Homeland Defense & Security
Information Analysis Center

Investigating Ultrastructural Mechanisms of TBI Using X-ray Diffraction

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Ashley Eidsmore, CCDC ARL
Dr. Jason McDonald, CCDC ARL

May 29, 2019

Introduction

HDIAC & Today's Topic

HDIAC Overview

What is the Homeland Defense & Security Information Analysis Center (HDIAC)?

One of three Department of Defense Information Analysis Centers

Responsible for acquiring, analyzing, and disseminating relevant scientific and technical information, in each of its eight focus areas, in support of the DoD and U.S. government R&D activities

HDIAC's Mission

Our mission is to be the go-to R&D/S&T and RDT&E leader within the homeland defense and security (HDS) community, by providing timely and relevant information, superior technical solutions, and quality products to the DoD and HDS Communities of Interest/Communities of Practice.

HDIAC Overview

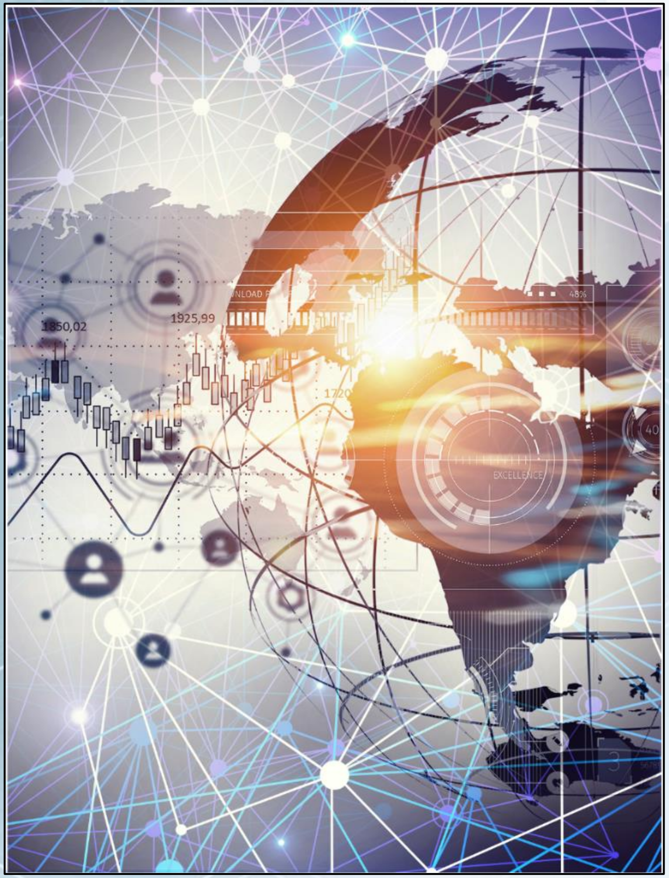
HDIAC Subject Matter Expert (SME) Network

HDIAC SMEs are experts in their field(s), and, typically, have been published in technical journals and publications.

SMEs are involved in a variety of HDIAC activities

- Authoring HDIAC Journal articles
- Answering HDIAC Technical Inquiries
- Engaging in active discussions in the HDIAC community
- Assisting with Core Analysis Tasks
- Presenting webinars

If you are interested in applying to become a SME, please visit HDIAC.org or email info@hdiac.org.



Presenters

Joseph Orgel is a multi-disciplinarian, scientist, and an educator. He is currently a tenured professor at the Illinois Institute of Technology, with past and present appointments in Biology, Physics, Biomedical Engineering, and Applied Health Sciences. Orgel leads investigations of brain pathological diseases, such as Alzheimer's and TBI, in collaboration with the U.S. Army Combat Capabilities Development Command's Army Research Laboratory (ARL). He also investigates connective tissue conditions including heart disease and arthritis at the National Institutes of Health Biotechnology Research Resource, BioCAT, as Associate Director. An awardee of the National Science Foundation's CAREER award, he has been a Section Editor of the Public Library of Science Journal, PLoS ONE, since 2008. He is the past-Chair of the Faculty Council of Illinois Tech and currently serves as the deputy vice provost for strategic initiatives and student success.

Presenters

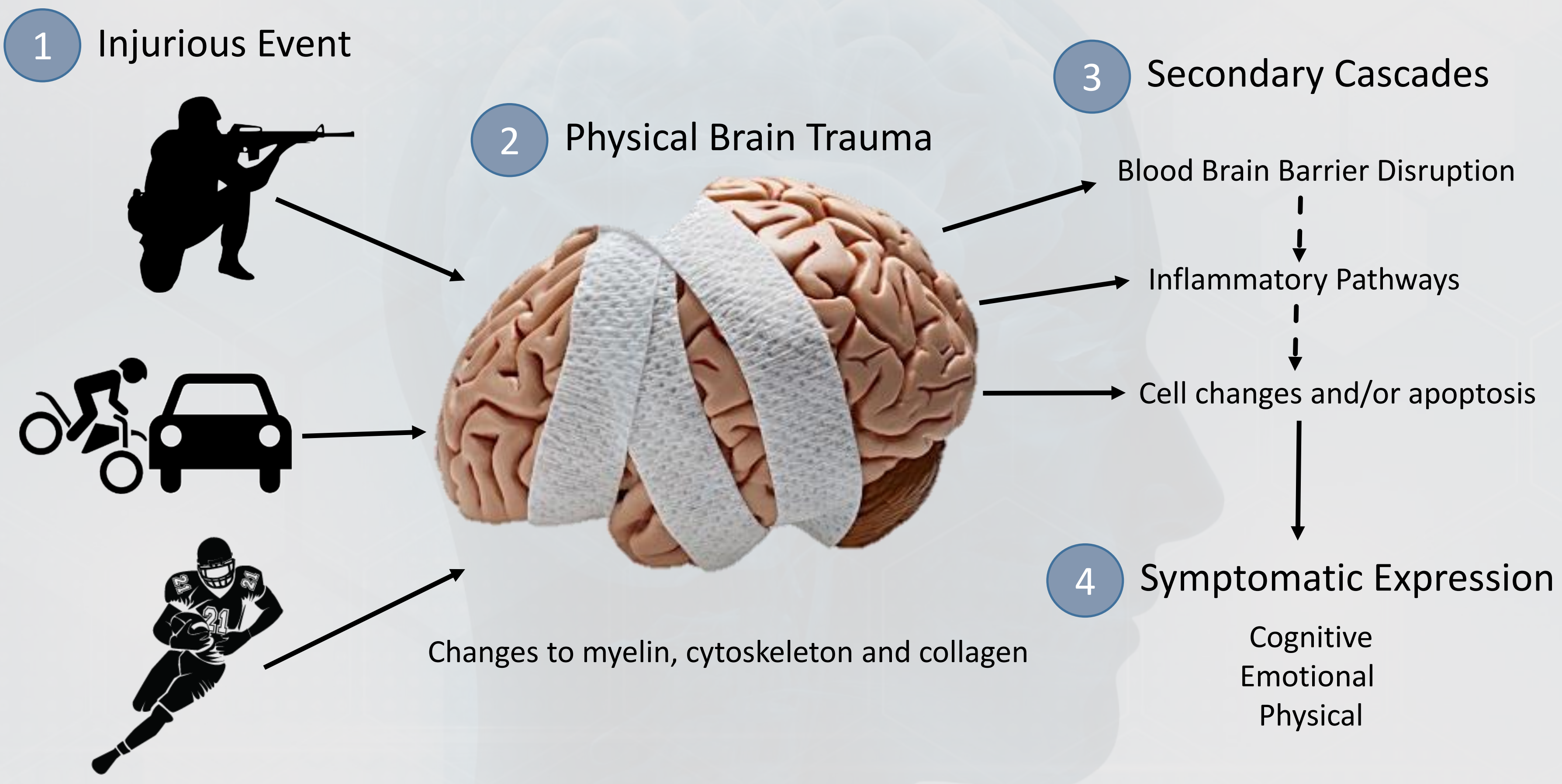
Ashley Eidsmore is an electrical engineer and brain injury researcher at the U.S. Army Combat Capabilities Development Command's Army Research Laboratory (ARL) and has over 10 years of experience working with the Department of Defense on brain injury-centric technologies. She holds both a Bachelor’s and Master’s degree in electrical engineering from Purdue University with a focus in biomedical imaging and sensing. Her thesis work focused on the development of a theory for the establishment and maintenance of neural communication within plastic brain regions based on finite-state machine ad-hoc network routing and stability convergence. The application of her theory included using electric-field generation-based reparative methods for restoring neural synchrony and reversing the effects of blast injury. Her current interests involve investigating and systematically representing how injurious states evolve at the ultrastructural level in direct response to head trauma and the manner by which these alterations evoke negative feedback cycles, which lead to a pathological response and presentation on the cellular and/or macroscopic level.

Presenters

Jason McDonald received a B.S. in physics from Oregon State University in 1991, and a Ph.D. in physics from Iowa State University in 1997. He was a postdoctoral scientist at The Applied Superconductivity Center at The University of Wisconsin in Madison, and then worked at Vector Fields Inc. from 1998 to 2004 on applications and code development of finite element software for electromagnetics. From 2004 to 2007 he worked at SAIC in Austin, Texas, in support of a Department of Defense EM Armor program. From 2007 to 2012 he was a member of the research staff at the Institute for Advanced Technology at The University of Texas, Austin, and worked on computational problems related to the Army and Navy railgun programs. He joined U.S. Army Combat Capabilities Development Command's Army Research Laboratory (ARL) in 2012, and has been involved with computational work, primarily finite element analysis in problems ranging from ballistic response of ceramics to cavitation in soft materials.

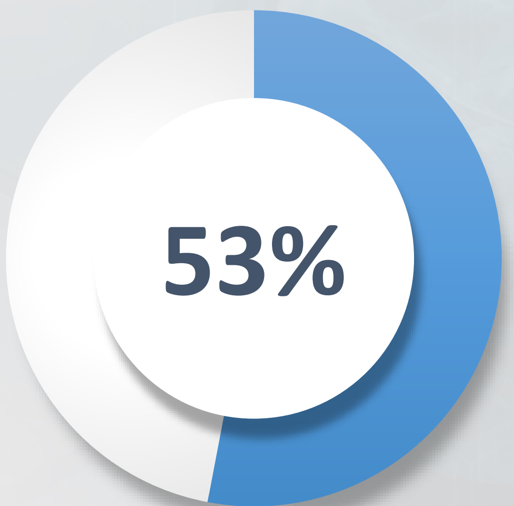
Overview

Traumatic Brain Injury



DoD Perspective - Brain Injury

Causes of Early Death during Iraq and Afganistan (2001-2011)[1]



BRAIN INJURIES

Brain Injury Severities (2017) [2]

MILD BRAIN INJURIES

1. Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., . . . Rasmussen, T. E. (2012). Death on the battlefield (2001–2011): implications for the future of combat casualty care. *Journal of Trauma and Acute Care Surgery, 73*(6), S431-S437.
2. Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSB)

Army Examination of Brain Injuries

Outcome examples from brain injury grouped by respective risks.

Immediate Lethality

- Apnea
- Critical Tissue Ablation

Incapacitation

- Loss of consciousness
- Vestibular Motor Damage

Secondary Lethality

- Coagulopathy
- Sepsis
- Acute Respiratory Distress Syndrome (ARDS)

Long-Term Outcomes

- Myelinopathy
- CTE
- Protein Disorders

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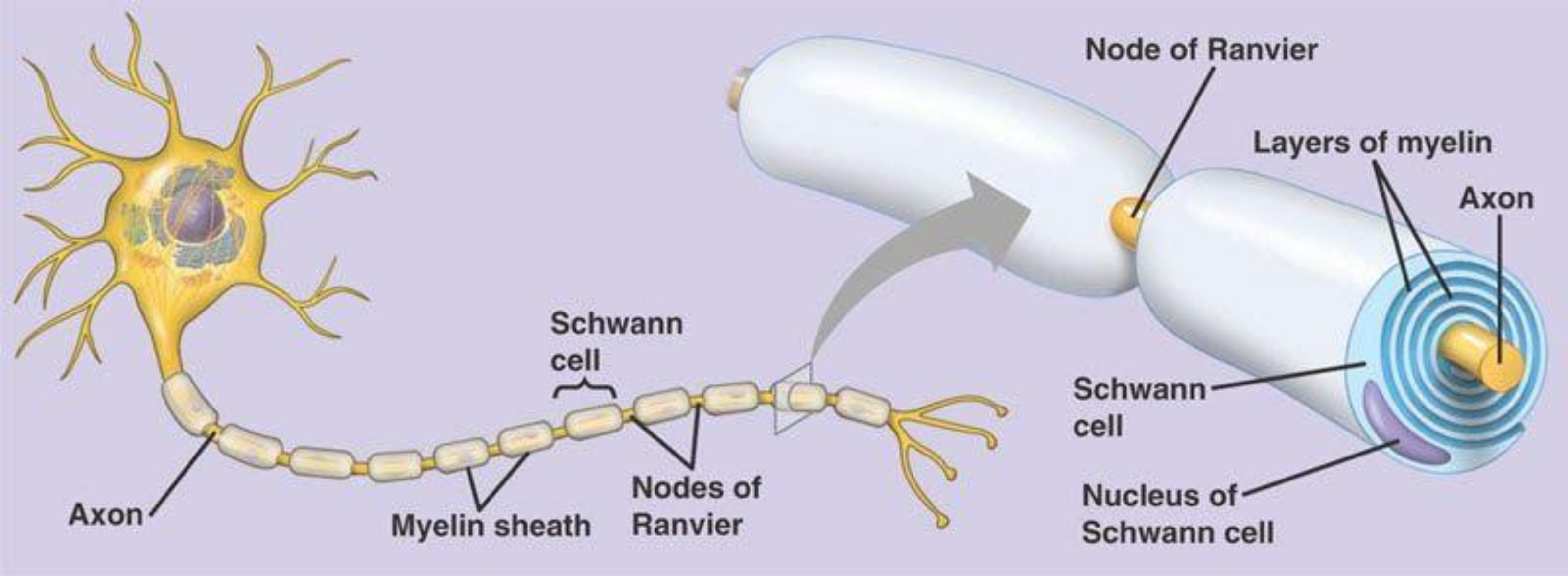
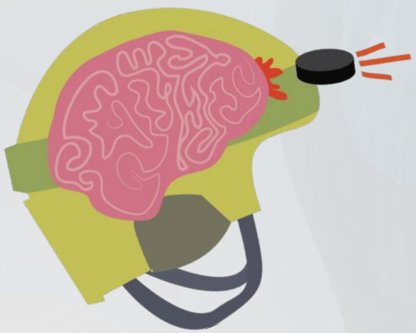
Myelinopathy

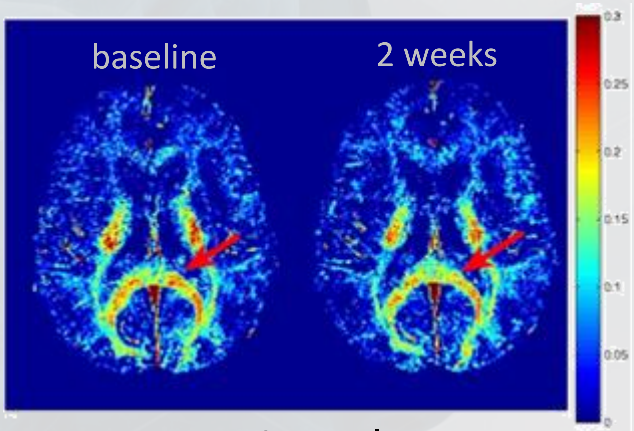
: Degeneration, improper structuring, or loosening of the myelin sheath in neurons.



Myelinopathy

Motivation: Individuals who have **widespread myelin damage**, mostly in the form of "loosening" of myelin, **perform much lower on cognition tests** and are more likely to sustain chronic concussive outcome in response to injury[1]





t=0 — **Injurious Event Occurs**

?

t=2 weeks — **Myelin loosening seen in individuals with decreased cognitive test performance**

1. Wright, Alexander D., et al. "Myelin water fraction is transiently reduced after a single mild traumatic brain injury–A prospective cohort study in collegiate hockey players." *PLoS One* 11.2 (2016): e0150215.

Our Team

Joseph Orgel (PhD)
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Illinois Institute of Technology

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Illinois Institute of Technology

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DePaul University

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Army Research Laboratory (CCDC ARL)

Jason McDonald (PhD)
Physicist
Combat Capabilities Development Command's
Army Research Laboratory (CCDC ARL)

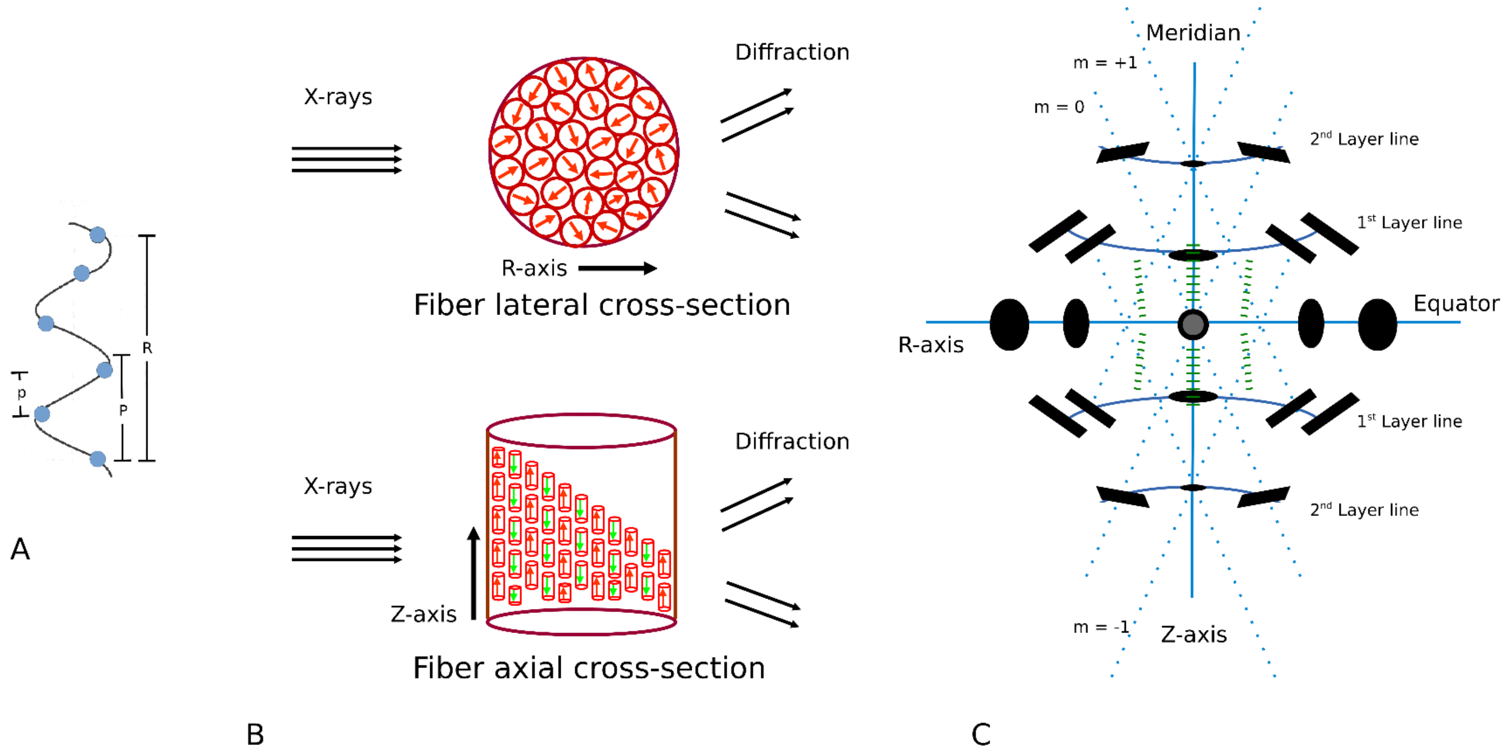
Argonne National Laboratory

The Biophysics Collaborative Access Team (BioCAT)

- State-of-the-art x-ray facilities for the study of the structure and dynamics of biological systems
- Characterization of <nm, native structure and arrangement of biomaterials
- Development of novel imaging techniques and technologies

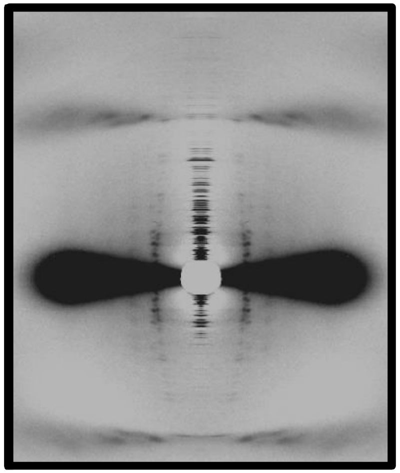
The APS is a Department of Energy User Facility located at Argonne National Laboratory and funded by the Office of Science (Basic Energy Sciences).

Past use of X-Ray Diffraction (XRD)

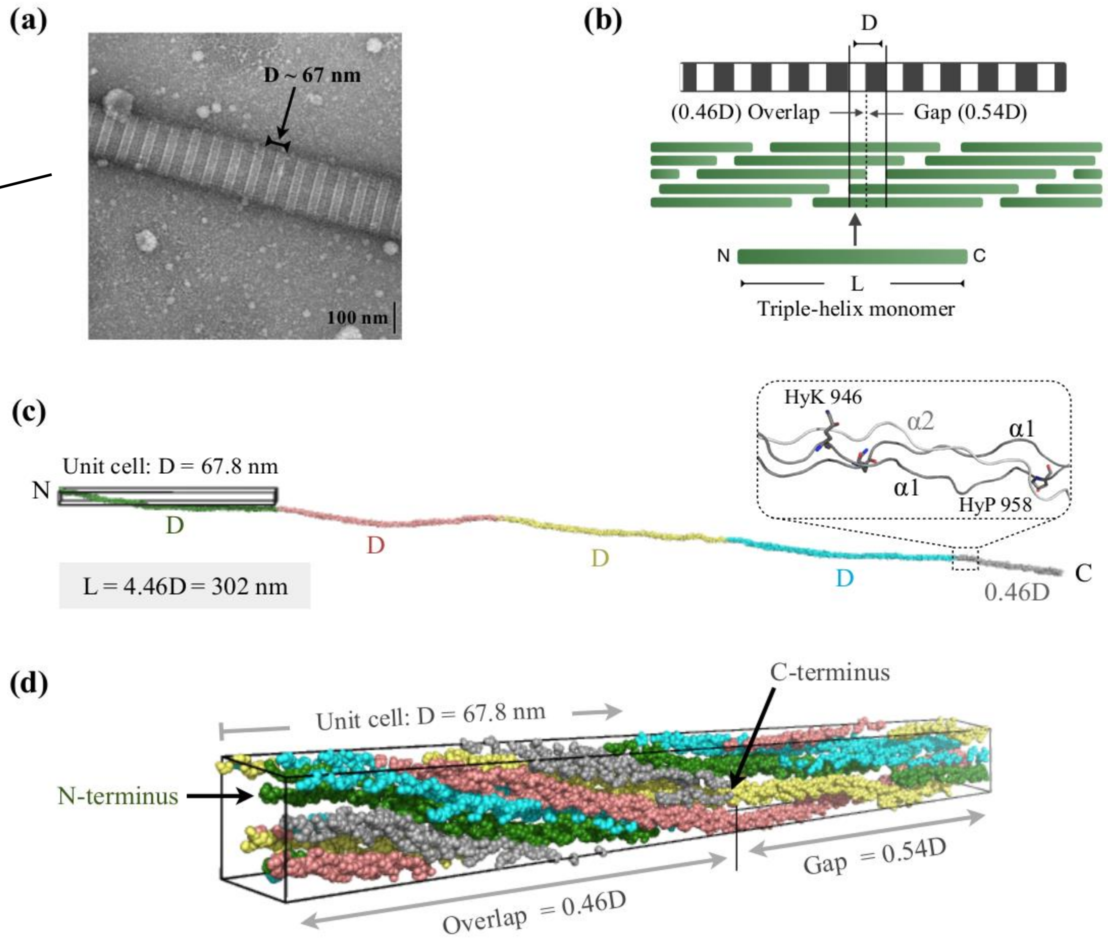


Orgel, Joseph PRO, and Thomas C. Irving. "Advances in Fiber Diffraction of Macromolecular Assembles." Encyclopedia of Analytical Chemistry (2014).

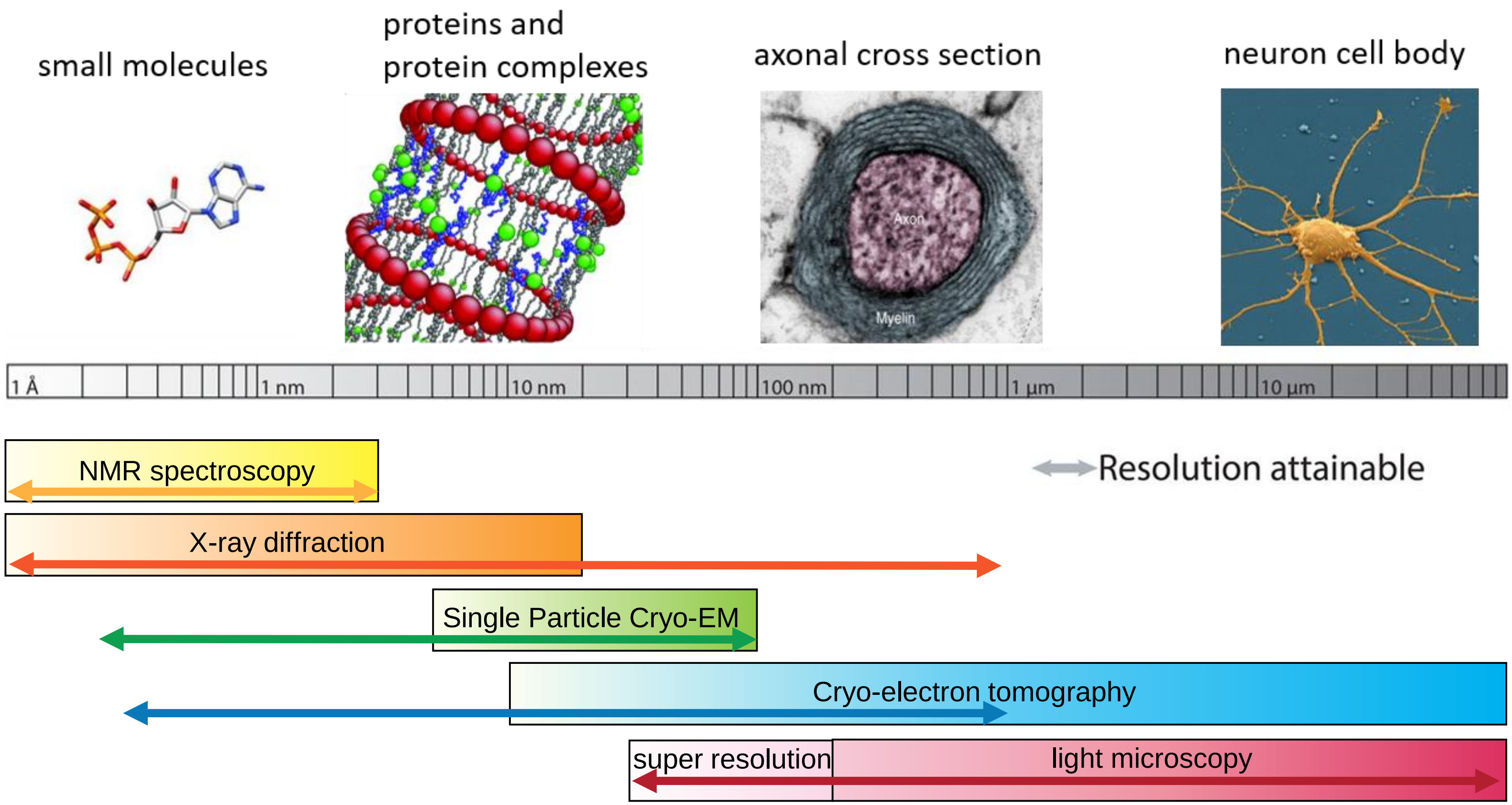
XRD and the Study of Biological Materials



Molecular data

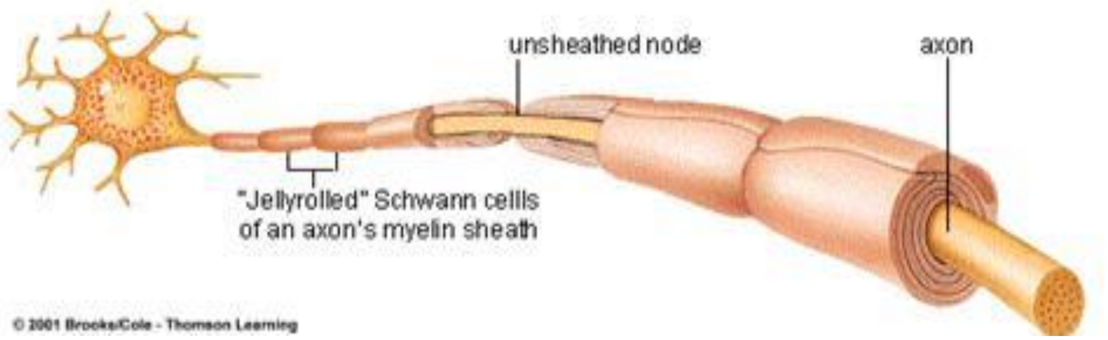


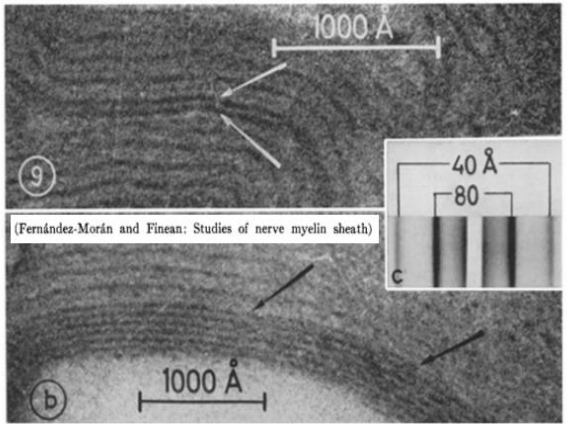
Advantage of using XRD over other imaging methods

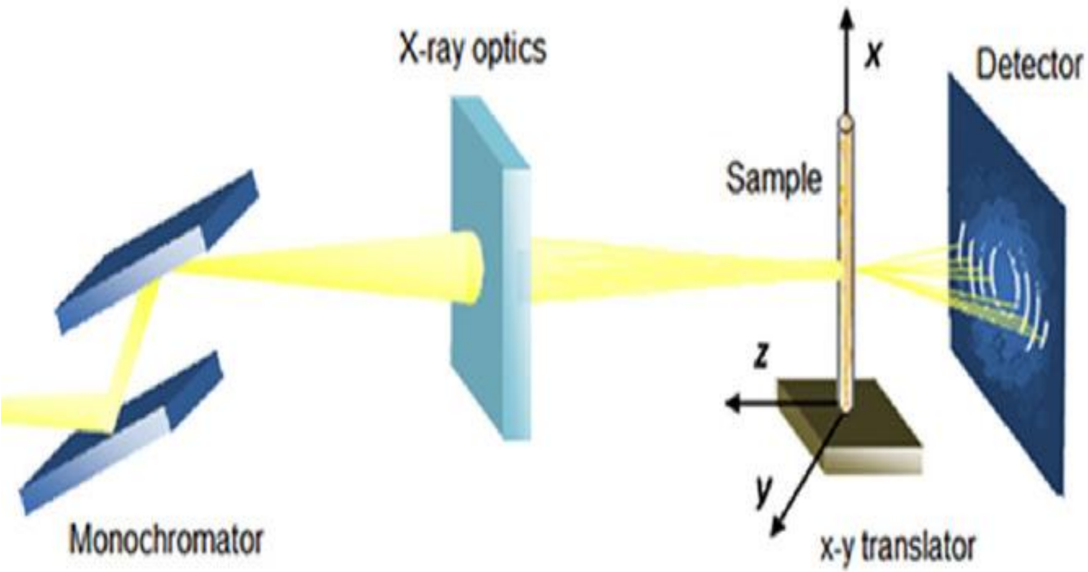


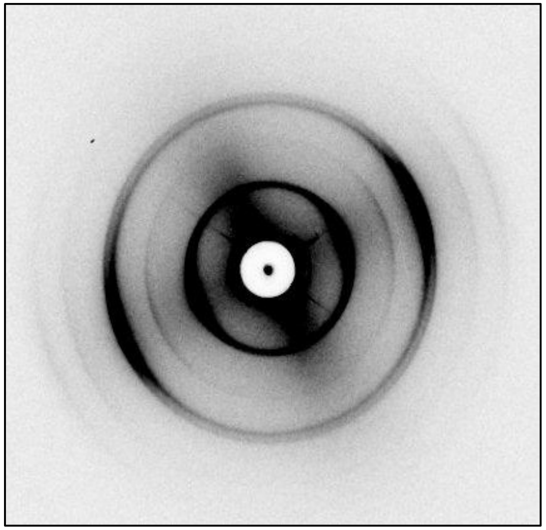
1. Image modified from Hutchings, J., & Zanetti, G. (2018). Fine details in complex environments: the power of cryo-electron tomography. *Biochemical Society Transactions*, *46*(4), 807-816.

Examination of Myelin Structure using X-Ray Diffraction (XRD)



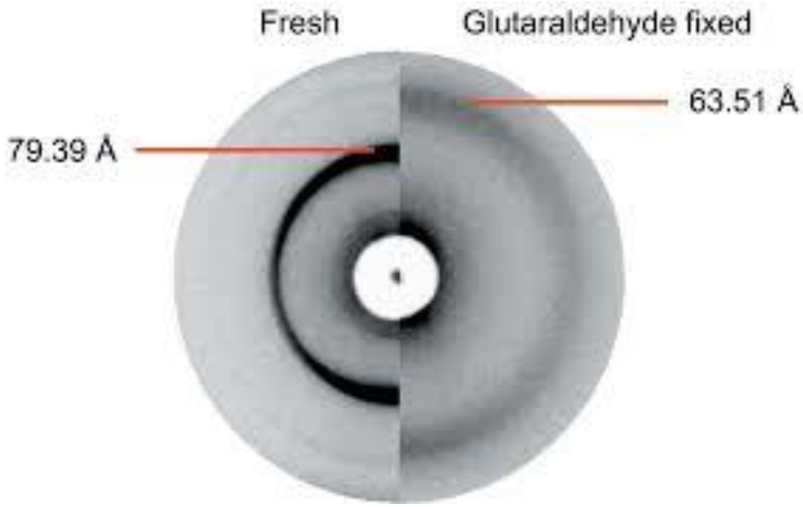




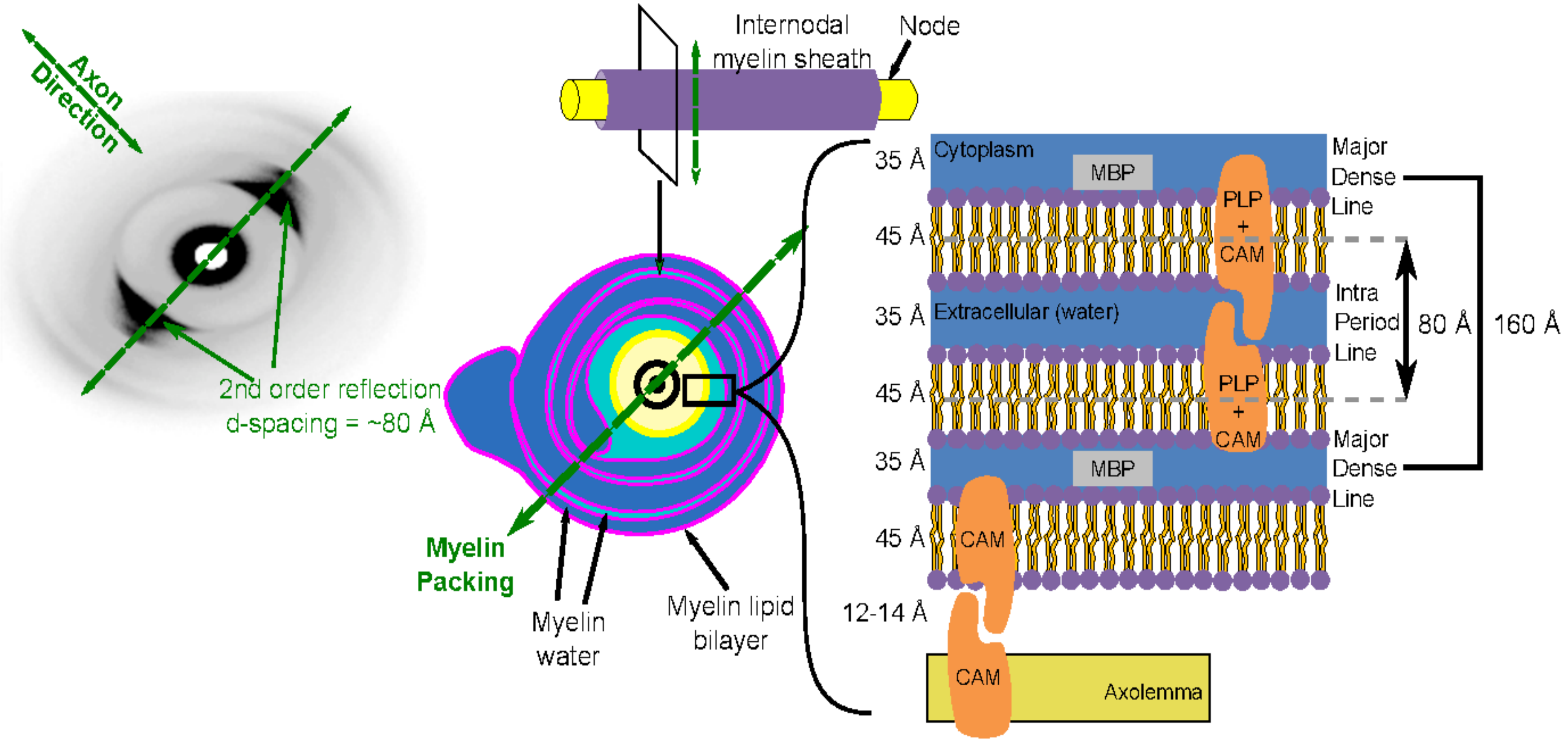


Advantage of using XRD over other imaging methods

Changes to myelin in fixed tissue:



Examination of Myelin Structure using X-Ray Diffraction (XRD)



Examination of Myelin Structure following Mechanical Insult

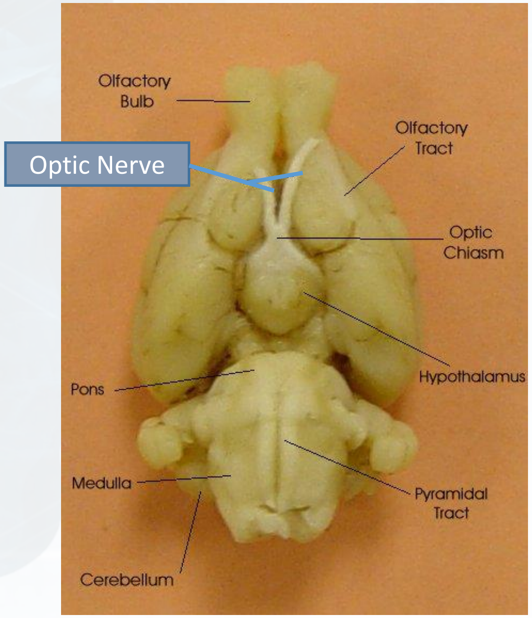
Objectives:

- Determine initial structural changes exhibited in myelin in response to mechanical load
- Evaluate loading thresholds for observed changes to occur

Experimental Approach:

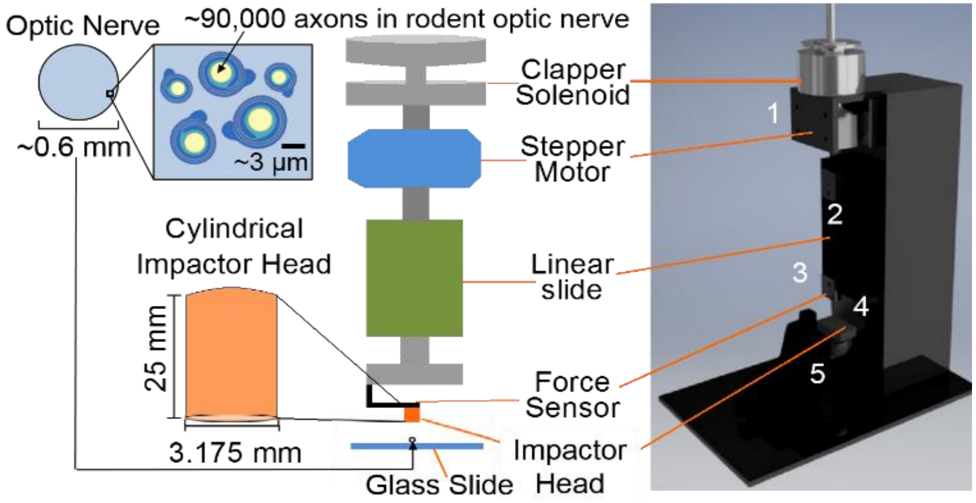
Impact Loading Groups:
(impactor force – hold time – estimated avg optic nerve pressure)

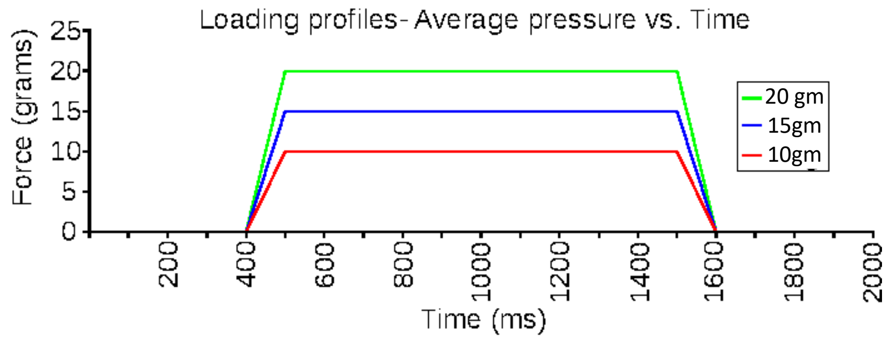
- Level 1 – 10 gm – 1 sec – ~ 7.45 psi
- Level 2 – 15 gm – 1 sec – ~11.19 psi
- Level 3 – 20 gm – 1 sec – ~14.93 psi



Examination of Myelin Structure following Mechanical Insult

Experimental Setup:

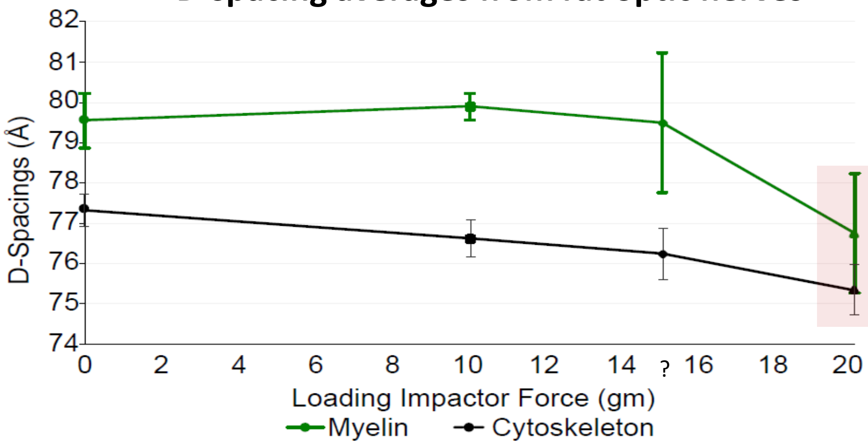




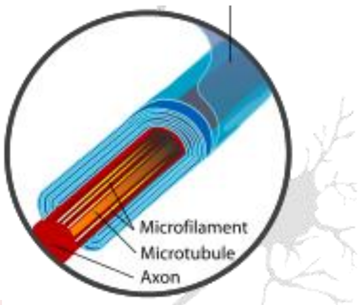
Examination of Myelin Structure following Mechanical Insult

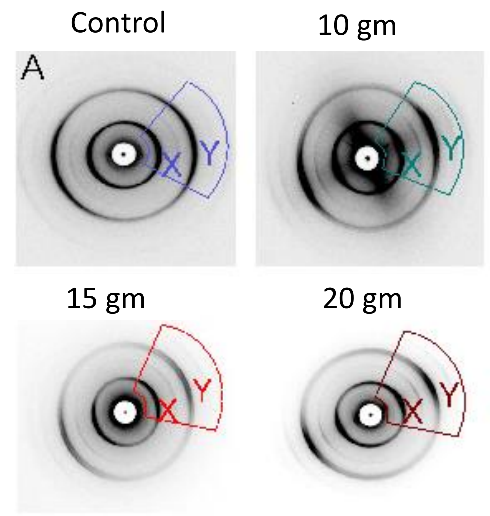
Results:

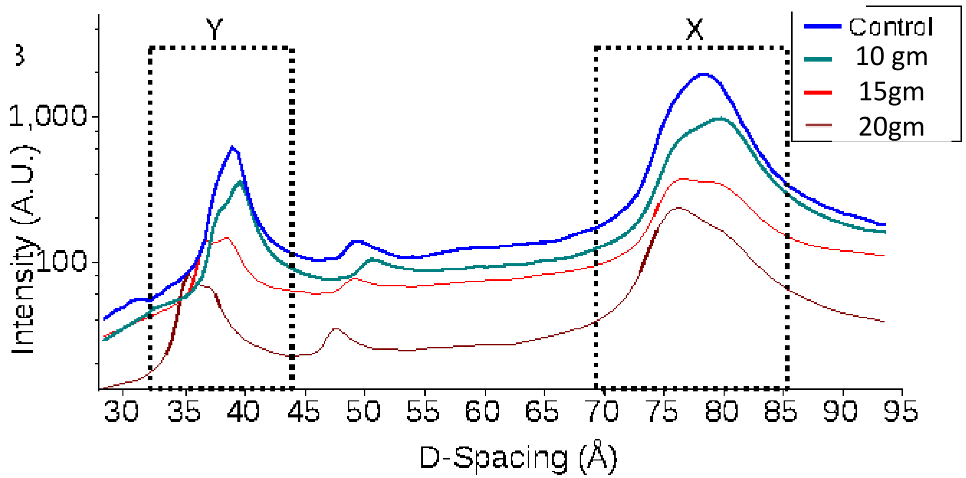
D-spacing averages from rat optic nerves



Myelin	Control	10 gm	15 gm	20 gm
Mean (**Å**)	79.55	79.90	79.50	76.74
Std. Dev	0.69	0.33	1.73	1.49
No. of Observations	100	100	100	100



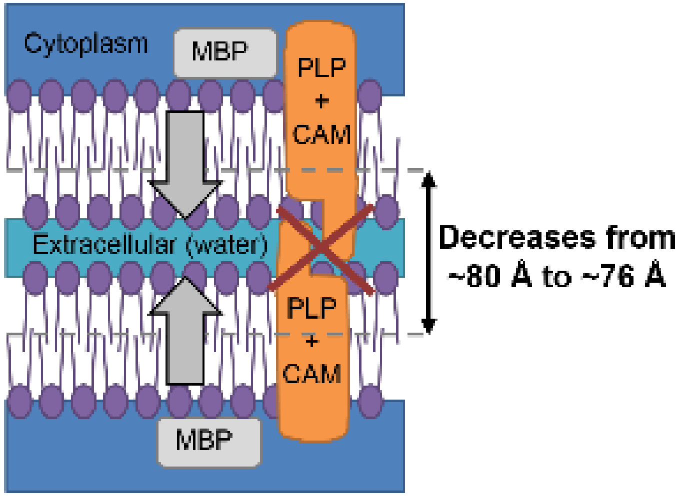




Examination of Myelin Structure following Mechanical Insult

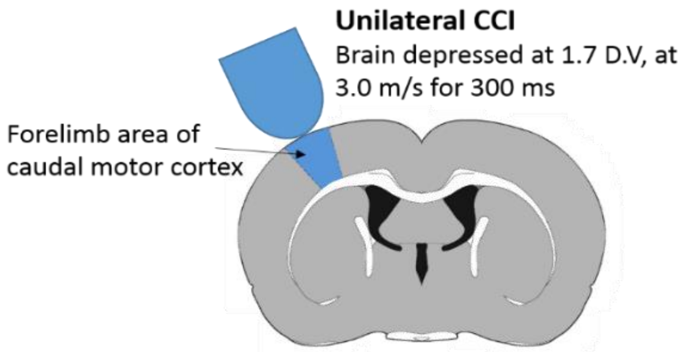
Conclusions:

- Notable alteration to myelin packing was observed to occur between an estimated pressure range of 11.19 - 14.93 psi which closely resembles pressure ranges of 10 -15 psi reported in literature to induce secondary mTBI pathologies [1]
- Reduced 2nd order d-spacings we believe result due to water loss between myelin layers
- We hypothesize the observed collapse of myelin laminar structure likely damages embedded extracellular proteins responsible for myelin and cytoskeletal maintenance

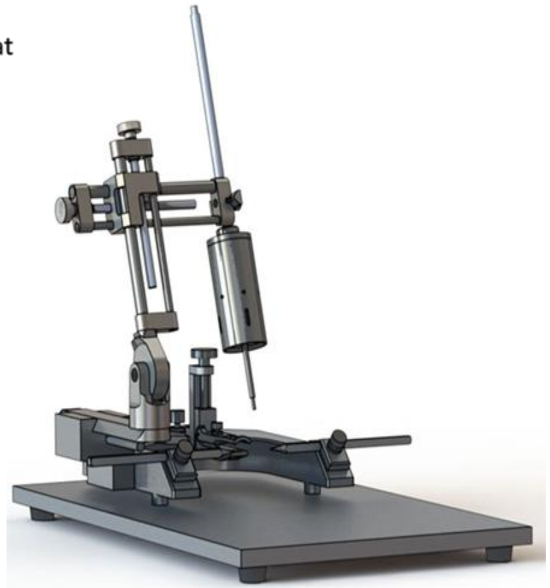


1. Piehler, T., et. al (2016). Understanding Effects of Traumatic Insults on Brain Structure and Function. Weapons and Materials Research Directorate, US Army Research Laboratory Aberdeen Proving Ground United States.

Pilot Examination

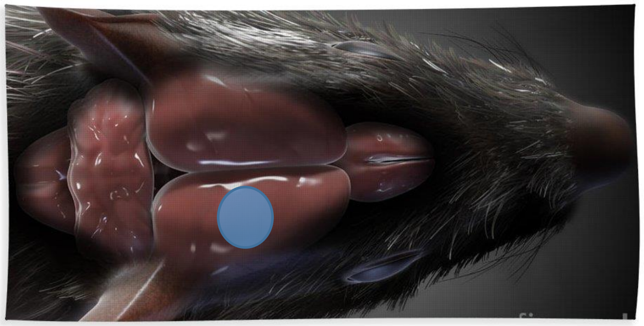


Slice view of rodent brain



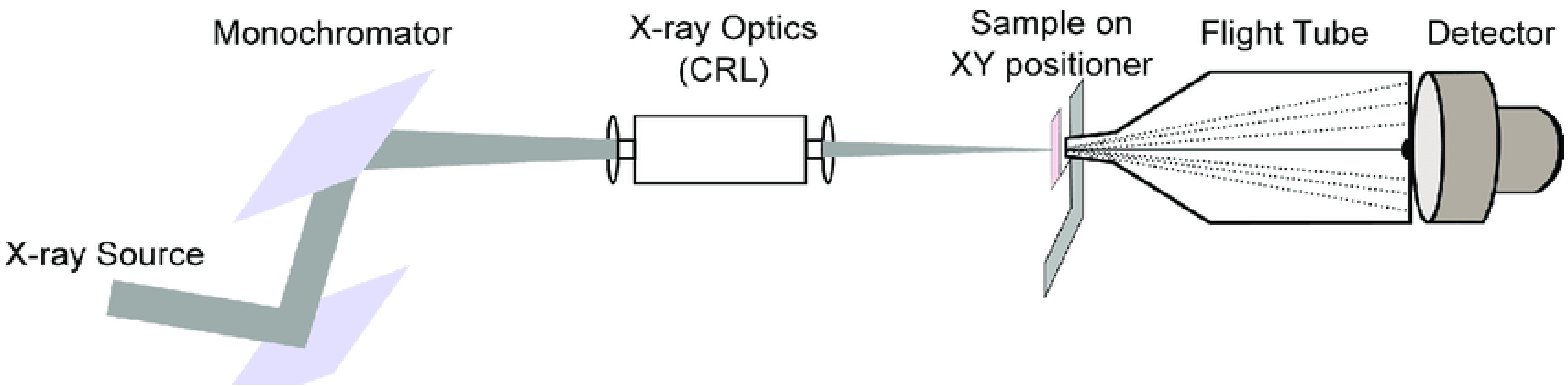
Closed cortical Impact (CCI) Device

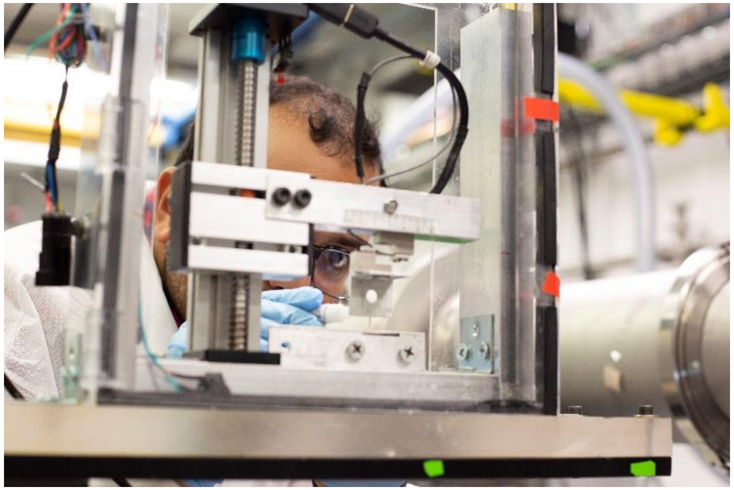
Pellet Reaching Task

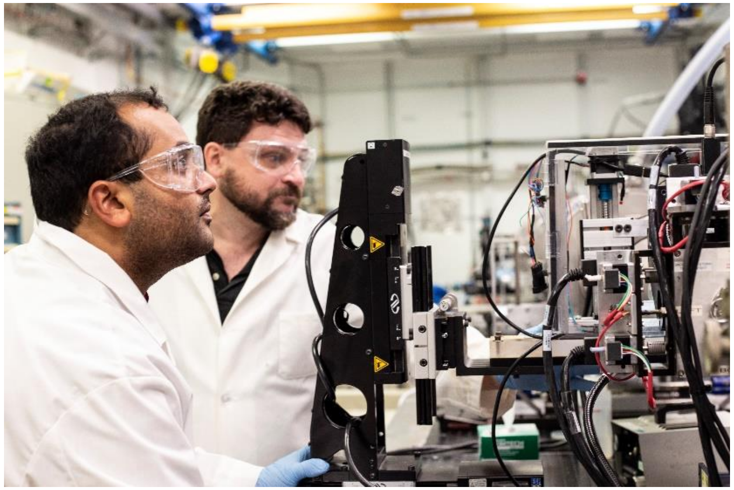


Top view of rodent brain

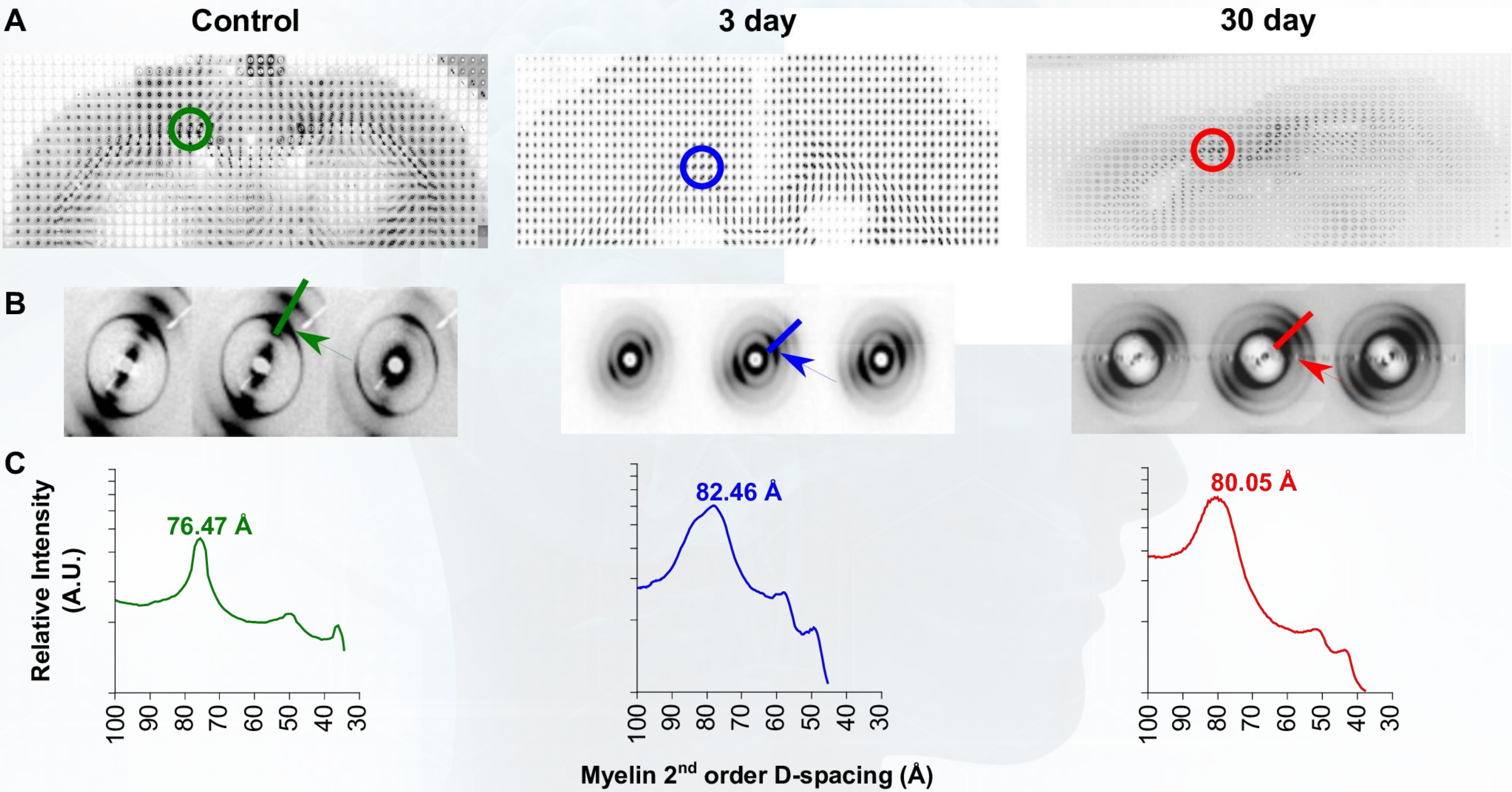
Development of XRD Imaging Methodology





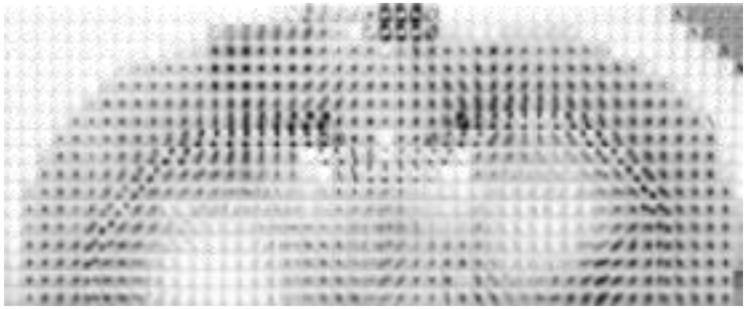


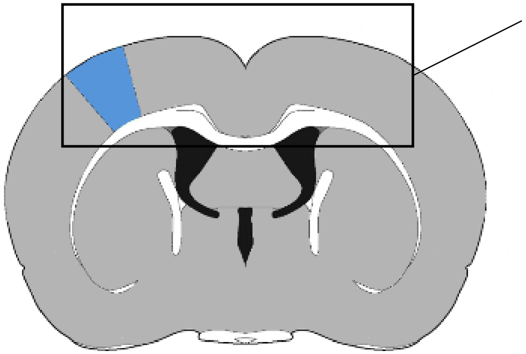
Composite Scanning Images



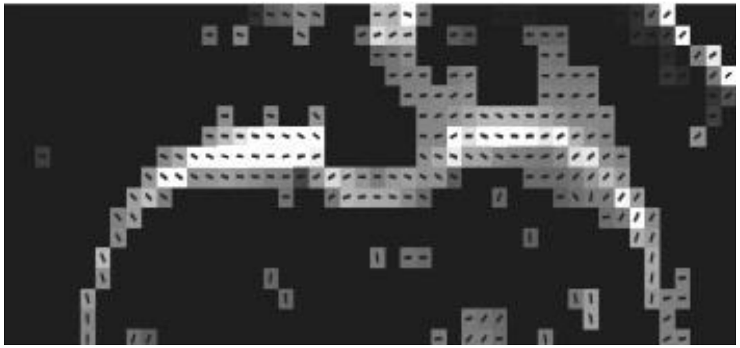
Visualization of d-spacing Changes in Myelin

Composite XRD Scanning Images

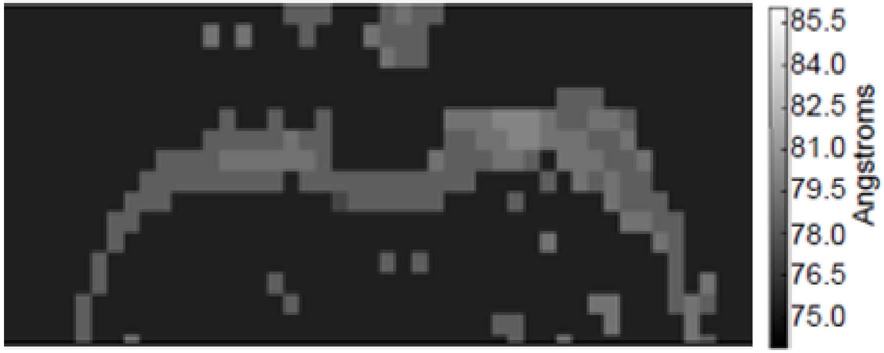




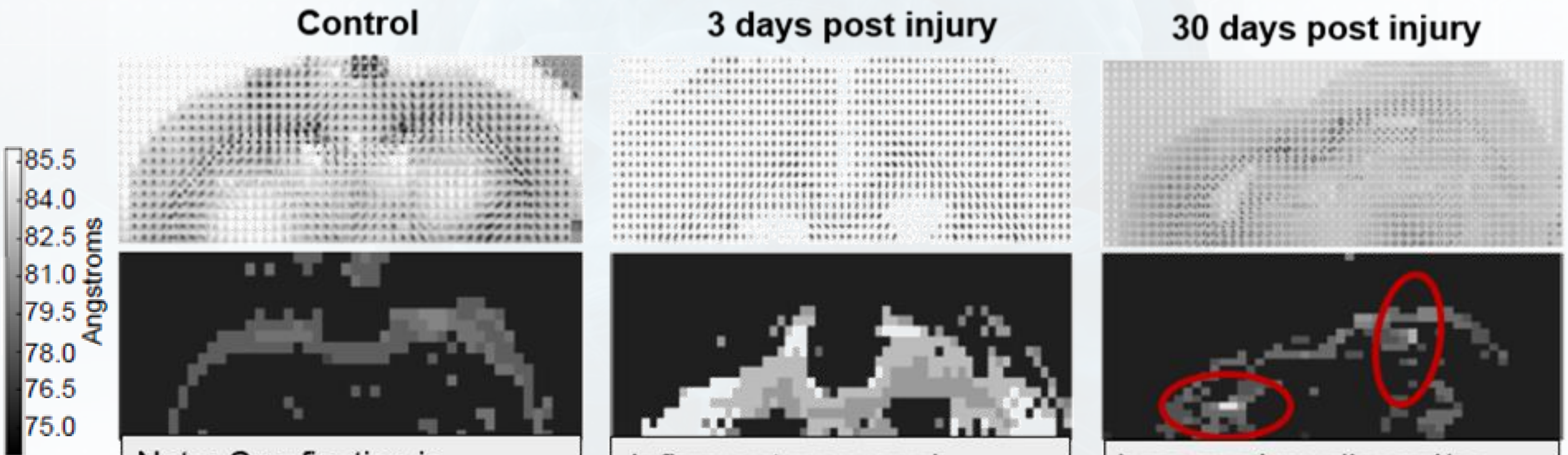
Dominant Axon Orientation Vectors



2nd Order Myelin d-spacing Measurements



Observed Outcomes

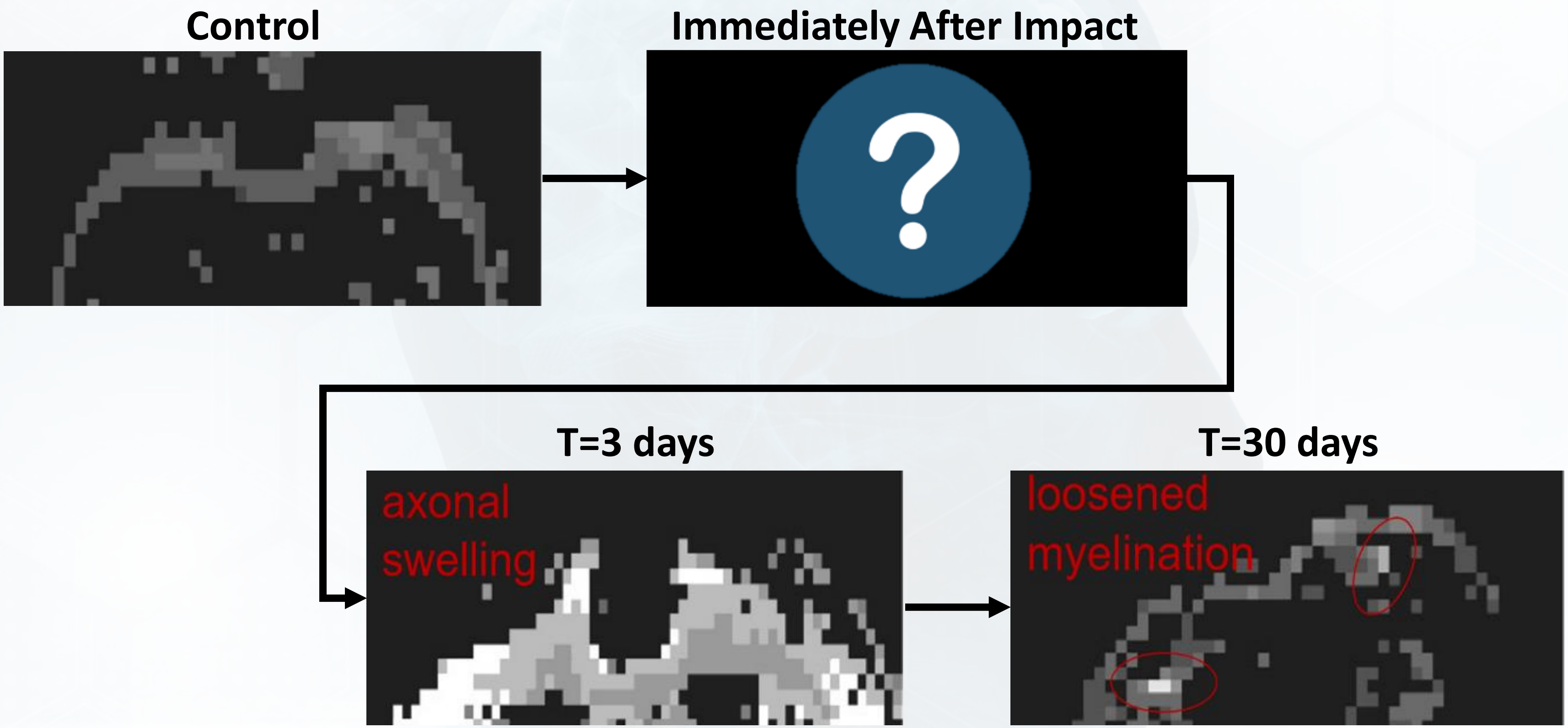


Note: Cryofixation in sample caused a uniform (~5%) disturbance to structure at all time points

Inflammatory axonal swelling seen in both hemispheres in form of myelin d-spacing increase

Loosened myelin and/or abnormal remyelination present around impact site and in opposing hemisphere

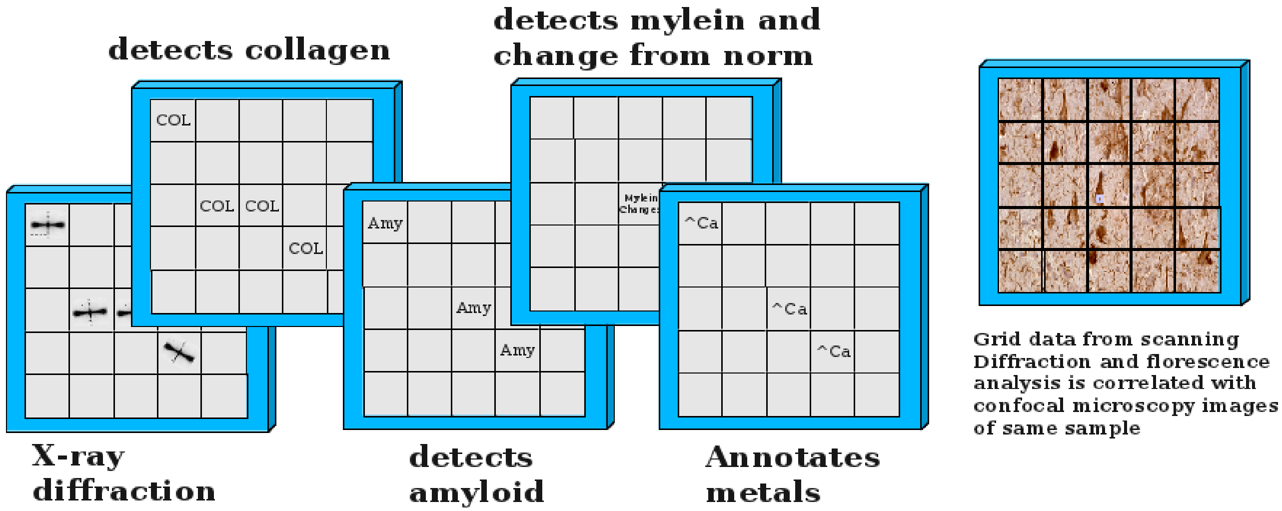
Future Work



Control
Immediately After Impact
T=3 days
axonal
swelling
T=30 days
loosened
myelination

Potential to Extend Developed Methodologies

Developed XRD methodologies may be extended to investigate further structure → function relations



Schematic of composite data correlation: X-ray diffraction, fluorescence, and light microscope data

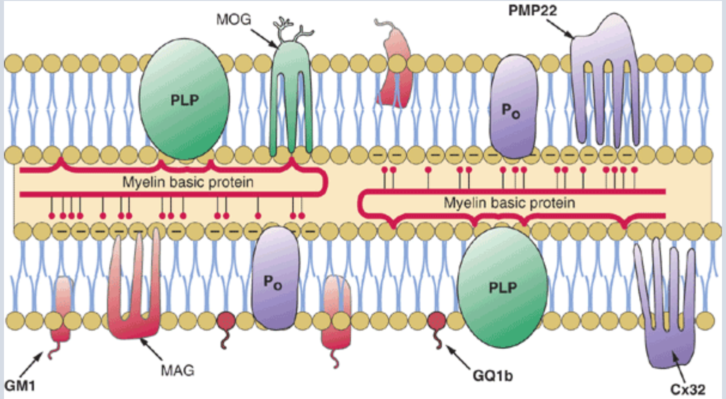
Orgel Group Future Projects

Current and near term projects:

- **Establish dose to structural change (injury threshold/s)**
  - *ex-vivo* human tissue (builds on current data)
  - *in-vivo* animal model of TBI (T=0 and finer force and acceleration ranges)
  - generation of quantified injury outcome assessments for patients suffering accidents using these data and computational methods
- **Heart valve material properties for material and method design in repair**

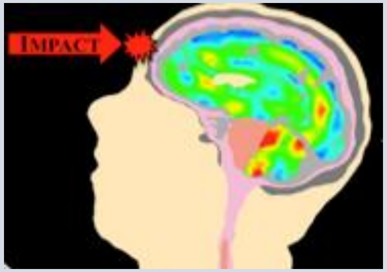
Warfighter Relevancy

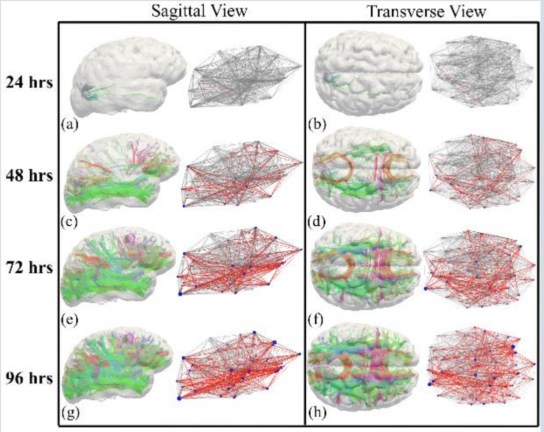
XRD data may be used in the future to:



https://i.pinimg.com/originals/ca/7e/df/ca7edfaeee2c5063b15df3b56fb4ae5b.gif

Identify up-stream targets for pharmaceutical interventions





Inform predictive brain injury models for use in design and testing of armoring systems

Thank you for your attention!

Questions?

If you are interested in learning more about TBI research, the BioCAT, or any of the efforts discussed in this webinar, please reach out to info@hdiac.org