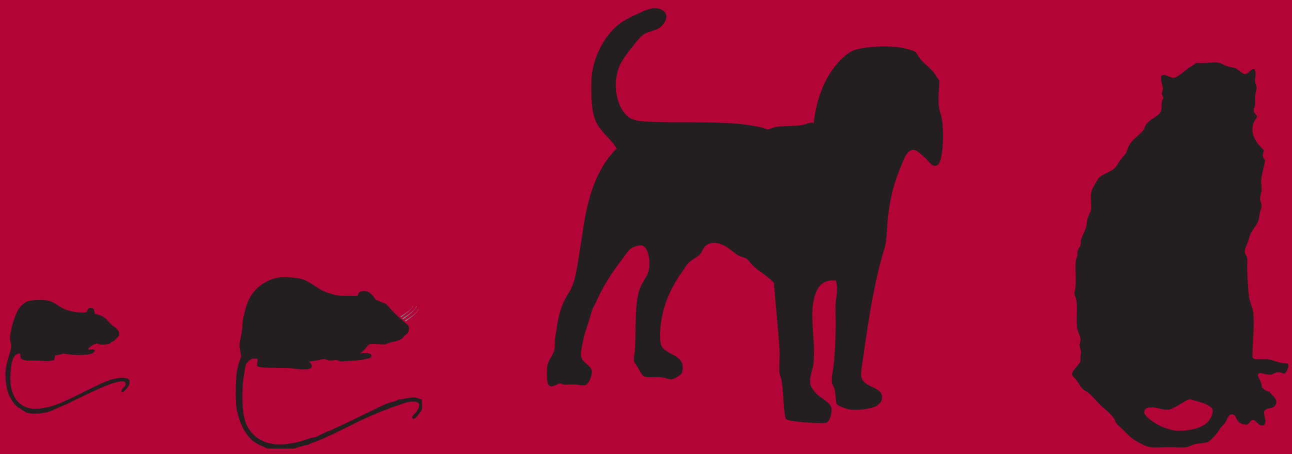
Research Models of Traumatic Brain Injury



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Opportunity for Improvement

A recent publication in Nature has drawn attention to concerns about the ability for current animal models to translate into human therapy (Xiong, Mahmood & Chopp, 2013). The authors made several suggestions to help improve model translation. Recommendations included: monitoring biomarkers for longer periods of time after injury, employing more than one injury model, and using clinically meaningful large animal models prior to starting any human clinical trials.

DSI's solutions enable continuous or intermittent collection of physiologic data over weeks or months across multiple species, supporting all three recommendations.

Understanding TBI Research Models

The ability to study injury-induced changes in physiology makes in vivo Traumatic Brain Injury (TBI) models essential for neurotrauma research.

Among the numerous models available, the four most commonly used in TBI research include fluid percussion injury (FPI), weight-drop impact acceleration injury, controlled cortical impact (CCI) injury, and blast injury.

Regardless of the model used to create brain injury, it is essential to control the mechanical force used to induce injury so that the resulting injury is quantifiable and reproducible.

Fluid Percussion Injury (FPI)

FPI is induced by a pendulum impacting the piston of a fluid filled reservoir. This generates a pressure pulse which is transferred to intact dura through a craniotomy creating brief displacement and deformation of brain tissue. The severity of injury may be controlled by the strength of the pressure pulse. The location of FPI is controlled by where on the dura the impact occurs.

FPI replicates clinical TBI without skull fracture including intracranial hemorrhage, brain swelling and progressive damage to the grey matter. Midline FPI is used in assessing diffuse brain injury such as those associated with sport and blast injuries. Lateral FPI is widely used in neurotrauma research for both mechanistic studies and for drug screening.

FPI does not replicate moderate-to-severe TBI as that is often associated with skull fracture and contusions across multiple ridges.

Weight-drop Impact Acceleration Injury

With the Weight-drop model, the skull is exposed (with or without a craniotomy) to a free falling, guided weight. Injury severity can be altered by adjusting the mass of the weight and the height from which it falls. There are several variations of the weight-drop model including Feeney's, Shohami's, Marmarou's, and Maryland's.

Weight-drop models are inexpensive, easy to perform, and closely mimic several types of human TBI including concussion, contusion, traumatic axonal injury, and hemorrhage. However, there is also a great deal of variability in injury severity due to the manual manipulations available.

Controlled Cortical Impact Injury

CCI injury is created by driving a rigid impactor onto the exposed, intact dura through a unilateral craniotomy lying most often between bregma and lambda. This injury mimics cortical tissue loss, acute subdural hematoma, concussion, axonal injury, blood–brain barrier (BBB) dysfunction and even coma. Associated damage can be widespread, acutely resulting in cortical, hippocampal and thalamic degeneration.

The location and severity of injury may be easily controlled and lead to cognitive and emotional deficits which can last up to one year post-injury.

CCI is a reproducible injury model which mirrors several types of human TBI including concussion, contusion, traumatic axonal injury, and hemorrhage. Large animal studies allow for experiments which model the intensive care unit experience, and therefore may see more success in translation to clinical treatments than other models.

Blast Injury Model

Blast injury is induced by placing the subject in a tube and detonating an explosive resulting in a compression wave. Injuries are diffuse and impact upon the brain also results from other areas (e.g. thoracic effect).

This model replicates TBIs that soldiers experience and those in which external injuries are not always apparent. The non-impact injury is characterized by diffuse cerebral brain edema, extreme hyperemia and a delayed vasospasm.

There is currently significant variation in the methods used blast injury induction. As such, additional development of standard models is of particular importance. Identification of appropriate biomarkers must also be included in this effort.

Physiologic Biomarkers of TBI

Across all injury models a broad range of physiologic parameters are used for quantifying TBI including intracranial pressure, sleep quality (EEG and EMG), seizure (EEG), blood pressure, respiration, temperature, and activity.

These physiologic endpoints are most commonly measured in mice, rats, rabbits, cats, dogs, sheep, swine and nonhuman primates. Various telemetric and hardwired solutions are available depending upon the animal model used.

To improve the potential for translation from animal model to the clinical environment, DSI recommends careful consideration of study length, selection of injury models, and choice of animal model when designing your studies.

References for various physiologic measurements used in TBI research are provided below.

Intracranial Pressure

Bauman, RA, Ling G, Tong L, et al. An Introductory Characterization of a Combat Casualty Care Relevant Swine Model of Closed Head Injury Resulting from Exposure to Explosive Blast. Journal of Neurotrauma. 2009 Jun;26(6):841-60.

Sleep

Petraglia AL, Plog BA, Dayawansa S, et al. The Spectrum of Neurobehavioral Sequelae after Repetitive Mild Traumatic Brain Injury: A Novel Mouse Model of Chronic Traumatic Encephalopathy. Journal of Neurotrauma. July 2014; 31(13):1211-1224.

Seizure

Guo D, Zeng L, Brody DL, Wong M. Rapamycin Attenuates the Development of Posttraumatic Epilepsy in a Mouse Model of Traumatic Brain Injury. PLoS ONE. 2013; 8(5): e64078.

EEG and EMG

Petraglia AL, Plog BA, Dayawansa S, et al. The Spectrum of Neurobehavioral Sequelae after Repetitive Mild Traumatic Brain Injury: A Novel Mouse Model of Chronic Traumatic Encephalopathy. Journal of Neurotrauma. July 2014; 31(13):1211-1224.

Furtado M, Rossetti F, Yourick D. Use of Telemetric EEG in Brain Injury, Modern Telemetry, Dr. Ondrej Krejcar (Ed.), InTech, 2011.

Blood Pressure

Larson BE, Stockwell DW, Boas S, et al. Cardiac reactive oxygen species after traumatic brain injury. The Journal of Surgical Research. 2012;173(2):e73-e81.

Respiration

Engel O, Akyüz L, da Costa Goncalves AC, et al. Cholinergic Pathway Suppresses Pulmonary Innate Immunity Facilitating Pneumonia After Stroke. Stroke. 2015 Nov;46(11):3232-40.

Vermeij JD, Aslami H, Fluiter K, et al. Journal of Neurotrauma. December 2013; 30(24): 2073-2079.

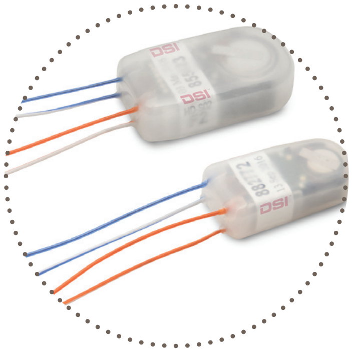
Temperature & Activity

Thompson HJ, Hoover RC, Tkacs NC, et al. Development of Posttraumatic Hyperthermia after Traumatic Brain Injury in Rats is Associated with Increased Periventricular Inflammation. Journal of Cerebral Blood Flow & Metabolism. 25(2):163-176.

Products Used in Traumatic Brain Injury Research

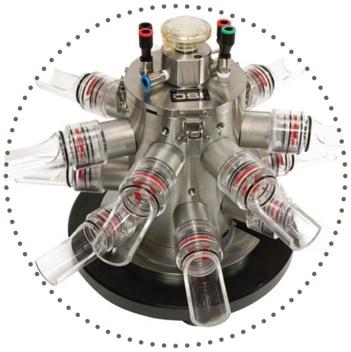
TELEMETRY

Implantable telemetry is designed for stress-free continuous data collection in small and large animals.



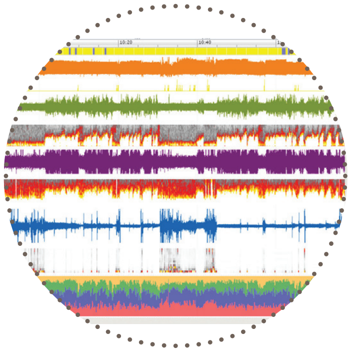
RESPIRATORY

Buxco hardware & software is for collecting respiratory data and reporting results in the fastest, and most reliable manner.



SOFTWARE

NeuroScore is designed to efficiently analyze large, continuous data sets common to sleep and seizure studies.



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