

Project Title: In Vivo AxCaliber MRI

Principal Investigator: Peter J. Basser, Ph.D.

ABSTRACT

Traumatic brain injury (TBI), a signature injury in both Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), continues to pose complex clinical challenges for both diagnosis and therapy of affected service personnel. Generally, TBI patients present with a spectrum of symptoms. Their management is complicated by the time after injury they are evaluated (e.g., hyperacutely, acutely, or chronically) and the likely presence of previous TBI. The relationship between the mechanism of injury and the neuropathological and neurophysiological sequelae is still poorly understood. No established computational models exist to predict the stress and strain distributions in the brain following TBI, or suggest their neurological consequences. No biomarkers exist to predict disability or help follow recovery of TBI patients. No established treatments have been effective, providing comprehensive long term improvement in patient status.

Given this state of affairs, the development of non-invasive, *in vivo* quantitative imaging biomarkers, that measure key neuroanatomical features of white matter pathways in the CNS, would be transformative, potentially improving TBI diagnosis, therapy, understanding its pathophysiology, the development and assessment of computational and animal models, and the assessment of the efficacy of rehabilitation and regenerative strategies.

Diffusion Tensor MRI (DTI), an MRI method we invented and developed at the NIH has already been shown to be useful in assessing changes in the brain following TBI. The Fractional Anisotropy (FA), Direction-Encoded Color (DEC) maps, and DTI Tractography can all be used to assess the integrity of potentially affected white matter pathways. The mean apparent diffusion coefficient (ADC) is also sensitive to changes in cellularity and local cell membrane breakdown, providing complementary information about tissue status.

Although DTI is sensitive in characterizing changes in white matter fiber architecture at the gross anatomy length scale, DTI-derived parameters (e.g., the FA and ADC) are not sufficiently specific to enable one to distinguish between and among various disorders or the associated mechanisms that cause these changes. A more comprehensive description of water diffusion in and around axons and within fascicles could address this current limitation of DTI in white matter.

To attempt to improve both the sensitivity and particularly the specificity of diffusion MRI-based biomarkers, we are developing a family of novel “*In vivo* MRI histology methods” that are intended to provide information currently obtainable only by neuropathological analysis of *ex vivo* tissue specimens. These MRI methods can potentially yield more specific information about tissue microstructure and microarchitecture. One example is double Pulsed-Field Gradient (d-PFG) MRI, which measures correlations between net displacements of water molecules. Another example, which is the subject of this grant, is *AxCaliber* MRI, which provides a direct measurement of the axon diameter distribution (ADD) within different white matter pathways.

The ADD is a neuroanatomical quantity, but it plays a critical neurophysiological role since an axon’s diameter scales linearly with its conduction velocity. Moreover, the ADD is related to a fascicle’s maximum rate of transfer of information. The ADD can affect the arrival times of nerve impulses to regions where they project so pathologically induced changes in the ADD potentially can affect the temporal sequencing and relative strength of nerve impulses exchanged between and among different brain regions. A reasonable working hypothesis that we are advancing is that some of the disabilities observed in TBI may result from a change in the ADD, which in turn, can affect the —choreography of neural impulses between different brain regions, resulting in motor impairments, behavioral abnormalities and/or cognitive deficits, depending on the particular white matter pathway(s) affected by the trauma. Such a hypothesis not only could explain the range in severity of TBI symptoms from subtle to severe but also the diversity of symptoms. It is also lends credence to the use of the ADD an early neuroanatomical marker for possible pathological changes leading to impairment in motor performance, behavior, and cognition as well as a sensitive quantitative imaging biomarker for assessing and following the effect of therapeutic interventions.

Project Title: Neuroplasticity in control of executive function after TBI

Principal Investigator: Leonardo G. Cohen, M.D.

ABSTRACT

The purpose of the project is to use functional magnetic neuroimaging (fMRI) and concurrent transcranial magnetic stimulation (TMS) techniques to understand changes in neural connectivity associated with the ability to inhibit a response such as suppressing an undesirable urge (i.e., habitual impulse), a common deficiency after traumatic brain injury (TBI), even with mild TBI. Previous neuroimaging studies investigating changes in brain activation associated with TBI-induced cognitive deficits largely focused on the effect of structural integrity of the brain and task-related regional BOLD signal change. However, the extent of changes in the connectivity of neural networks supporting response inhibition (i.e., functional connectivity) and the strength of causal connections (i.e., effective connectivity) between brain regions after TBI remain unknown. Changes in functional and effective connectivity are likely an important factor underlying functional impairment and recovery after TBI. Understanding how brain regions interact within the functional network engaged in response inhibition has the potential for isolating causes of the deficiency in response inhibition after TBI, and to serve as a basis for developing informed strategies of clinical and rehabilitative interventions for patients with TBI.

The objectives of the study are: 1) to determine whether a specific prefrontal-basal-ganglia (PBG) neural network important for the inhibition of a motor response is also engaged in the suppression of undesirable habitual impulses, 2) to determine the extent to which changes or disruption in the neural connectivity within the PBG inhibitory network can account for the deficiency in response inhibition after mild to moderate traumatic brain injury (mTBI). Specifically, two experimental studies will be carried out. Experiment 1 is designed to determine whether the PBG inhibitory network is engaged in the suppression of an undesirable habitual impulse. Subjects will perform simple response-inhibition tasks during fMRI scans. Experiment 2 will involve simultaneous / concurrent TMS-fMRI techniques with behavioral tasks. Single-pulse TMS during fMRI scans will be applied to the right pre-supplemental area (pre-SMA) and the right inferior-prefrontal cortex (rIPFC) when subjects are at rest. The right pre-SMA and rIPFC are important components of the PBG network. Measuring TMS-induced activation during rest can provide task-independent measurements of the strength of the network connectivity. Task independent network connectivity will be correlated with the fMRI activation within the network when subjects are performing response-inhibition tasks. Concurrent TMS-fMRI approach provides a method in quantifying the extent to which changes in the active (i.e., task-dependent) and resting (i.e., task-independent) neural connectivity within the PBG network is associated with the deficiency in response inhibition after mTBI. Additional behavioral measures, DTI, and high resolution structural MRI images will also be acquired in a separate session for all subjects. We expect that abnormalities in white matter integrity (with diffusion tensor imaging [DTI]) connecting these critical regions will also correlate with task-independent and dependent connectivity.

Project Title: Predicting Outcome after Mild TBI: Brain Indices of Structure and Function

Principal Investigator: Connie C. Duncan, Ph.D.

ABSTRACT

The purpose of this prospective, longitudinal cohort study is to improve the ability to predict posttraumatic stress disorder (PTSD) in service members who have sustained mild traumatic brain injury (TBI). Service members who have sustained impact-induced and blast-induced mild TBI, and for comparison purposes, those who have sustained a trauma-related injury but no TBI (non-TBI), will be assessed over six months to see who develops PTSD, and if there are similarities among those who do. This information would allow development and application of interventions to target vulnerable individuals, with the goal being the prevention of PTSD.

Measures of brain structure (MRI/DTI/SWI) and function (event-related potentials and neurocognitive testing) will be evaluated at baseline to identify potential markers of risk for PTSD. Outcome will be evaluated three and six months after the baseline assessment using psychiatric interviews (Clinician Administered PTSD Scale [CAPS] and the Structured Clinical Interview for DSM-IV [SCID]), as well as measures of post-concussion symptoms, overall health status (including headache), emotional distress, and perceived quality of life. The full brain assessment battery will be re-administered after six months to explore the course of changes in brain structure and function associated with mild TBI. Whereas the effects on brain structure and function of impact-induced TBI have been described, blast-induced TBI is a relatively new injury with largely unknown immediate and long-term effects. Thus, a secondary aim of this study is to characterize brain changes following mild TBI as a function of impact- versus blast induced trauma.

Project Title: PET Imaging of Neuroinflammation in TBI

Principal Investigator: Masahiro Fujita, M.D., Ph.D.

ABSTRACT

Brain damage following traumatic injury (TBI) is a result of direct mechanisms, such as mechanical injury to the brain and vasculature, as well as indirect (secondary) mechanisms, such as inflammation. While CT and MRI can help visualize the result of an inflammatory process in the brain, i.e. the development of cerebral edema, neither can be used to document active inflammation. The peripheral benzodiazepine receptor (PBR), which is recently renamed as translocator protein (TSPO) is highly expressed in microglia and reactive astrocyte, has been used as a biomarker for positron emission tomography (PET), and is suggestive of an active inflammatory process. Recently we developed a new PET ligand [11C]PBR28, which images TSPO with high levels of specific binding. We have successfully applied [11C]PBR28 in a number of brain disorders such as epilepsy, multiple sclerosis, and HIV infection with minor cognitive motor disorder, and are detecting neuroinflammation. The objective of the exploratory phase of this study is to explore whether [11C]PBR28 PET imaging show changes in subjects with TBI who have shown MRI or CT abnormalities.

Twenty subjects diagnosed with TBI and 20 healthy age matched volunteers will be studied.

No study has been performed to detect increase in TSPO in living TBI subjects. Therefore, we start the study with an exploratory phase where we perform [11C]PBR28 PET scans in TBI subjects who have shown abnormalities in MRI or CT. If the results of this exploratory phase are positive, i.e., [11C]PBR28 PET detects increases in TSPO in the areas where MRI or CT have shown abnormalities, we will extend the project to study longitudinal changes in TSPO in those subjects with MRI or CT abnormalities and also extend the study by including TBI subjects who do not show abnormalities in MRI or CT.

Project Title: Field Deployable Near Infra-Red Imaging/EEG Multi-Modality System for Assessing TBI in the Field
Principal Investigator: Amir H. Gandjbakhche, Ph.D.

ABSTRACT

Traumatic brain injury (TBI) is known to be one of the signature injuries of the war veterans. Majority of mild TBI patients, show normal structural magnetic resonance imaging (MRI)/computed tomography (CT) scans, however, they generally experience cognitive deficits, including problems with memory, reduced attention, and the inability to concentrate on a single task. These cognitive impairments, if not diagnosed and treated properly, could significantly impact patient's quality of life. Although, rehabilitation techniques can be employed to improve TBI related cognitive deficits, the need for functional imaging technologies that could help physicians to select the most effective recovery method for each individual, still remains.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive technique which employs light to measure the local changes in oxyhemoglobin and deoxyhemoglobin concentrations associated with brain activity. Compared to other well-established brain imaging modalities, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), this technique offers unique features, including having a higher temporal resolution (in order of milliseconds, and having the potential to be developed as a portable system. The technique can also tolerate subject motion to a larger extent than fMRI.

Understanding how brain regions interact with each other during the execution of a cognitive function is also significantly important for studying dynamics of cognitive processes in the brain, which might be impacted during the brain injury. Combining NIRS with Electroencephalography (EEG) in a multi-modal imaging setting, would allow us to correlate the brain hemodynamic response (from NIRS) to neuronal activity (from EEG) and gain better understanding of the brain functionality.

The ultimate goal of this project is to develop a multi-modal NIRS/EEG portable instrument and capture the dynamics of brain interactions on two different scales by combining EEG (neuronal) and NIRS (hemodynamic) techniques. The instruments will have potential applications both in a hospital environment, to provide greater availability of care to a large segment of the TBI population, and also in the battlefields, to enhance the crucial early triage stages of patient care. The former case is directly relevant to the case of war veterans, and the latter applies not only to in-theatre deployments but also could be utilized in civilian ambulances. Furthermore, the development of such wearable technologies for cortical functional imaging would increase the number and scope of the experiments available to the clinician.

The project involves several different aspects, from theoretical analysis and modeling, to design, implementation, and experimental validation. There are several questions that need to be addressed so that the unique features of the technology could be further used for the population whom existing brain imaging techniques are unsuitable for. The aim of this project is to address these questions.

Project Title: Natural History TBI Civilian Recruitment & Early Imaging

Principal Investigator: Lawrence L Latour, Ph.D.

ABSTRACT

The primary goal of this project is to remove the logistical barriers that inhibit MR imaging of acute TBI patients at two community hospitals (in analogy to what we have done for acute stroke at these centers) so that the natural history of pathology can be documented and studied with imaging. Our objective is to generate natural history data for cohort-based comparisons to serve as the basis for future hypothesis-driven protocols and to contribute to the clinical and physiological understanding of traumatic brain injury (TBI) through the description of manifestations of the injury and the relationship among radiological, hematological, clinical variables and standard functional/cognitive outcome measures

Specific Aims

I. Document and contrast pathology seen on MRI and CT in patients presenting with suspect TBI. Descriptive and inferential statistics will be used to describe the prevalence of specific imaging markers and their relationship to history, demographics, symptoms, admission, and outcome. The working hypothesis is that clinical severity will be associated with the extent and diversity of pathology seen on MRI and CT images.

II. Describe the temporal evolution of imaging markers over the first week, and at 90 days. It is hypothesized that some of the injury seen acutely, such as BBB disruption, cortical ischemia, and extravagated blood, will not be as conspicuous at later time points. Incidence of pathology visible on sub-acute imaging will be estimated in cohorts categorized using acute findings.

III. Provide an evaluation, in confederation with CNRM protocols, in order to:

- a. Compare and contrast imaging findings on military personnel and civilians
- b. Obtain baseline data for computational neuro-anatomical studies
- c. Provide a recruitment pathway to CNRM study and treatment protocols

This is a prospective cohort study. Three hundred male and female adult subjects with history of recent head injury with or suspected non-penetrating acute TBI, will be enrolled. Subjects presenting to the emergency department or trauma service at Suburban Hospital (Bethesda, MD) and Washington Hospital Center (DC) with a history of recent head injury will be studied during the course of their hospital stay and after discharge. Subjects will be stratified according to findings into cohorts for comparison. We anticipate approximately 80% of subjects will be classified as mild TBI, concussion, or no injury, with approximately two thirds of those subjects enrolled being discharged directly from the emergency department.

Subjects will be studied at three time points; i) within 48 hrs of index event, 1-7 days later, and at 90 days. MRI, blood collection, and computerized cognitive testing will be obtained at all three time points. When possible, CT images obtained as part of standard care will be collected to use for study purposes. Study subjects will be given the option of enrolling in protocol No. T-CC-0186 “*Long Term Clinical Correlates of TBI: Imaging, Biomarkers, and Clinical Phenotyping Parameters*”, Leighton Chan, PI for the 90 day study procedures. Data will be shared between the protocols and coded data will be shared with the protocol CNRM-004 “*Biorepository and Informatics Warehousing*”.

Project Title: Radial Diffusion-weighted MRI Acquisitions for Diffusion Tensor imaging of TBI

Principal Investigator: Carlo Pierpaoli, M.D., Ph.D.

ABSTRACT

Traumatic brain injury (TBI) is a major cause of death and disability that has markedly increased with the recent military efforts. Despite the overwhelming need to effectively diagnose and treat TBI patients, no reliable classification system exists. This is in part due to the heterogeneity of TBIs. Developing in vivo imaging methods that are quantitative and noninvasive may provide vital information about tissue microstructure that can be used to generate a pathoanatomical classification system to improve TBI diagnosis and provide relevant biomarkers to measure the effectiveness of proposed treatments.

Diffusion Tensor Magnetic Resonance Imaging (DTI) has become a powerful tool in medicine for non-invasive neurological studies. DTI can provide information about the micro-architecture and integrity of tissue, particularly white matter, through quantitative parameters such as mean diffusivity, fractional anisotropy, directionally encoded color (DEC) maps, and fiber tractography. The utility of DTI has recently been demonstrated in patients with TBI. In fact, changes in calculated DTI parameters have been shown to correlate with clinical outcome during recovery following severe TBI. Because the diffusion tensor is a quantitative measure, it permits comparisons across subjects and over time.

The main purpose of this research is to acquire higher-resolution and better quality DTI data. To achieve this goal a radial fast spin-echo (FSE) sequence has been developed for high-resolution DTI of in vivo brain at 3T that allows sub-millimeter isotropic voxels to be acquired in areas of strong magnetic field inhomogeneity. This sequence not only makes visualization of fine structures possible, but also enables data acquisition in areas with susceptibility variations like those experienced at air/tissue or paramagnetic material/tissue interfaces. However, one issue that needs to be overcome for high-resolution imaging with longer scan time is the gradual movement of the tissue of interest out of the imaging plane. The originally proposed solution uses real-time information about patient position from video to correct the acquisition on the fly. Our current solution also uses real-time information about position to correct the acquisition in real-time, however, the new solution being incorporated utilizes recurrent imaging data to correct for motion.

In the process of comparing the calculated diffusion parameters obtained from data acquired with radial-FSE with those calculated from the standard single-shot echo-planar imaging (SSEPI) sequence, a ubiquitous fat artifact was identified in SSEPI data acquired at 3T, which was likely to affect the quality of radial data also. In the current year, we focused in finding a solution to this problem. We developed and tested a solution for robust fat suppression for in vivo SSEPI and radial DTI and a manuscript detailing our research has been accepted for publication in *Magnetic Resonance in Medicine*.

The main outstanding tasks our research seeks to accomplish in the coming two years include:

- 1) Implementation of achieved technical improvements in all scanners that can be used for clinical CNRM research.
- 2) Development of code for real-time motion correction,
- 3) Scanning of TBI patients with these improved techniques.

Project Title: Independent Predictors of PTSD and Post Concussive Syndrome in OIF/OEF Veterans

Principal Investigator: COL Michael J Roy, MD, MPH

ABSTRACT

Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are linked to worsened physical and mental health, functional impairment, and greater healthcare utilization. TBI is a point of injury diagnosis, but Post Concussive Syndrome (PCS) is analogous to the more persistent PTSD. Current treatments are often ineffective, and many afflicted military service members (SMs) never return to duty. Upon return from deployment, many SMs experience an initial honeymoon period during which symptoms are limited in number and scope, but this is frequently followed by a sharp increase in symptoms within months. Identification of independent predictors of PTSD and PCS upon return from deployment could facilitate early intervention to prevent disability.

The purpose of this study is to perform a comprehensive baseline assessment, to include demographics, neuropsychological assessment, genetic and neuroendocrine assays, brain imaging and synchronization, vestibular, olfactory, and psychophysiological measures, of 128 National Capital Area SMs within 6 weeks post-deployment. Subsequent follow-up evaluations at 3, 6, and 12 months will primarily assess for interim development of PTSD or PCS. We will then conduct serial univariate and multivariate analyses to identify the baseline factors that are most strongly associated with the subsequent development of PTSD and PCS.

This is a prospective cohort study of initially healthy combat veterans, recruited within 6 weeks after return from Iraq or Afghanistan, with serial evaluations to identify both those who develop PTSD or PCS, as well as factors obtained at the time of the initial evaluation that prove to be most strongly associated with subsequent PTSD and PCS.

We anticipate the need to screen at least 260 SMs in order to establish a cohort of 128 who are eligible and agree to participate. Prior psychophysiological measures indicate 102 SMs are needed to have 80% power to discern a relationship between heart rate response to startle and PTSD, so starting with 128 allows for 20% loss to follow up. After obtaining written informed consent from eligible SMs, the baseline assessment will include: a medical history and physical exam, blood samples for genetic and neuroendocrine measures, questionnaires, psychophysiological measures at baseline and in response to stimuli, brain synchronization assessments, imaging studies, posturography, and olfactory, vestibular, and neuropsychological testing. Questionnaires, imaging, serum catecholamine assays, and baseline physiologic measures will be repeated at 3, 6, and 12 months. Univariate analysis will identify all baseline measures associated with the subsequent diagnosis of PTSD or PCS at $p < 0.15$. Multiple regression analysis will then be applied to identify which of these measures are most strongly associated with subsequent PTSD and PCS.

Project Title: The impact of repetitive mild TBI based on a closed head injury model and serial FDGmicroPET.

Principal Investigator: Kimberly Byrnes, Ph.D.

ABSTRACT

Eighty percent of the 1.5 million brain injuries reported every year are classified as ‘mild’ and a majority of these patients are likely to incur a second mild TBI. Early studies have shown that moderate to severe traumatic brain injury (TBI) in humans induces measurable metabolic changes via a neurochemical cascade. Within the first week after a severe brain injury, both regional and cerebral hyperglycolysis (increase in glucose utilization) has been documented in several patients. After peaking, cerebral glucose metabolism decreases to a broad minimum lasting up to one month followed by a slow increase lasting for months. A similar temporal change in glucose utilization has been observed in several rodent models, including lateral fluid percussion (LFP) and open or closed skull controlled cortical impact (CCI) injury in rats, with a metabolic depression lasting from 1 to 10 days. However, even though mild brain injury is the most clinically and militarily relevant injury, glucose metabolism changes have not been studied in mild TBI.

A second injury sustained during this metabolically depressed period may result in worse damage compared to a second injury sustained after recovery. For example, the addition of a second injury, such as ischemia after LFP or multiple mild non-penetrating brain accelerations exacerbates ATP reduction. Worsened locomotor impairment and axonal damage have also been reported after brain injuries separated by 24 hours. This transient vulnerability was observed at injury time separations of 3 and 5 days but not at 7 days. These studies, however, did not correlate this transient conditioning with temporal glucose metabolic recovery or CBF transition. Nor has a study been done to quantify glucose metabolism changes after mild TBI in rodent models. Further, the time dependence of either a protective or a detrimental effect of a second injury is unclear. Therefore, we proposed to investigate the post-injury metabolism of injured rat brains using fluorodeoxyglucose (^{18}F) (FDG)-microPET to determine the effect of different metabolic states on the outcome of a second brain injury.

We hypothesized that FDGmicroPET could be used to visualize and quantify metabolic depression after a mild TBI, and that a second injury inflicted during hyperglycolysis, prior to the onset of the metabolic depression (< 6 hours), will have a protective ‘conditioning’ effect, while an injury inflicted during the injury-induced metabolic depression will synergistically add to functional deficits.

To investigate this hypothesis, we proposed two specific aims. Aim 1 would determine the temporal metabolic profile of the cortex and sub-cortex after mild TBI in rats. This aim utilized the LFP and closed head CCI TBI models, which result in mild functional deficits with diffuse axonal damage to investigate the temporal profile of glucose metabolism using ^{18}F FDG-microPET. Aim 2 would assess the motor and cognitive deficits of a second brain injury inflicted during periods of increased glucose metabolism, reduced glucose metabolism, and metabolic recovery.

Utilizing the model in aim 1 that optimally results in a measurable glucose metabolism change, a second injury would be inflicted at the peak of hyperglycolysis, the peak of hypoglycolysis, the middle of the metabolic depression, or after the metabolism returned to normal levels in order to determine the dependence of functional outcome after a second injury on the brain’s metabolic state. The results from these studies will provide essential information on the role of metabolic recovery on brain vulnerability.

Project Title: Imaging the GABAergic system in PTSD using ^{11}C -flumazenil PET

Principal Investigator: Dima Hammoud, M.D.

ABSTRACT

The primary objective of this study is to contribute to the understanding of Posttraumatic stress disorder (PTSD) in the setting of non-penetrating traumatic brain injury (TBI) through PET imaging using ^{11}C -Flumazenil (FMZ). We will characterize central GABAergic system function in TBI patients with PTSD, and in non-PTSD patients, using PET imaging with ^{11}C -FMZ. We will correlate the degree of ^{11}C -FMZ binding abnormalities with time elapsed since the original physical and/or psychological trauma in PTSD patients.

20 male and female adult subjects will be recruited: 10 patients with TBI and PTSD and 10 healthy volunteers with no PTSD and no history of TBI. The subjects will be recruited from NIH, affiliated hospitals/clinics, in the community and through protocol number: 10-CC-0118.

This is a prospective cohort study of subjects with documented non-penetrating acute TBI, and documented PTSD, as well as healthy control subjects. Subjects will be stratified according to psychiatric evaluation. Subjects will not be treated with experimental therapies as part of the research study. This study will provide no direct benefit to subjects.

The main outcome measure will be the ^{11}C -FMZ binding potential. Other outcome measures will include Magnetic Resonance Imaging (MRI) anatomical findings, and other parameters such as Diffusion Tensor Imaging (DTI) derived parameters.

Project Title: Characterization of the Controlled Cortical Impact Rat Model of TBI Based on Serial Monitoring of Metabolic Changes by MicroPET

Principal Investigator: LCDR Reed Selwyn, Ph.D.

ABSTRACT

TBI is a significant clinical problem accounting for substantial morbidity and mortality in the young. TBI affects approximately 20% (~300,000) of the veterans of Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF) with the majority undiagnosed and untreated. Despite the devastating consequences of TBI, to date there are no effective treatment paradigms that decrease injury acutely, or enhance recovery in the long term. Clinical FDG-PET studies in TBI patients have demonstrated an uncoupling between cerebral oxidative metabolism and cerebral glucose metabolism (CGM). Specifically, oxidative metabolism is reduced by almost 50% in the acute period following TBI while a short-lived increase in CGM is observed. This increase in CGM is followed by a long-term metabolic depression lasting weeks or longer, even though oxidative metabolism normalizes. CGM response and uncoupling phenomenon has been observed in rats following LFP TBI. Since CGM changes in FDGPET in the LFP model in the rat parallels what is observed clinically, new treatments can be evaluated using glucose response as an outcome measure and, thus, facilitating the potential translation to the clinic. In addition, FDG PET has shown abnormalities in TBI patients that were not observed using MRI or CT. Also, over 30% of anatomical lesions on MRI are associated with larger and more widespread metabolic abnormalities. These results suggest that metabolic information provided by FDG-PET complements MRI results and extends the understanding of the brain's response to injury. To date, there has been only one longitudinal study in a LFP rat model in which FDG-microPET (μ PET) monitored changes in CGM at days 2, 5 and 10.¹³ Likewise, natural history for mild, moderate or severe CCI models in the rat have not been reported using FDG- μ PET to evaluate temporal changes in CGM. Furthermore, improvement in quantitative analysis techniques, image processing software, and spatial resolution available on the CNRM μ PET scanner will allow for 3D acquisitions with higher spatial resolution, shorter acquisition times and high sensitivity to changes in CGM in the rat brain.

Aim 1 is a cross-section study in which rats will undergo baseline FDG- μ PET followed by severe CCI injury and subsequent follow-up PET and MRI studies at specific time points. These results will provide a better understanding of the inter-subject variability at specific time points post CCI and will correlate metabolic information with imaging-pathological results.

In Aim 2, the CGM natural history changes of mild, moderate and severe CCI will be determined using FDG- μ PET over 28 days and correlated to MRI anatomical changes and behavioral studies. Inter and intra subject variability of CGM of mild, moderate and severe CCI injured rats will be determined from the serial FDG- μ PET studies providing information on the sensitivity and specificity of the technique to small changes in impact piston depth. Moreover, results from this pilot study will provide valuable data on the biological variance and the reproducibility and reliability of CGM as a biomarker. These results will be available for CNRM investigators to use as basis for determining sample-size and power calculations for novel therapies that may alter metabolism following CCI injury. In addition, by comparing CGM at specific time points for animals used in Aim 1 and 2 it will be possible to determine if there is an effect of multiple anesthesia exposures on CGM and how it may impact future designs of experimental CCI injury studies in rats.

Military Relevance: TBI, with sequelae ranging from mild to severe, has become the signature combat casualty of the conflicts in Iraq and Afghanistan. It accounts for the most frequent causes of morbidity and mortality on the battlefield. Development of hyperacute therapies for head injury is among military medicine's highest priorities. Despite decades of research, however, to date, we have little to offer to improve outcome post-TBI aside from supportive measures and the monitoring and maintenance of intracranial pressure. A greater understanding of the utility of FDG-PET and metabolic changes post-TBI at the basic science level as described in this proposal should lead to translational therapies aimed at increasing cerebral oxidative metabolism and glucose utilization that will result in improvements in cellular survival and regeneration in and around the injured area in the brain.

Project Title: Estimation of Brain Biomechanics using MRI

Principal Investigator: Dzung Pham, Ph.D.

ABSTRACT

In order to better predict and treat impairments resulting from brain trauma, a fundamental understanding of how the brain responds to head motion is required. In this project we will perform the first three-dimensional measurements of the brain during mild head acceleration in living human subjects. The model places a human subject in a magnetic resonance (MR) scanner with an apparatus that supports the head and allows a specific range of motion. The support is latched in such a way that it can be released by the subject, travel a short distance, and come to a rigid stop. The resulting acceleration/deceleration is small (in the range of normal activities, such as jumping from a height of 1-2 feet) but sufficient to derive valuable information on brain biomechanics. Using highly novel MR acquisition and post-processing techniques, deformation of the human brain can be detected and quantified in vivo.

Project Title: Enhanced software tools for analysis of diffusion MRI in TBI and PTSD

Principal Investigator: Carlo Pierpaoli, Ph.D.

ABSTRACT

Diffusion Tensor Imaging (DTI) can provide essential information for the diagnosis of traumatic brain injury (TBI) and could represent an important tool for the assessment of potential brain structural damage in post-traumatic stress disorder (PTSD). Despite these advantages, DTI is still not developed as a robust clinical tool.

The goal of this project is to provide a software pipeline to process DTI data that would significantly improve the accuracy and reproducibility of DTI results for CNRM investigators and potentially for the larger community of scientists and clinicians involved in TBI research.

This goal will be accomplished by adding to an existing state-of-the-art DTI processing pipeline, contained in the software package TORTOISE (www.tortoise.org), four additional modules. These modules include: 1) Dual-compartment tensor analysis for removal of cerebro-spinal fluid (CSF) contamination, 2) Removal of physiological noise artifacts, in particular cardiac pulsation artifacts, in low redundancy DTI data, 3) Analysis of additional tensor features that are informative of local architectural features of white matter (e.g. the skewness of the eigenvalues) and 4) tools for analysis of data for a diffusion specific phantom for the calibration of DTI experiments. The phantom will be provided with instructions for a calibration protocol.

The enhanced software will be distributed to all interested CNRM investigators, and training sessions both with general courses and individualized help sessions will be provided.