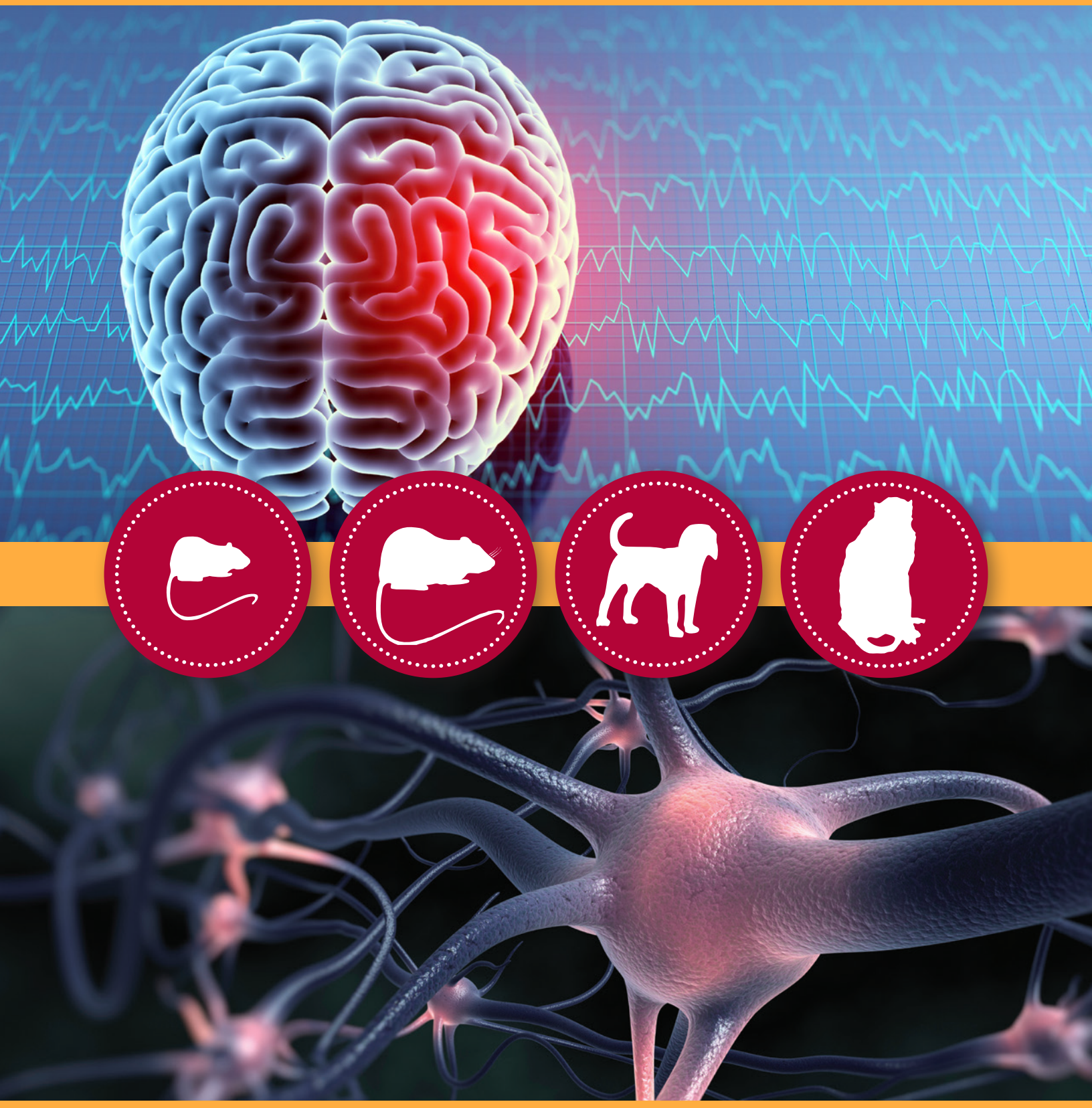
Advancing Research

In Vivo Research Approaches in the Study of Neurological Disease and Psychiatric Disorders



In Vivo Research Approaches in the Study of Neurological Disease and Psychiatric Disorders

Neurological disease and psychiatric disorders are some of the most heavily funded research areas today. Although tremendous strides have been made, the study of the brain and spinal cord leaves many questions unanswered. Scientific research programs across the globe are working on the cause, prevention, and treatment of neuroscience disorders. From academic institutions to nationally lead initiatives, each are aggressively trying to find ways to help reduce the staggering numbers of people affected on an annual basis.

This paper provides researchers with the following information: a) a summary of the most commonly researched neurological disease and psychiatric disorders, b) observations regarding *in vivo* physiologic endpoints of interest, and, c) the products used to collect these endpoints.

Although categorization of disorders is possible, the methods (and associated instrumentation) used in which scientists collect physiologic data to better understand the primary and secondary impact often overlaps from one discipline to the next. As such, the summary of DSI related neuroscience solutions is listed at the paper's conclusion, in the section titled "Products Used in Neuroscience Research".

Please visit https://www.datasci.com/solutions/neuroscience to view DSI's neuroscience solutions and a detailed list of some of the most relevant and insightful research from peer-reviewed journal articles.

Anxiety, Depression, and Fear

Mood disorders are currently ranked as one of the major disease categories worldwide. According to the World Health Organization, depression, the most common mood disorder, affects an estimated 350 million people of all ages. The various classifications of mood disorder each display symptoms and signs whose origins and biological substrates are only partly understood.

One of the major challenges with studying affective disorders is efficient and timely disease diagnosis and the development of more efficient pharmacological and non-pharmacological treatments.

In the research community, it is particularly difficult to study and develop treatments for mood disorders because animal models often do not share comparable behavioral/physiological signs or such disease symptoms do not mimic the human condition in a satisfactory manner.

Because of these limitations, scientists have tried to model and treat only a few of the symptoms that are present both in patients and in animal models. Some of the most robust and objectively measurable symptoms (also known as biomarkers) are represented by alterations of physiological parameters such as heart rate or body temperature.

A detailed study of these biomarkers can better clarify the biological substrates, and temporal dynamics of the disease, and help identify better treatments.

Physiologic biomarkers for a better translational approach for mood disorder models are:

- Autonomic nervous system dysregulation at the level of the heart, e.g. heart rate variability (HRV) changes
- Aberrant electroencephalogram (EEG) patterns in sleep stages (changes in frequency component/ sleep deprivation)
- Changes in thermoregulatory mechanisms (hyperregulation of the thermoregulatory center)

Suggested mood disorders research references:

Alenina, N. et al. (2009). Growth retardation and altered autonomic control in mice lacking brain serotonin. *Proc Natl Acad Sci U S A* 106, 10332-10337, doi:10.1073/pnas.0810793106.

Pattij, T. et al. (2002). Autonomic changes associated with enhanced anxiety in 5-HT(1A) receptor knockout mice. *Neuropsychopharmacology* 27, 380-390, doi:10.1016/S0893-133X(02)00317-2.

Sgoifo, A., Carnevali, L., Alfonso Mde, L. & Amore, M. (2015). Autonomic dysfunction and heart rate variability in depression. *Stress 18*, 343-352, doi:10.3109/10253890.2015.1045868.

Viviani, D. et al. (2011). Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. *Science* 333, 104-107, doi:10.1126/science.1201043.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia, affecting an estimated 35 million people worldwide and making it the 7th leading cause of death. AD is a neurodegenerative disease associated with beta-amyloid protein (plaque) accumulation on the outside of brain cells and intracellular neurofibrillary tangles that restrict cell to cell communication. Genetic, environmental, and lifestyle factors have been linked to contributing factors of varying Alzheimer's disease stages.

Scientists look at a number of physiologic measurements when studying AD and its devasting effects:

Electroencephalogram

EEG has been used as a tool for diagnosing AD in clinical populations for several decades.

Indicators of Alzheimer's disease in EEG include:

- Shift of the power spectrum to lower frequencies - Common visual EEG approaches allow the ability to look for an increase in delta and theta activity and the reduction of alpha and beta activity
- Decrease in coherence of fast rhythms - A mathematical approach to look at the synchronicity of neuronal patterns from spatially separated scalp EEG leads
- EEG complexity changes – Increased omega complexity and lower synchronization likelihood are also observed in AD in the 0.5–25Hz frequency ranges

Sleep

Clinical populations affected by AD show distinct sleep architecture compared to control populations.

Indicators of Alzheimer's disease in sleep include:

- Reduced percentage of slow wave sleep
- Broken sleep periods during resting hours
- Amount of REM sleep is reduced, especially at advanced stages of disease

Respiratory

In AD populations, there is a blurred distinction between the disease and the patient's actual cause of death. Shortness of breath, disruptions in the flow of oxygen, pneumonia, and other respiratory disorders are often observed; leading to a lower quality of life. Some research suggests a connection between commonly prescribed sedatives to AD patients and its potential risk of increased respiratory complications.

Sleep

Current research suggests a bidirectional correlation between elevated blood sugar levels and Alzheimer's disease. Some scientists have gone as far to call Alzheimer's Disease type-3 diabetes. On the other hand, Platt and colleagues have found that an Alzheimer model can lead to diabetes complications (type II).

A recent study published in the journal Scientific Reports, report that glycation related damage to specific enzymes may be a critical part in the progression Alzheimer's Disease. These scientists now hope to detect similar changes in blood samples rather than brain.

Circadian Rhythm

Disturbances with circadian rhythm are seen in the early stages of Alzheimer's Disease. Indicators of AD while studying circadian rhythm include:

- Increased evening activity
- Alterations in core body temperature
- Eating habits and alterations in fasting/feeding cycles

Suggested Alzheimer's disease research references:

Czigler B, Csikos D, Hidasi Zm et al. (2008). Quantitative EEG in early acute Alzheimer's disease patients—power spectrum and complexity features. *International Journal of Psychophysiology*. 68(1):75-80.

Kassaar O, et al. (2017). Macrophage Migration Inhibitory Factor is subjected to glucose modification and oxidation in Alzheimer's Disease. *Scientific Reports*.

Platt B, et al. (2016). Neuronal human BACE1 knock-in induces systemic diabetes in mice. *Diabetologia*.

Tsolaki A. (2014). Electroencephalogram and Alzheimer's Disease: Clinical and Research Approaches. *Hindawi*.

Epilepsy

A seizure is an episode of increased or irregular electrical activity in the brain. Seizures can happen in both humans and other animals, of all ages, and can be due to a variety of factors. Seizures can occur throughout the brain (generalized) or only in a single hemisphere or location (partial or focal). They can present as a single event or exhibit recurrent characteristics (epilepsy). Long term effects can include histopathological alterations in various brain regions, abnormalities in sleep, and neuropsychiatric disorders.

EEG data collection and analysis plays a critical role in pre-clinical research. A number of models in several species have been characterized and are used to unravel underlying etiology and pathophysiology, to test antiepileptic drugs, or the increased susceptibility to seizure (the lowering of a seizure threshold). Genetic models of seizure include spontaneous and reflex seizure (seizure caused by a stimulus such as sound). Alternatively, seizure can be induced in normal animals through electrical or chemical means and these induced seizures can be acute, chronic or spontaneous/recurrent.

New models are constantly in development to more accurately portray and treat seizures which are, at present, resistant to existing anti-epileptic drugs.

Suggested epilepsy research references:

Curia, Giulia, et al. (2008). The pilocarpine model of temporal lobe epilepsy. *Neuroscience Methods*, 172: 143-157.

D'Ambrosio, Raimondo, et al. (2010). What is an epileptic seizure? Unifying definitions in clinical practice and animal research to develop novel treatments. *Epilepsy Currents*, 10.3: 61-66.

Löscher, Wolfgang. (2011). Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. *Seizure*, 20: 359-368.

Suntsova, N., et al. (2009). A role for the preoptic sleep-promoting system in absence epilepsy. *Neurobiology of Disease*, 36.1: 126-141.

Movement Disorders

Movement disorders are the 3rd most common cause of disability worldwide. Such disorders can be classified according to their clinical manifestations and prevalence as:

- Parkinson's disease (PA) and Multiple System Atrophy (MSA) - Slowly progressing, neurodegenerative diseases which result from the loss of dopamine-producing brain cells
- Dystonia - The over-activity of the main muscles needed for a movement, extra activation of other muscles that are not needed for the movement, and simultaneous activation of muscles that work against each other
- Restless Leg Syndrome (RLS) - Often an unpleasant feeling in the legs that improves somewhat with moving them

Although clinically different, these disorders share symptoms commonly categorized as either Motor or Non-Motor Symptoms.

Motor Symptoms

The clinical manifestations are mainly tremor and motor coordination. Animal models are used study changes of electromyogram (EMG) power and frequencies.

Non-Motor Symptoms

Impairments of the autonomic nervous system or sleep architecture are considered very important because they occur prior to any manifestation of motor symptoms. The impairment can be quantified by measuring blood pressure, heart rate variability and changes during the rapid eye movement (REM) sleep stage. These changes are used as markers for early disease detection and disease progression.

Suggested movement disorder research references:

DeAndrade, M. P. et al. (2016). Electromyographic evidence in support of a knock-in mouse model of DYT1 Dystonia. *Mov Disord* 31, 1633-1639, doi:10.1002/mds.26677.

Fleming, S. M. (2011).Cardiovascular autonomic dysfunction in animal models of Parkinson's disease. *J Parkinsons Dis* 1, 321-327, doi: 10.3233/JPD-2011-11042.

Kuzdas, D. et al. (2013). Oligodendroglial alpha-synucleinopathy and MSA-like cardiovascular autonomic failure: experimental evidence. *Exp Neurol* 247, 531-536, doi:10.1016/j.expneurol.2013.02.002.

Verhave, P. S. et al. (2011). REM sleep behavior disorder in the marmoset MPTP model of early Parkinson disease. *Sleep* 34, 1119-1125, doi:10.5665/SLEEP.1174.

Schizophrenia, Attention Deficit Hyperactivity Disorder, and Autism

Although Schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and Autism are classified as different psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), recent research has revealed common genetic roots that may lead to shared symptoms among these psychiatric disorders.

To mimic comparable symptoms in animals, scientists have developed pharmacological and genetic approaches that have led to a focus on objective physiological and behavioral parameters. If such parameters are studied simultaneously, the information gathered would likely offer better insight into the disease progression and of a successful pharmacological treatment.

Shared symptoms/parameters include:

- Hyperactivity - These animals display an enhanced locomotor activity level that can be studied through changes in diurnal activity patterns or changes in sleep patterns
- Changes in social interaction and aggression - Models typically display reduced social interaction with increased aggression, along with altered EEG and Cardiovascular pattern levels
- Increased EEG frequency in gamma bands
- Behavioral impairment and increased arousal state

Suggested psychiatric disorder research references:

Ahnaou, A., Ver Donck, L. & Drinkenburg, W. H. (2014). Blockade of the metabotropic glutamate (mGluR2) modulates arousal through vigilance states transitions: evidence from sleep-wake EEG in rodents. *Behav Brain Res* 270, 56-67, doi:10.1016/j.bbr.2014.05.003.

Cross-Disorder Group of the Psychiatric Genomics, C. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381, 1371-1379, doi:10.1016/S0140-6736(12)62129-1.

Uhlhaas, P. J. & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 11, 100-113, doi:10.1038/nrn2774.

Sleep

Since the discovery of the electroencephalogram in 1924, it is possible to gain insight in the activity of the brain. From that time on, both humans and animals have been extensively studied in the field of sleep research. Such studies have revealed that impaired sleep quality increases the chance of developing cardiovascular and neurological disorders.

With the use of biopotential leads, the different stages during sleep can be identified. Sleep is determined by physiological changes in EEG together with the EMG and EOG (electrooculogram - eye movement). Other variables including temperature, blood pressure and neuroendocrine function can be added to gain extra information about the circadian process.

The EEG recordings are classified into five frequency bands:

- Delta (0.5 to 4 Hz)
- Theta (4 to 8 Hz)
- Alpha (8 to11.5 Hz)
- Beta1 (11.5 to 15 Hz) and Beta2 (15 to 35 Hz)
- Gamma (30-100+ Hz)

According to the frequency contents and EMG/EOG activity, the sleep stages can be subdivided between REM sleep and non-REM sleep (light and slow wave sleep).

List of measured sleep parameters (but not limited to):

- Onset to slow-wave
- Onset to paradoxical (Small Animal)
- Onset to REM (Large Animal)

Suggested sleep research references:

Authier, S., et al. (2009). Video-electroencephalography in conscious non-human primate using radiotelemetry and computerized analysis: refinement of a safety pharmacology model. J*ournal of Pharmacological and Toxicological Methods*, 60.1: 88-93.

Crofts, H. S., et al. (2001). Investigation of the sleep electrocorticogram of the common marmoset (Callithrix jacchus) using radiotelemetry. *Clinical Neurophysiology*, 112.12: 2265-2273.

Tang X, Sanford LD. (2002). Telemetric Recording of Sleep and Home Cage Activity in Mice. *SLEEP*; 25: 677-685.

Traumatic Brain Injury

10 million people suffer a Traumatic Brain Injury (TBI) each year. To improve translation of preclinical results to clinical treatments, experiments in small and large animal models with acute and chronic evaluations following the TBI are recommended.

Several research approaches are used to study the impact of TBI:

Intracranial Pressure

Traumatic brain injury often results in increased intracranial pressure (ICP). TBI researchers often monitor ICP simultaneously with other neurological endpoints to understand the pathophysiology of brain damage. In fact, accurate, continuous monitoring at the preclinical stage is considered critical to the success of treatments in the clinic.

Sleep

Sleep disturbances occur in 30-70% of individuals following traumatic brain injury (TBI). As progression and/or treatment of sleep disturbances can indicate lessening or worsening secondary affects, many researchers incorporate the assessment of sleep into their studies with the use of biopotential leads to monitor both EEG and EMG signals.

Seizure

At least 1 in 5 TBI patients develop epilepsy in the first week post-injury. Risk of developing epilepsy is elevated for at least a decade after injury occurs, suggesting existence of a treatment window. However, preventative treatments have been largely unsuccessful in decreasing long-term risk.

Temperature

The ability to monitor core body temperature helps scientists better understand recovery and treatment approaches. Posttraumatic Hyperthermia (PTH), often occurs post-injury and negatively impacts recovery. Mild therapeutic hypothermia is neuroprotective against multiple brain insults, and can reduce seizure incidence and severity in some cases.

Respiration

Patients with TBI often experience pulmonary complications including respiratory failure, pneumonia, acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Common parameters studied include resistance and compliance and pulmonary function testing.

Suggested TBI research references:

Chavko M. (2015). Advances in Intracranial Pressure Monitoring and Its Significance in Managing Traumatic Brain Injury. *International Journal of Molecular Sciences*. 16:28979-28997.

Kiwon L, Rincon F. (2012). Pulmonary Complications in Patients with Severe Brain Injury. *Critical Care Research and Practice*. Article ID 207247, 8 pages. doi:10.1155/2012/207247.

Thompson HJ, Hoover RC, Tkacs NC, Saatman KE, McIntosh TK. (2005). 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. doi:10.1038/sj.jcbfm.9600008.

Vespa PM, Nuwer MR, Nenov V, et al. (1999). Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *Journal of Neurosurgery*. 91:750-60.

Viola-Saltzman M, Watson NF. (2012). Traumatic Brain Injury and Sleep Disorders. *Neurologic Clinics*. 30(4):1299-1312. doi:10.1016/j.ncl.2012.08.008.

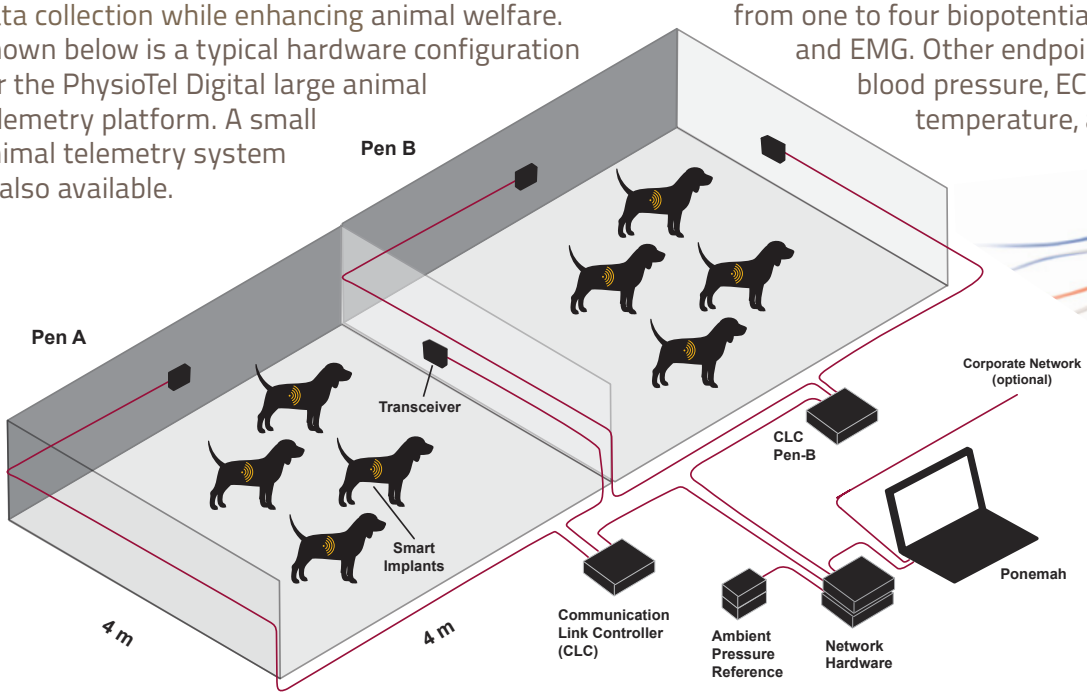
Xiong Y, Mahmood A, Chopp M. (2013). Animal models of traumatic brain injury. *Nature Reviews Neuroscience*; 14: 128-142. doi:10.1038/nrn3407.

Products used in Neuroscience Research

Implantable Telemetry

DSI PhysioTel™ Implantable Telemetry is designed for acquiring physiologic data from conscious, freely moving laboratory animals—providing stress-free data collection while enhancing animal welfare. Shown below is a typical hardware configuration for the PhysioTel Digital large animal telemetry platform. A small animal telemetry system is also available.

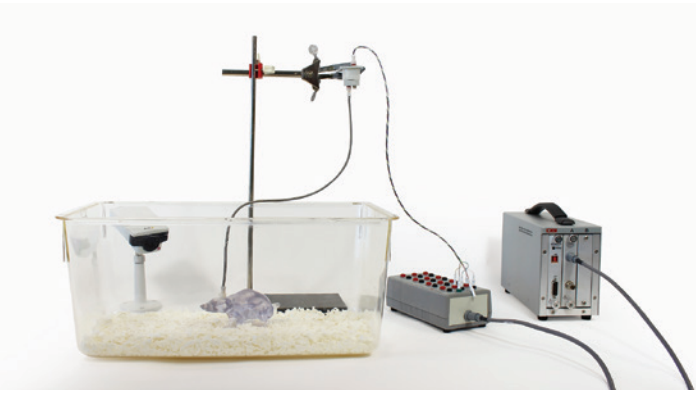
Whether studying neurodegenerative diseases, sleep, or epilepsy, scientists who desire to wirelessly collect physiologic endpoints choose DSI telemetry. Collect from one to four biopotential channels, typically EEG and EMG. Other endpoints frequently include blood pressure, ECG, intracranial pressure, temperature, activity and many more.



Hardwired Monitoring System

DSI's hardwired (tethered) solutions provide a minimally invasive method to offer continuous measurement (EEG, EMG, EOG, etc.) during neuroscience studies with small animals. Tethered solutions allow monitoring of up to 12 EEG/EMG channels per animal.

A setup would include use of electrodes, wires, and commutators. EEG and/or EMG signals from this tethered approach are brought into **DSI's Ponemah™** software platform by the use of digital signal conditioners/amplifiers.

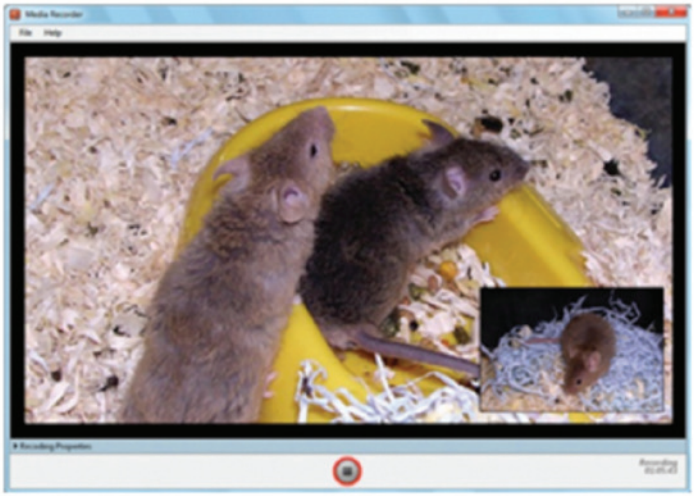


Respiratory Endpoints

DSI's FinePointe software and hardware allow end users to obtain respiratory endpoints that may be associated with neurological disorders. Endpoints may include respiratory rate, tidal volume, airway resistance, and pulmonary compliance. Unrestrained whole body plethysmography is a quick, easy to screen test compounds and run longitudinal studies. The anesthetized resistance/compliance model and pulmonary function testing system are available if additional respiratory endpoints are required.

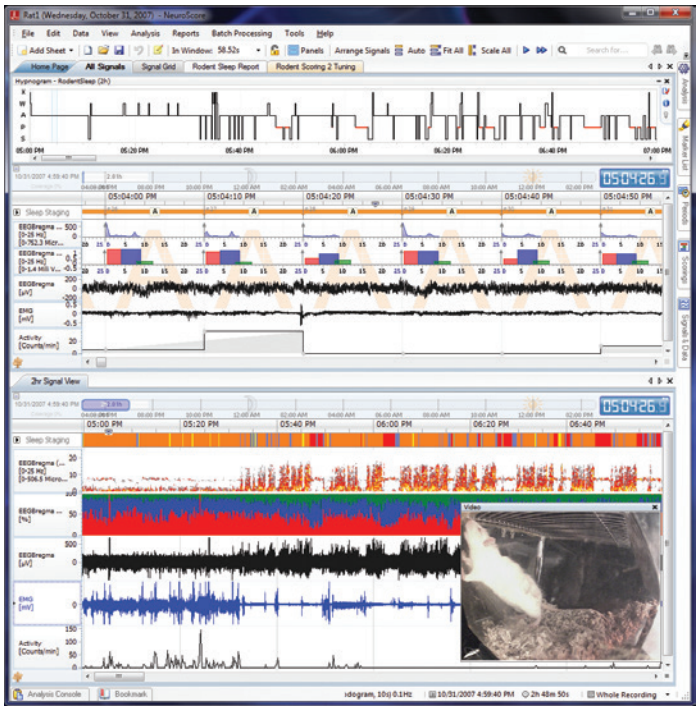
Video Acquisition

DSI has partnered with Noldus Information Technology, the leading solution provider for human and animal behavioral research for 25 years, to offer scientists a better video experience. By integrating the Noldus Media Recorder and DSI's Ponemah Physiology Platform, scientists can synchronize physiologic and video data to help confirm various sleep stages and verify EEG seizure activity.



NeuroScore Software

After data acquisition has taken place, **DSI's NeuroScore™** software can be used to efficiently analyze chronic data sets common to neuroscience studies. This modular platform offers sleep scoring, seizure detection, video synchronization, and batch processing capabilities.



Ponemah

Ponemah is a complete physiological data acquisition and analysis system ranging from an acquisition interface unit and software to a complete PC-based scientific workstation. The multi-application platform uses state-of-the-art digital technology to automate the data analysis routinely performed in physiology, pharmacology and toxicology laboratories. The Ponemah system controls the flow of data from the collection of the incoming signal to data summary and final report generation.

DSI ▪ 119 14th St. NW, Suite 100, St. Paul, MN 55112
T: +1 (651) 481 7400 ▪ F: +1 (651) 481 7404 ▪ Toll free: 1 (800) 262 9687
www.datasci.com ▪ information@datasci.com

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