network topology: construction, integration, segregation, influence, and resilience. I discovered altered network integration and network influence in TBI structural networks, in addition to altered network resilience in TBI structural and functional networks, with no alterations to network segregation. My results indicate altered information exchange capacity, participation capacity, and flexibility of the TBI brain network.

Discussion. The nearly universal acquisition of head CT scans following trauma necessitates the inclusion of their findings in discerning injuries. These head CT scans are often accompanied by a radiology report containing expert-level interpretation in unstructured narrative text format, which makes retrieving information challenging. The outcome of my first contribution addresses this and can be used to partition patients into meaningful groups based on physical measurements.

A notable portion of TBI patients do not have clinical findings on hospital admission head CT scans yet display pathologies on MRI consistent with microstructural damage. Efforts to capture this damage have been extensive. However, there are discrepancies in identifying the location of microstructural damage and the direction of changes in measurements quantifying it. Part of this is due to an incomplete assessment of the diffusion tensor shape. The outcome of my second contribution addresses this deficiency, provides an assessment of underlying pathophysiological mechanisms associated with microstructural disturbances, and postulates candidate predictors of microstructural damage in TBI.

The construction and study of connectomes, a field known as connectomics, provides a theoretical framework for understanding the brain as a complex network. Since microstructural disturbances in TBI lead to disruptions to the structural network, quantifying these disruptions are crucial for describing TBI pathophysiology, yet this quantification has not yet been previously tackled. The outcome of my third contribution addresses this and establishes more suitable methods for TBI structural network construction, which may aid in the precise identification of vulnerable brain regions.

Quantification of diffuse injury over the entire structural network is required to appreciate network dysfunction. Naturally, this can be addressed by assessing alterations to connectome topology. The outcome of my fourth contribution addresses this and establishes the impact of alterations to network topology in TBI, which may lead to improvements in patient monitoring by assessing the progression of these topological alterations towards standardized levels.

Impact. In summary, my dissertation is uniquely positioned to create valuable contributions towards identifying neuroimaging biomarkers that will catalyze research on TBI. I expect my contributions will lead to a significant shift in current TBI research by adopting novel network analysis and machine learning methods that go beyond conventional approaches and ultimately improve the lives of the TBI-afflicted.

Graduate Student Projects

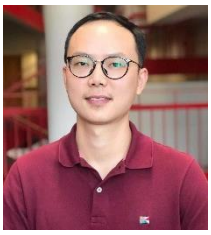
Maggie Mahan, PhD

- Maggie has been with the lab for over three years and has focused her dissertation work on classifying the nature of mild traumatic brain injury using advanced MRI imaging. She was awarded her PhD from the University of Minnesota in May 2019. To view the abstract for her dissertation you can visit

Marcela Bravo, MS Candidate

- Marcella is a student from the Department of Bioinformatics and Computational Biology at the University of Minnesota who is completing her thesis project with our lab. Her work is focused on whether or not clinical studies focusing on treating traumatic brain injuries are publishing their results, and whether or not there characteristics differ between published and unpublished trials.

Zhuliu Li, PhD Candidate



- Zhuliu is a student from the Department of Computer Science at the University of Minnesota and is co-mentored by Dr. Rui Kuang. His work is focused on classifying the nature of brain injury utilizing multiple objective markers including cerebrospinal fluid around the brainstem on CT, blood based biomarkers, and eye-tracking data.

Sam Naden, MS Candidate

- Sam is also a student from the Department of Computer Science at the University of Minnesota that recently joined our lab. He will be working on a project to develop an algorithm that can predict the risk of developing a brain bleed based on automated analysis of cerebral atrophy and blood thinner use in the Veteran population. Sam is also co-mentored by Dr. Rui Kuang.

Emily Kilen, MD Candidate

- Emily is a third year medical student at the University of Minnesota who spent her summer with our lab developing an automated algorithm to differentiate cerebrospinal fluid present within anatomical landmarks and produce a volumetric output.

Michael Koller, MD Candidate

- Michael is also a third year medical student at the University of Minnesota who spent a summer in our lab working on a project which compared outcomes between different types of cranioplasty material. He presented his work at American Association of Neurological Surgeons earlier this year and has a manuscript submitted.

Brett Sterk, MD Candidate

- Brett is a second year medical student at the University of Minnesota who spent this past summer in our lab working on a project focused on predicting those brain injury subjects that will progress to brain death compared to those that will recover. He is currently finalizing a manuscript for submission.

Mark Gormley, MD Candidate

- Mark is a second year medical student at the University of Minnesota who is currently working on a project with our lab that is focused on evaluating the capacity of US trauma centers to provide timely surgery for acute spinal cord injury patients.

Ranveer Vasdev, MD Candidate

- Ranveer is also a second year medical student at the University of Minnesota. With our lab, he has been working on a project highlighting the legal implications of delayed surgical treatment for acute spinal cord injuries. He is currently finalizing a manuscript for submission.

<u>Grant Funding</u>

Minnesota State - Office of Higher Education (OHE)

Veterans Merit Award

Abbott Diagnostic Labs

<u>Incredible Generosity</u>

Tim and Helen Healy

James and Patti Anderson

Steve Barron, Family, and Friends
