

Understanding the effects of TBI on the brain

Cohen Veterans Bioscience is supporting the development of an imaging database containing 3,000 individuals to understand the background on which TBI leaves its imprint.

The Problem

Advanced neuroimaging can now detect microscopic changes in brain structure caused by mild traumatic brain injury. These injuries are referred to as mild because they do not cause brain damage that is visible to the naked eye on a standard MRI. But their long-term effects can be insidious — in up to 20% of cases, mild TBI leads to long-term cognitive or behavioral problems.

Doctors currently rely mostly on patient-reported symptoms to diagnose these cases, and can offer little prognostic information about long-term effects.

A neuroimaging technique could dramatically improve the identification of affected individuals and allow physicians to predict patients' risk of long-term problems such as cognitive decline, dementia, or chronic traumatic encephalopathy (CTE).

The Obstacles

Currently, the biggest obstacle to such a tool is the lack of information about the range of normal microscopic variation in brain structure detectable by advanced techniques such as MRI diffusion tensor imaging (MRI-DTI). Though researchers can document differences between groups of people with TBI and controls using statistical methods, specific differences that are powerful enough to provide diagnostic and prognostic information in individuals have not been identified.

The first step toward finding these signatures is to produce a large MRI-DTI database of people without traumatic brain injury.

In up to 20% of cases, mild TBI leads to long-term cognitive or behavioral problems.

OUR GOAL

To support the development of an imaging database containing 3,000 individuals to understand the background on which TBI leaves its imprint.



TBI IMAGING REFERENCE LIBRARY

Our Partner:

The American College of Radiology (ACR) Head Injury Institute

Working with the American College of Radiology (ACR) Head Injury Institute, Cohen Veterans Bioscience will recruit study centers to perform standardized MRI scans on 3,000 adult volunteers, collect demographic information and perform neurocognitive assessments. This data will form the basis for a library documenting population variation in brain structure as measured by state-of-the-art neuroimaging. Standards developed by the project for performing imaging and assessing volunteers will also be made available to the research community, so that future efforts can both add to the library and use it as a resource in the study of people with TBI.

About The American College of Radiology (ACR) Head Injury Institute



The ACR Head Injury Institute was formed to help advance the diagnosis, understanding and treatment of head injuries. One of the greatest needs in the advancement of head injury medicine is the identification and development of biomarkers — such as microscopic structural differences in the brain — that can help identify the nature and severity of a head injury. The Head Injury Institute brings a broad and deep range of capabilities and relationships to this challenge.

SUPPORT THE LIBRARY

Donate to help us scan individuals for the library.





COHEN BRAIN COLLECTION

Understanding the Biology of PTSD and TBI

Cohen Veterans Bioscience and the Harvard Brain Tissue Resource Center have partnered to establish the Cohen Brain Collection, the largest focused collection of PTSD & TBI human brain tissue from veterans and civilians.

The Problem

Since ancient times, direct study of human brain tissue has provided insights into how the nervous system works. Even with modern techniques such as brain imaging and genetics, repositories of donated human brains are a critical resource. They remain enormously valuable in studying genetic, molecular and anatomical aspects of brain function and in understanding conditions such as schizophrenia, Alzheimer’s disease and autism.

Yet of 8,000 brains at Harvard University’s Brain Tissue Resource Center — the largest brain collection in the United States — none were donated on the basis of a PTSD or TBI diagnosis.

The Goal

The initial, 3-year goal is to collect 100 brains both from individuals diagnosed with PTSD and/or TBI, as well as a set of controls from people who were exposed to emotional or head trauma during their lives but did not experience long-term consequences.

The collection will be made freely available to investigators requiring brain tissue for research in PTSD and TBI. Tissue will be processed using best practices to allow classical histology investigations as well as newer “omics”-based analyses that look at gene activity and levels of protein and metabolic products.

Our Partner

The Harvard Brain Tissue Resource Center (HBTRC) has been established at McLean Hospital since 1978, as a centralized resource for the collection and distribution of human brain specimens for brain research.



McLean HOSPITAL
HARVARD MEDICAL SCHOOL AFFILIATE

Register as a Donor

You can bequeath the gift of knowledge by registering to donate your brain to this important work.
cohenbraincollection.org

Financial Support Will:

- Raise awareness and expand the collection network.
- Fund the processing of an additional 500 brains.
- Bring state-of-the-art technologies to the Bank.
- Establish a Research Fund to enable access by scientists from around the world.



Expanding the PTSD Genetic Database

Cohen Veterans Bioscience is now working with the Stanley Center for Psychiatric Research on a global effort that will dramatically increase the scale of PTSD genetics research.

The Problem

Studies have shown that genetics influences a person's risk of developing PTSD after experiencing trauma. But the precise genes involved have not been identified. It has become clear that studies involving tens of thousands of subjects will be required to find genetic links to complex psychiatric diseases. Until now, however, the largest genome-wide searches for links to PTSD have involved fewer than 1,000 cases, and of four published studies, none have found consistent results.

In schizophrenia, a field where researchers spent decades searching in vain for genetic associations, genome-wide searches did not find reliable associations until about 20,000 subjects had been sampled. After a study published last year that included more than 100,000 samples, researchers have now found well over 100 genetic variants associated with schizophrenia risk. That effort, spearheaded by the Broad Institute's Stanley Center for Psychiatric Research, provides valuable lessons for the pursuit of genes linked to PTSD.

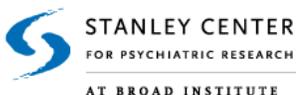
Until now, the largest genome-wide searches for links to PTSD have involved fewer than 1,000 cases.

Our Goal

The primary goal of this effort is to expand the current PTSD genetic database to more than 70,000 samples in less than one year, building from roughly 5,000 cases and 15,000 controls originally collected over three years through volunteer efforts. The additional samples come from researchers around the world, and are being collected along with extensive data on trauma history from both cases and controls. Through this effort, CVB and the Stanley Center are making PTSD a priority for a field that has traditionally focused on more easily diagnosed and characterized conditions such as schizophrenia, autism and depression.

Our Partner:

The Stanley Center for Psychiatric Research at Broad Institute



The mission of the Stanley Center for Psychiatric Research at Broad Institute is to reduce the burden of serious mental illness through research. Based on a conjunction of powerful new enabling technologies, a committed interdisciplinary faculty from the Harvard, MIT, and Harvard-affiliated hospital communities,

the exceptional people, resources and collaborative ethos of the Broad Institute, and the remarkable philanthropy of Ted Stanley, the Stanley Center is galvanized to make progress against the ravages of severe mental illness.

Participate

If you are a researcher who has a PTSD cohort with GWAS data or DNA samples, consider donating to the global genetics program.

Financial Support Will:

- Fund genotyping of additional samples in 2017.
- Perform secondary risk analyses based on gender, trauma type, age and other factors.



Advancing the development of valid animal models for PTSD

AMP-IT-UP: Alliance for Models of PTSD, Innovative Technologies and Uniform Practices

The Problem

The use of rodents in psychology research is so familiar that the rat in a maze is a common metaphor. But it can be hard to imagine how animals could provide useful information about complex disorders like PTSD. Rats can't describe flashbacks, nightmares or intrusive thoughts, even if they do experience such symptoms.

Nevertheless, researchers have developed multiple ways of reproducing PTSD-like behavior in rodents. After being subjected to frightening experiences such as prolonged exposure to predator odors or confinements, some rodents score higher on tests that assess anxiety by measuring their tendency to avoid open spaces and hug the walls of a maze. These animal models of PTSD possess what animal behavioral scientists call "face validity" — behaviors analogous to those of humans with the disorder.

But in order to be useful in testing potential diagnostics and treatments, these animal models must also demonstrate what researchers call "construct validity" — evidence that the behavior is driven by an underlying process that approximates what is thought to happen in humans with PTSD. Though current animal models of PTSD may possess face validity, none have been investigated in enough depth to establish their construct or predictive validity.

Our Goal

In 2016, CVB hosted a workshop to review existing animal models of PTSD and increase their usefulness in developing new diagnostics and therapies. That workshop resulted in AMP-IT-UP, the Alliance for Models of PTSD, Innovative Technologies and Uniform Practices.

AMP-IT-UP will:

- Collect and synthesize all available information about animal models of PTSD.
- Identify intermediate phenotypes (constructs) in humans that can harmonize with rodent models to facilitate the development of a translatable preclinical toolbox.
- Develop best practices standards for reproducibility and robustness for generating preclinical models and performing studies that use them.
- Conduct research to fill knowledge gaps.



Translational Toolbox

Preclinical Animal Modeling Program

Additionally, AMP-IT-UP will explore innovative new technologies that will help us to decipher neural circuit function with high resolution in preclinical animal models.

We will fund:

- Application of innovative nano- and imaging technologies that expand the armamentarium for preclinical PTSD research.
- Development of computational modeling approaches to provide a complementary modeling approach to animal models and to integrate knowledge garnered from them.

New technologies allow researchers to examine neural circuits in great detail, making it possible to compare brain activity in an animal model against that of people with PTSD. By taking this approach, researchers will be able to produce animal models that are appropriate for testing diagnostics and treatment.

Our Partners:



CVB will partner with PsychoGenics, a preclinical contract research organization, to create screening tools for R&D development.

PsychoGenics is a preclinical contract research organization with expertise in central nervous system and orphan disorders. It is known for its cutting-edge translational approach to research, customized solutions, the breadth and quality of its work, as well as its ability to identify statistically relevant changes that help clients quantify the efficacy of treatments before they move into the clinic.



CVB will partner with imec, the world's largest nanotechnology consortium, to test innovative new technologies for applications in PTSD preclinical modeling.

IMEC is an internationally renowned research institute that performs research in different fields of nanoelectronics.

IMEC is headquartered in Leuven, Belgium, and has offices in the Netherlands, Taiwan, USA, China, India, Nepal and Japan.

Financial Support Will:

- Fund development of a first generation of translational animal models of PTSD.
- Establish best-practice standards and screening tools for use by the research community.
- Fund technology projects that enhance our ability to understand the circuits that underlie PTSD and accelerate the discovery of new diagnostics and treatments.



RAPID-Dx: Research Alliance for PTSD/TBI Innovation and Discovery Diagnostics

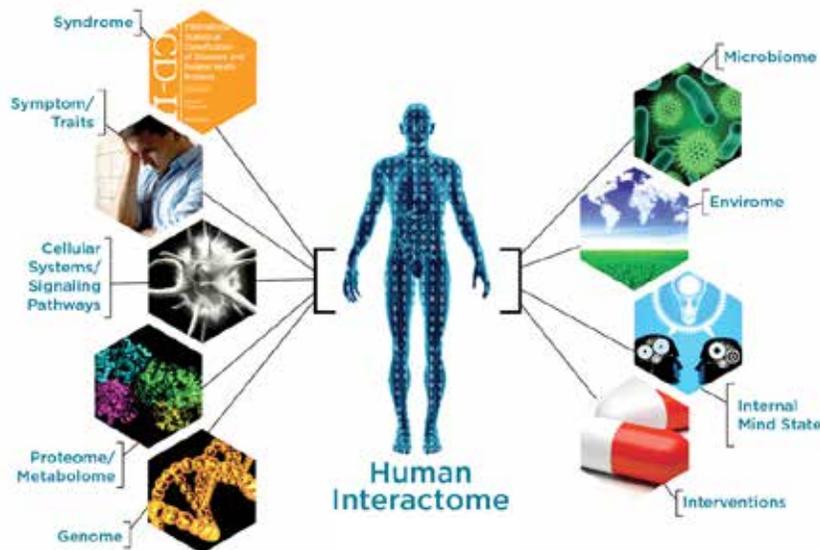
Collecting data and performing studies necessary to validate proposed biomarkers and qualify successful and relevant candidates for development as clinical diagnostics.

The Problem

There are 636,120 ways to combine the various symptoms that are used to classify PTSD in DSM-V, the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, underscoring the heterogeneity and complexity of classifying individuals who present with undiagnosed symptoms. The identification of discrete diagnostic biomarkers for PTSD remains elusive, despite an extensive body of work that identifies psychological, genomic, and physiologic risk and etiologic factors for disease.

Biomarkers need to undergo a rigorous process of discovery, replication and regulatory validation to be useful as diagnostics and many biomarkers published in the literature have not been independently replicated, while many studies are underpowered due to a lack of resources and other factors. Further, it is unlikely that only a few markers will be sufficient to diagnose such complex diseases, yet few studies have taken a systems approach to identify combination markers that are predictive.

With new scientific tools that offer a comprehensive view of gene, protein and metabolic activity, brain circuits and physiology, as well as computing advances that allow large data sets to be searched, analyzed and manipulated, we now have the ability to understand in detail how PTSD and TBI rewire the brain. This knowledge can be translated into diagnostics and treatments that help patients.



What is needed are large-scale, high-quality molecular, imaging, biosensor and phenotypic data that will allow us to map out all the subtypes of PTSD and TBI and the computational toolbox to map out pathways and circuits that underlie risk and pathogenesis.

Biomarkers & Diagnostics

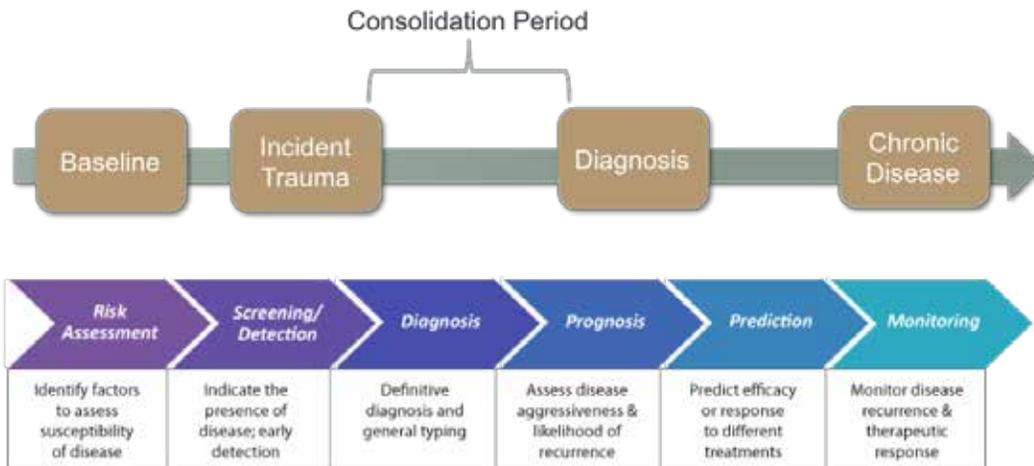
Biomarker Discovery Collaborative

Our Goal

RAPID-Dx will focus on bringing together large biomarker and imaging legacy datasets into a centralized cloud-based data platform for interrogation by a multi-disciplinary group of experts including clinical, biomarker, and computational.

Specific Goals of the Alliance include:

- Landscape of available legacy PTSD biomarker datasets and bio-fluid samples for analysis.
- Exhaustive literature review of the most promising bio-fluid and imaging biomarkers in PTSD and related trauma disorders.
- Due diligence evaluation (performance) of the most advanced, validated bioassay platforms.
- Develop Statistical Analyses Plans for biomarker discovery and replication.
- Establishment of a CNS Data Commons.
- Roadmap for discovery and development of portfolio of PTSD & TBI Diagnostics.



Brain Research and Innovation Network (B.R.A.I.N.) – Data Commons

Goals for the Data Commons:

- Enable Data-Driven Accelerated Discovery through a Unified Data Repository.
- Overcome data hurdles and big data challenges that impede discovery.
- Current IT solutions cannot contend with scale and variety.
- Enable the combining, interpreting and analyzing of vast and disparate data types from different sources with sophisticated visualization and analytics tools.
- Realize the potential of machine learning and predictive modeling.
- Safeguard and Protect Data Integrity and Access.
- Promote Collaboration a Multidisciplinary Research Community.

Our Partners:

In collaboration with the Open Commons Consortium and the University of Chicago, CVB will build the B.R.A.I.N. computing platform to integrate existing knowledge and enable crowdsourced scientific inquiry.

In collaboration with Alliance Partners, Fraunhofer SCAI and Exaptive, Inc. we are building a PTSD & TBI KnowledgeMap™, an analysis and data-mining tool that will integrate clinical, biomarker, genetic, epidemiological and other data relevant to PTSD & TBI. It will include easy-to-use interactive visualizations for people to search vast data in an accessible manner. The partnership will also establish an ongoing process for incorporating new research as it becomes available.

In collaboration with Exaptive Inc., we are building a Cognitive Network™ platform to create an interconnected research community in which researchers can leverage the Exaptive Xap Builder to create interactive data applications to analyze the data collected in the B.R.A.I.N. Commons.

About the Open Commons Consortium



The OCC is a U.S.-based 501(c)(3) not-for-profit corporation founded in 2008. It manages data commons and cloud computing infrastructure to support scientific research: Open Science Data Cloud,

Project Matsu (OCC & NASA), and the OCC NOAA Data Commons. The OCC also enables researchers to submit data, and harmonizes these data for import into the OCC.

About Fraunhofer Institute for Algorithms and Scientific Computing



The Fraunhofer Institute for Algorithms and Scientific Computing conducts research in the field of computer simulations for product and process development, and is a prominent corporate partner in the industrial and science sectors. SCAI designs and

optimizes industrial applications, implements custom solutions for production and logistics, and offers calculations on high-performance computers. Its services are based on industrial engineering, combined with state-of-the-art methods from applied mathematics and information technology. The team of Martin Hofmann-Apitius has used their knowledge extraction capabilities to successfully generate a large research model of Alzheimer's Disease. More information is available at www.scai.fraunhofer.de/bio.

About Exaptive Inc.



Exaptive is a software company whose mission is to lower the barriers to analyzing and collaborating with data. The Exaptive platform enables software developers and researchers to interchange and experiment easily with different analytics tools, suggests relevant techniques users haven't tried yet, and connects

users to others working on related projects. The goal is to reveal new approaches and make it easy to try them, so that gaining new insight happens faster and big breakthroughs are more frequent. Users can also leverage others' work or monetize their own work as a part of a combinatorial marketplace. More information is available at www.exaptive.com.



Biomarkers & Diagnostics

Biomarker Discovery Collaborative

Participate

If you are part of a large cohort PTSD or TBI biomarker research program and would like to register to be considered for the RAPID-Dx Grant Application program, please contact info@cohenbio.org.

Financial Support Will:

- Support biosample analysis of large study cohorts.
- Build computational modeling tools.
- Fund data-mining and computational analysis research.
- Support open-science collaboration through B.R.A.I.N.

