

The Study of Cognitive Rehabilitation Effectiveness

The SCORE clinical trial is a randomized controlled treatment trial evaluating the effectiveness of cognitive rehabilitation in post-deployment military service members who sustained a concussion.

*Chapter 7:
Imaging Support
for the Study of
Cognitive
Rehabilitation
Effectiveness
Clinical Trial:
Overview*

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Congress established DVBIC in 1992 after the first Gulf War in response to the need to treat service members with TBI. DVBIC's staff serves as the Defense Department's primary TBI subject matter experts. DVBIC is part of the U.S. Military Health System and is the TBI operational component of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE). Learn more about DVBIC at dvbic.dcoe.mil.

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SCORE Disclaimer

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Chapter 7: Imaging Support for the Study of Cognitive Rehabilitation Effectiveness Clinical Trial: Overview

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Rationale and Significance

The Imaging Support for the Study of Cognitive Rehabilitation Effectiveness (iSCORE) is an adjunct to the congressionally mandated Study of Cognitive Rehabilitation (SCORE) in mild traumatic brain injury (mTBI). These studies are being conducted at the Brooke Army Medical Center (BAMC) Traumatic Brain Injury Service in San Antonio, Texas.

The longitudinal nature of the SCORE project provides a unique opportunity to objectively elucidate imaging biomarkers that are linked to cognitive rehabilitation therapy (CRT) effectiveness in this group, as well as characterize the changes that take place during the course of treatment. Identifying the significant baseline imaging variables that predict CRT response, as well as characterizing the temporal changes in the brain associated with CRT response, will provide unique and clinically valuable information that can be used to inform future efforts at rehabilitation in this patient population.

The iSCORE trial is a joint endeavor between investigators and clinicians within the Traumatic Brain Injury Rehabilitation Clinic at BAMC, investigators in the Defense and Veterans Brain Injury Center, and the neuroradiology staff in the Department of Radiology at BAMC.

A substantial literature in civilian sports injury suggests that cognitive and clinical symptoms follow a predictable course in most people with mTBI, also known as concussion. The majority will demonstrate improvement in the hours and days post-injury.^{2,3} In fact, in one sample of 635 concussed athletes, 85 percent were reportedly symptom free within 1 week of injury.^{2,4} A small case study of special operation forces in Afghanistan confirms initial post-concussion cognitive changes that resolve quickly with proper rest and supportive treatment.⁵ The 15 percent who report ongoing symptoms after injury primarily complain of headaches, dizziness, inability to concentrate, and nausea.

Approaches to the treatment of mTBI in acute and chronic epochs are largely unknown in service members, particularly in regard to cognitive symptoms. In fact, there is a limited research basis for making these important clinical treatment decisions.⁶ The existing studies on mTBI treatment are problematic due to methodological limitations (i.e., small sample sizes, varying definitions of CRT, mixed groups, poor treatment designs) making it difficult to determine the utility of such treatments. Given the number of service members who have sustained TBI during deployment, developing an efficacious, evidenced-based treatment regimen is critical.

SCORE is a prospective, randomized, controlled treatment trial of CRT for Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF) service members with a history of mTBI and

persistent (3 to 24 months post-injury) cognitive complaints. See Chapters 1, Study of Cognitive Rehabilitation Effectiveness Clinical Trial: Overview, and 6, Implementation of the SCORE Clinical Trial in DoD and VA Healthcare Settings: Administrative Considerations, for more details.

Participants are recruited from consecutive patient referrals to the TBI Service at BAMC. Patients who meet eligibility criteria and consent to participate in the treatment trial are randomly assigned to one of the following four, 6-week treatment arms of the study:

1. Psychoeducational control group
2. Non-therapist directed, computerized CRT
3. Therapist-directed individualized CRT
4. Integrated interdisciplinary CRT combined with cognitive-behavioral psychotherapy (CBT)

All participants enrolled in the study continue to receive the standard of care in management of chronic post-concussion symptoms, consistent with the VA/DoD Clinical Practice Guideline for the Management of Concussion/mild TBI,⁴⁵ regardless of treatment assignment. Study participants who are assigned to treatment Arms 2, 3, or 4 receive manualized CRT during the 6-week treatment phase of the study.

Data Collection

Study participants are evaluated before treatment is initiated, as well as at 3, 6, 12, and 18 weeks following the start of treatment. Data collection includes pre-treatment baseline assessments and peri-/post-treatment outcome assessments of demographic information, injury-related variables, self-report inventories, neuropsychological testing, and functional status (e.g., work status; healthcare utilization). Data collected during the course of this study are designed to determine the following:

1. Effectiveness of CRT in mTBI
2. Components of CRT that are the most effective (i.e., psychoeducational materials, therapist direction, CBT, etc.)
3. Individual baseline demographic characteristics (i.e., motivation, participation, co-morbidities, multiple concussions, etc.) that predict better CRT outcomes

Given the rigor and the prospective nature of this study, the extension of SCORE with multimodal imaging data for each participant provides a unique opportunity to better understand the neuropathology following mTBI and the neural mechanisms associated with its treatment. This improved understanding will help predict treatment outcomes.

Filling the Knowledge Gap

Persistent cognitive and emotional complaints following mTBI often lead to reduced functional outcomes that include difficulty with job performance and changes in quality of life. The efficacy of CRT for persistent cognitive complaints in military mTBI is relatively unknown, even though two smaller randomized treatment trials suggest that multidisciplinary cognitive rehabilitation and emotional support improve outcomes (anxiety, depression and working memory) for persons with chronic post-concussion symptoms following mTBI,¹ particularly in those with pre-injury psychiatric disorders.⁷ The underlying mechanisms that determine different treatment outcomes are also unknown, especially their associated findings with medical imaging.

Filling this knowledge gap is the intent of iSCORE. One goal of iSCORE is to develop neurobiologically sound predictive models of response to treatment and long-term outcomes in military personnel with mTBI. In addition, to complement and expand upon the cognitive and behavioral measures of the SCORE study, neurophysiological measures of sense of effort (SOE) that likely play a role in CRT response will be examined.

Thus, data from this clinical trial will have immediate clinical impact in evaluation of patients and in selecting the best treatment approach for a given patient.

iSCORE Aims and Hypotheses

iSCORE was designed to address the following:

- **Aim 1.** To determine and fully characterize baseline structural and functional differences between mTBI patients and extra-cranial trauma control participants using state-of-the-art in vivo structural and functional magnetic resonance imaging (MRI). Emphasis will be placed on determining the significant baseline structural and functional biomarkers that can predict positive CRT response.
 - Hypothesis 1: Reduced cortical thickness in the frontal gyri, anterior cingulate, and medial temporal lobes will be associated with poorer baseline function as well as predict negative response to CRT.
 - Hypothesis 2: Reduced white matter (WM) integrity as measured with diffusion tensor imaging (DTI) and tractography in the arcuate fasciculus, cingulate gyrus, fornix, and uncinate fasciculus will be associated with poorer baseline function as well as predict negative response to CRT.
 - Hypothesis 3: The typical deactivation of the default mode network associated with cognitive activity will be lessened by the presence of mTBI when compared to controls. The strength of the regional connectivity in the resting state network will be associated with CRT effectiveness.
 - Hypothesis 4: Functional connectivity of attention, executive control and SOE networks in the resting state will be associated with baseline function and connectivity coupling strength will predict response to CRT.
- **Aim 2.** To determine and statistically model the effects of treatment on structural and functional MRI biomarkers using longitudinal prospective imaging data collected during and after CRT.
 - Hypothesis 5: Those experiencing a positive response to CRT will demonstrate the most improvement in cortical thickness measures and DTI scalar and tractography metrics.
 - Hypothesis 6: There will be a significant improvement in the resting state and functional MRI (fMRI) task connectivity in those responding positively to CRT.
- **Aim 3.** To examine the relationship between SOE, functional/cognitive outcomes, and functional/resting state fMRI measures.
 - Hypothesis 7: SOE measured during and outside of fMRI assessment, will be increased in mTBI relative to controls and that this increase will be reflected in regional brain activation patterns and effective connectivity.
 - Hypothesis 8: SOE measured during and outside of fMRI assessment will show improvements (reduced cortical activation) over time in patients responding successfully to CRT.

Research Design and Methods

Research Design

iSCORE is a prospective, controlled neuroimaging and neurophysiological evaluation of military service members with mTBI undergoing CRT for persistent (3 to 24 months post-injury) cognitive complaints.

Potential participants include all subjects (N=160) recruited and consented to participate in the randomized clinical trial (SCORE) conducted in the BAMC TBI Service. A summary and objectives of the iSCORE study are provided to individuals following enrollment in SCORE. Those willing to participate are screened for eligibility (no contraindications for MRI). Signed informed consent and Health Insurance Portability and Accountability Act, also known as HIPAA, authorizations are obtained from all eligible participants before enrollment. In addition, this proposal will recruit from the Radiology Department at BAMC 60 participants with extra-cranial orthopedic injuries, who will act as controls for the mTBI patients.

iSCORE inclusion criteria are the same as for the SCORE trial. Participants in the study will be drawn only from the SCORE participants, with the addition of the requirement of no MRI contraindications.

Inclusion criteria

1. Diagnosis of mTBI as defined in the VA/DoD Clinical Practice Guideline for the Management of Concussion/mild TBI⁴⁵ which occurred during deployment in support of OEF/OIF
2. Injury occurred within past 3-24 months
3. Ability to understand and communicate in English

For the control participants, inclusion criteria are:

1. History of extracranial traumatic injury
2. Ages 18 to 40
3. No history of mTBI within the last 3 years
4. No history of mTBI with symptoms lasting longer than 48 hours
5. Ability to understand and communicate in English

Exclusion criteria

Potential participants are excluded if they have any of the following:

1. Any concurrent medical conditions (e.g., blindness)
2. Major psychiatric disorders (e.g., psychosis)
3. Neurologic disorder (e.g., seizure disorder)
4. Documented history of moderate or severe TBI
5. History of penetrating brain injury
6. Spinal cord injury with loss of use in upper extremities

In addition, potential participants are excluded if using narcotic pain medications daily (exclusion criteria for SCORE as well) or if they have any MRI contraindications (i.e., metal in body, pregnancy).

A standard clinical form was used to assess each participant for MRI contraindications. Given the mechanism of injury in many of these patients (e.g., improvised explosive device), particular attention is paid to screen potential participants for shrapnel or other metal exposure.

Assessment Schedule

Once enrolled, this study requires a minimum of three and a maximum of five encounters. The number of encounters with research team members depends on the time since participants sustained their last mTBI. Regardless of when the injury occurred, each participant is assessed at baseline (week before entering CRT), 3 weeks into CRT (treatment midpoint), and the week following treatment completion. Additional assessment time points for participants with more recent injuries are added at 3 and 6 months post treatment.

Behavioral assessment measures

Self-administered behavioral assessments are administered at baseline, the week following treatment completion, 3 months post-treatment completion, and 6 months post-treatment completion. See Table 7.1 for a description of behavioral measures.

Table 7.1. Behavioral Measure Descriptions

Behavioral Measures	Description
Profile of Mood States	A widely used instrument to determine common mood states. This is a 65-item list of adjectives of mood (e.g., unhappy, exhausted, lively) with an associated Likert scale. ⁸
Perceived Stress Scale	A widely used 10-item scale used to assess the degree to which situations in one's life are appraised as stressful. Items were designed to assess how unpredictable, uncontrollable, and overloaded respondents feel. ⁹
NEO Five Factor Inventory	A widely used instrument comprised of 60 items. The instrument is based upon the five-factor model of personality and measures openness, conscientiousness, extraversion, agreeableness, and neuroticism. ³
Behavioral Inhibition/Activation Scale	This scale is a 24-item Likert-type personality scale developed to assess motivational responses to reward and punishment. ¹⁰
Centers for Epidemiological Studies-Depression	This widely used 10-item depression inventory has been frequently used in mild traumatic brain injury ⁹⁴ to assess depressive type feelings and behaviors during the past week. ¹¹
Satisfaction with Life Scale	This brief instrument is a 5-item test designed to measure global cognitive judgments of satisfaction with one's life. ¹²
Revised Social Anhedonia Scale	This 40-item scale assesses any decrease in pleasure derived from interpersonal sources and non-physical stimuli. ¹³
Revised Physical Anhedonia Scale	This 61-item instrument assesses any decrease in pleasure with typically pleasurable physical stimuli such as food, sex, and settings. ¹³

These measures are supplementary to the behavioral and cognitive measures administered by SCORE and assess several aspects of mood, personality, and quality of life that might impact response to CRT or be impacted by CRT. Time for assessment is approximately 35 minutes.

In addition to these measures, the World Health Organization Brief Quality of Life is administered at the last time point assessed for each participant as a secondary outcome measure. This 26-item

instrument was designed to assess the individual’s quality of life perceptions in the context of their individual culture and value system¹⁴ and will be used to evaluate the effects of CRT on the quality of life in these participants.

Sense of effort testing

To complement and expand upon the cognitive and behavioral measures in SCORE, neurophysiologic measures of SOE will be collected inside and outside the scanner. SOE is assessed outside the scanner using the Effort Expenditure for Rewards Task (EEfRT).¹⁵ This computer-administered paradigm is based on the concurrent choice paradigm,¹⁶ and in a series of repeated trials, requires participants to choose

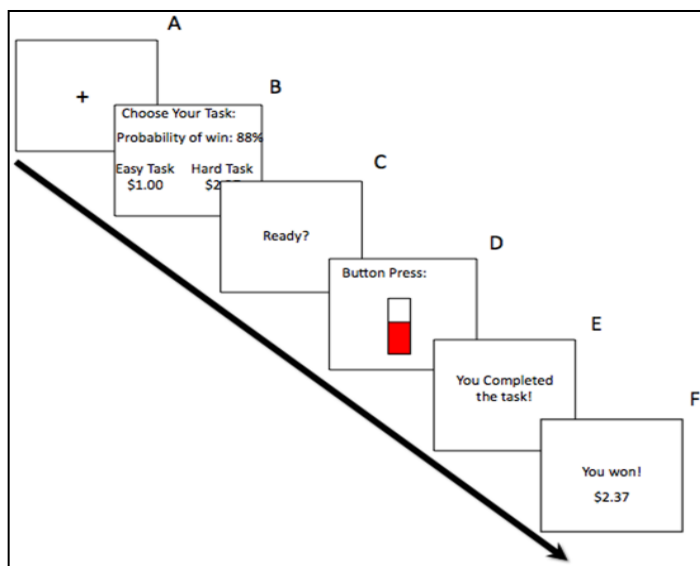


Figure 7.1. Schematic representation of EEfRT trial

between performing a “hard-task” or an “easy-task” to earn a variable amount of money. See schematic diagram of a single trial in Figure 7.1.

In addition to the varying reward magnitude, trials are also presented with differing probability levels for reward receipt. Combined, the choice allows the examiner to determine how much effort-based decision making is modulated by reward magnitude and/or the probability of reward receipt. The measurements obtained from completion of this task include the percentage of hard task choices for a given probability and reward value.

Inside the scanner, the Iowa Oral Performance Instrument (IOPI) is used to measure SOE. Pressure exerted on an air-filled bulb using the hand is detected and displayed digitally by a light-emitting diode (LED) display on the IOPI, and output to a computer via a custom-designed hardware interface (18.4 mV/kPa amplification; A:D 8-bit conversion; 88 Hz sampling rate). The output is linear up to at least 250 kPa, well within the functional range needed for this study.

Using the IOPI, SOE is assessed using two tasks: 1) Percent effort (%E), and 2) Constant effort (CE) tasks. Additionally, the determination of strength is necessary to establish a target performance level for the CE task. The order of the tasks is fixed so that the groups will have similar experiences before each task, allowing for direct comparison of tasks across groups. Differential carry-over of task effects between groups cannot be ruled out, however.

Each participant’s maximum strength (Pmax) is assessed outside the scanner by asking the participant to “squeeze as hard as you can” on the IOPI hand-bulb. The maximum over three trials will be used as a reference for the other two tasks.

Inside the scanner, participants squeeze the IOPI bulb for 5 seconds at 10 different levels of effort, from 10 to 90 percent in 10 percent

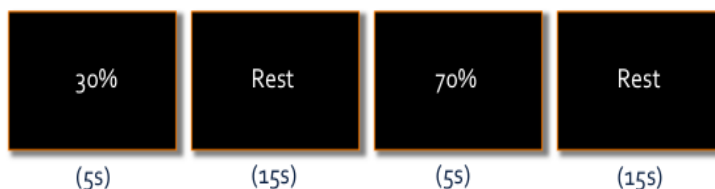


Figure 7.2. Estimated effort schematic

increments, randomly ordered without replacement (see Figure 7.2), according to procedures described elsewhere.¹⁷

The investigator instructs the participant to “squeeze to x percent of your maximum effort” for 5 seconds, and then they are allowed to rest for 15 seconds. Participants perform this task three times for each of the 10 effort levels without feedback. In addition to the imaging data, the raw data from the instrumentation is analyzed by plotting the targeted effort level against the Pmax to create a curve for each trial.

The CE task is conducted according to the method published previously.¹⁸ Briefly, subjects squeeze the bulb viewing a display to achieve the desired starting level (see Figure 7.3). The display is



Figure 7.3. Constant effort schematic

adjusted so that a bar in the middle of the display represents 25 percent, 50 percent, or 75 percent of the subject’s Pmax. Subjects are instructed to adjust the middle bar to match the height of the two stationary bars by adjusting their effort on the bulb. They are given 5 seconds before a blank screen comes up for 30 seconds, during which the

subject must maintain the same effort. Then the subject is given 60 seconds of rest before the next trial is presented.

CE trials result in pressure-by-time curves usually characterized by an exponential decay to a non-zero asymptote. The curves will be fitted to the equation $F(t) = \exp(b - a*t) + c$, where a represents the rate of pressure decay, c is the asymptote or residual pressure, and b is the antilog of eKc , from which the **y-intercept [the value of $F(t)$ at $t=0$]** can be determined. The time constant (**TC**), defined as the inverse of the parameter a in the fitted exponential equation, will be used to characterize the rate of declining pressure early in each trial as effort is held constant. The TC essentially represents the amount of time it takes for the pressure curve to decrease to approximately one-third of its total excursion.

MRI assessment measures and post-processing methods

Regardless of time point, each participant will undergo MRI assessment. The baseline, the week following treatment completion, 3-month post- treatment completion, and 6-month post-treatment completion scanning session will include the following MRI sequences:

- T1 Alzheimer’s Disease Neuroimaging Initiative (ADNI) volumetric anatomical
- Proton density (PD)/T2 dual echo
- Fluid attenuated inversion recovery (FLAIR)
- Susceptibility weighted image (SWI)
- 64 direction diffusion weighted image
- Blood oxygen level dependent (BOLD) resting state functional image
- Two task-dependent functional MR images
- Computed spectral imaging (CSI)
- Single voxel spectroscopy image (magnetic resonance spectroscopy, or MRS)

The specific parameters for each sequence are provided in Table 7.2. The 3-week MRI assessment is abbreviated and only includes the T1 ADNI volumetric anatomical, the BOLD resting state functional image, and the two task dependent functional MR images.

Table 7.2. Protocol for Anatomic, DTI, and fMRI

Sequence	Slices	Thickness/ Gap (mm)	FOV (mm)	Nominal voxel size	Reconstructed voxel size	Time	Other Parameters	Purpose
Sagittal 3D MPRAGE	176	1.0/0.5	256	1.0 / 1.0 / 1.0	0.5 / 0.5 / 1.00	6:02	TE/TR=2.6/2530 (ms), 512x512 matrix, Flip angle 7°, SENSE factor 2	3D high quality volumetric data Coregister to fMRI
Axial FLAIR	25	5.0/1.0	240	0.75 / 1.19 /5.00		3:00	TE/TI/TR=105 /1100/10000 (ms)	Lesion analysis Detect abnormalities
Axial FFE	46	3.0/0.0	256	0.80 / 0.80 /3.0	0.80 / 0.80 / 3.0	4:43	TE/TR=67/5770 (ms)	Lesion analysis FFE to detect blood product
Axial DTI (64 direction)	56	2.5/0.75	256	1.8 / 1.8 / 1.8	2.7 / 2.7 / 2.5	4:34 X 2	TE/TR=96/6600 (ms), foldover direction=AP, fat shift direction=P, b=0 and 1000 s/mm ² , two acquisitions and post averages	DWI and FA map to measure WM integrity
MRS	1	120/100 3D Box	240	7.5 / 7.5 /13.75	3.75 / 3.75 /6.87	4:11	TE/TR=135/1500; Centered of central brain including frontal lobe white matter and cortex, some of corpus callosum, and basal ganglia	3D CSI spectroscopy
MRS	1	2.5/0.0	240	25x25x20	25x25x20	11:00	TE/TR=30/1250; F2 spectral width 2000Hz over right hippocampus	Single voxel spectroscopy, metabolite evaluation
Axial Bold fMRI		3.5/0.2 interleaved	240	3.43 / 3.43 / 3.0	3.43 / 3.43 / 3.0	8:23	TE/TR=30/2500; SENSE factor 2.0, Flip angle 90°, foldover direction=AP, fat shift direction=P, dynamic scans=245	Task fMRI (effective connectivity)
Axial BOLD fMRI EPI	40	3.0/0.3 interleaved	240	3.43 / 3.43 / 3.0	3.43 / 3.43 / 3.0	8:23	TE/TR=30/3370 (ms), 120x120 matrix, SENSE factor 2.0, Flip angle 90°, foldover direction=AP, fat shift direction=P, dynamic scans=245	Resting state fMRI (functional connectivity)
AP=anterior to posterior BOLD=Blood Oxygen Level Dependent COSY= Correlated Spectroscopy DTI=diffusion tensor imaging DWI=diffusion weighted imaging EPI= echo planar imaging, Note: Total scanning time with additional preparatory survey scan(s) is approximately 75 minutes.			FA=fractional anisotropy FFE=fast field echo FLAIR=fluid attenuated inversion FOV=field of view MPRAGE=magnetization prepared gradient-echo sequence MRS=magnetic resonance spectroscopy			P=posterior SENSE=sensitivity encoding TE=echo time TI=inversion time TR=repetition time WM=white matter		

Review of MRI Findings

A board-certified neuroradiologist at BAMC, independent of group identification or outcome data, will review each participant's MR images. The images are reviewed for clinical abnormalities and/or clinical findings that might negatively affect CRT. Unexpected incidental findings result in clinical referrals to appropriate clinical specialties for additional assessment and subsequent treatment.

Image storage and data management

Imaging data will become part of the permanent clinical record for each active duty service member and stored in the picture archiving and communication system (PACS) in the BAMC Department of Radiology at. For the purposes of this clinical trial, imaging data will be retrieved from the PACS system and then stored in a de-identified/coded fashion (i.e., removing personal identifiers from the header) using a unique study-specific ID assigned when each participant is consented. Data will be stored on a secured study-dedicated computer system with redundant disk array (i.e., Redundant Array of Inexpensive Disks).

Structural imaging morphometry

Structural imaging analyses will include several automated and semi-automated processing routines to examine cortical and subcortical regions of interest. Structural imaging will include a T1-weighted magnetization prepared gradient-echo, or MPRAGE, volumetric sequence and the dual echo PD/T2 image. The T1 weighted sequence will be the primary scan of interest when examining the structural imaging data, while the T2 sequence will facilitate the integration of structural and DTI data by providing an intermediate registration target for the DTI data.

The T1 weighted sequence will proceed through automated and semi-automated processing steps including post-processing using the FreeSurfer software image analysis suite. Details of the procedures are described in journal articles published in 1999, 2000, and 2002.¹⁹⁻²¹ This processing includes motion correction of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical WM and deep gray matter (GM) volumetric structures (including hippocampus, amygdala, ventricles)¹⁹ intensity normalization, tessellation of the GM-WM boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue classes¹⁹.

Once the cortical models are complete, parcellation of the cerebral cortex into regions is performed based on gyral and sulcal structure. This method utilizes both intensity and continuity information from the entire 3-D MR volume in segmentation and deformation procedures to quantify cortical thickness. FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and field strengths.

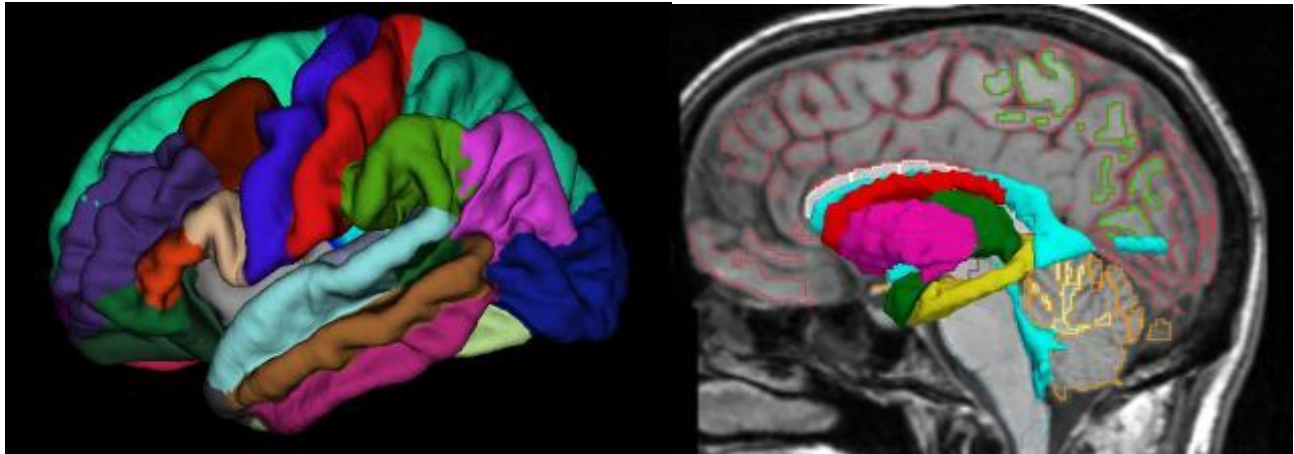


Figure 7.4. FreeSurfer cerebral cortex (left) and subcortical (right) segmentation examples

Recent versions of FreeSurfer also provide additional quantitative analyses of hippocampal subfields utilizing probabilistic maps generated from high resolution imaging of healthy adults.²² FreeSurfer routines have been shown to reliably and validly produce cortical and subcortical segmentation maps that can be quantified and examined for volume/area abnormalities (see Figure 7.4).

In the baseline data (Aim 1), we will focus on regions of interest (ROIs) that have been consistently described in the TBI literature as being primarily affected, including whole brain volume, gross and regional frontal/temporal lobe, hippocampal, and amygdala volumes and shape, as well as ventricular volume and shape. In addition, we will examine cortical thickness within and between participants using the image-based statistical tools in FreeSurfer (i.e., Qdec, mri_glmfit).

These morphometric features will be examined in the context of other clinical findings including head trauma load and cognitive/emotional findings.

Compared to cross-sectional studies, a longitudinal design can significantly reduce the effect of inter-individual morphological variability. To accomplish Aim 2, the longitudinal processing tools in FreeSurfer, which have been optimized for the purposes of interrogating prospective imaging data, will be used. The longitudinal scheme is designed to be unbiased with respect to the time point by creating a template volume using the imaging data from each time point.

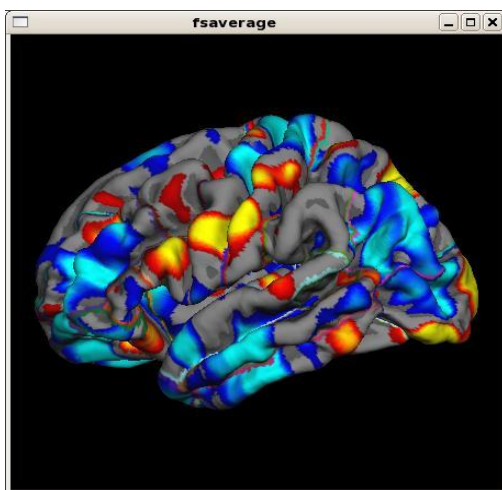


Figure 7.5. Illustration of change in an individual subject over time. Hot colors indicate more significant change over time

There are three basic steps involved. First, each imaging data set is processed using the default FreeSurfer processing routine (see earlier description). Second, a subject-specific temporally unbiased template is created using the default segmentation and surface reconstructions generated in the first step. Third, each imaging dataset is reprocessed substituting the default template with the new individual template image.

Data processed in this way can then be examined using the image based statistical tools within FreeSurfer to examine the location and rate of change within individual subjects over time (see Figure 7.5). In addition, analyses of critical clinical (i.e., CRT type, SOE, cognitive testing results) and

demographic (i.e., age, gender, rank) covariates can be examined to determine the effects of CRT on structural brain images.

Susceptibility weighted imaging

Susceptibility weighted imaging (SWI) has been shown to be sensitive to micro-hemorrhages that occur in the context of physical trauma to the central nervous system. More importantly, it has been shown to be predictive of functional outcome in patients with TBI.

This sequence will be analyzed using both automated and semi-automated methods for quantifying the number and volume of micro-hemorrhagic foci. This will be accomplished at two levels.

First, trained individuals will do a simple count of hemorrhagic lesions visualized with SWI. Two separate raters unaware of diagnosis, CRT assignment, or time point will undertake counting. To ensure validity of the counts, inter- and intra-rater reliability will be examined by randomly reinserting data sets already counted for recounting within and across raters and monitored by staff not involved in the counting. Any differences will be resolved with consultation between raters.

Second, two raters will manually trace each lesion. The number of voxels occupied by each lesion will then be summed across slices resulting in a volume measure in millimeters³. Reliability will be monitored in a similar fashion as described above with regards to the lesion counting.

Lesion count and volume in the baseline data can be used to address Aim 1 by first examining the difference in these measures between mTBI patients and controls and second by determining the predictive ability of the measures to predict response to CRT.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) has been shown to be sensitive to abnormalities in mild TBI patients highlighting the potential of this method to detect subtle abnormalities in the micro/macro structure of white matter integrity caused by physical forces of trauma. Diffusion imaging will consist of a 64-direction scan that will be used to quantify diffusion scalar metrics (fractional anisotropy [FA], mean diffusivity [MD], axial and radial diffusion) within the defined regions of interest. The increased number of directions used in this protocol will also improve the resolution of orientation information, especially within areas of complex white matter where crossing or kissing fibers complicate tractography algorithms.

Selection of neuroanatomic sites for analysis were guided by the literature on neuropathology of TBI documenting vulnerability of parasagittal regions to diffuse axonal injury,²³ recent reports of DTI in civilian TBI²⁴⁻²⁸ and military cohorts,²⁹ and studies documenting the development of reliable tract of interest methods. We will utilize several methods to examine high contrast diffusion imaging group and individual abnormalities associated with TBI and the effects of CRT in this cohort.

Initially, we will perform group analyses using FMRIB software library's (FSL's) Diffusion Toolkit (FDT). This method includes preprocessing of images including eddy current correction to correct for distortions for different gradient directions and simple head motion. Diffusion tensors and maps of FA, MD and eigenvalues will be generated using DTIFit in FSL. Group differences can be accomplished in a voxelwise analysis using FSL's Tract Based Spatial Statistics (TBSS).³⁰

Fitting a tensor model to the raw diffusion data using FDT will create the scalar maps. Using FMRIB's nonlinear image registration tool, known as FNIRT, all the diffusion images are then realigned to a standard space (i.e., MNI). An averaged scalar metric image is created for the group

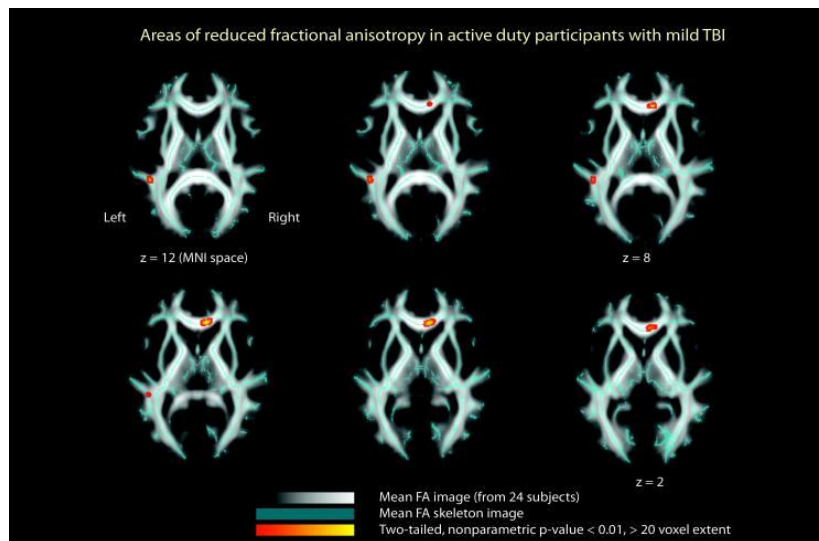


Figure 7.6. Illustration of TBSS method using blast injury pilot data

based statistics (Aim 1). In addition, the baseline imaging abnormalities associated with negative response to CRT (Aim 1) also can be examined.

However, TBSS has several weaknesses that may affect findings. First, because it uses a group analysis approach, subtle and not so subtle individual abnormalities with unique spatial distributions may not overlap sufficiently to produce statistically significant differences. To identify the unique spatial distribution of DTI abnormalities, the normative data from the orthopedic extra-cranial injured participants will be used to develop a DTI template to which individual TBI patients can be compared directly (see Preliminary Data Section for an example of findings using this method).

With consultation from Dr. Martha Shenton's group at the Brigham and Women's Hospital in Boston, Massachusetts, templates for each scalar metric of interest will be developed separately by first registering images to a common space (i.e., Montreal Neurological Institute, known as MNI) across the range of control participants.

Conceptually, average images that include the voxel-wise mean and standard deviation can be derived across the range of control participants. This will result in a template image containing at each imaging voxel the mean and standard deviation for each of the scalar metric maps (FA, ADC, axial and radial diffusivity). Finally, statistical comparisons to the template image can be accomplished using z-tests, where the scalar maps of a single subject are compared to the template scalar map on a voxel-wise basis in atlas space. This type of analysis should improve our ability to capture unique abnormalities within subjects and may be important in predicting the variable response to CRT (Aim 1). Particular attention will be paid to spatial distributions that may predict response to CRT by collapsing individual label maps across the group of CRT responders to determine any optimal spatial patterns.

Second, TBSS assumes that registration between and across subjects is accurate. Even though registration has greatly improved over the years, it is still vulnerable to individual variation in subject-specific anatomy as well as partial volume effects and errors especially in regions containing areas of both high and low anisotropy such as around ventricles.²⁸ Therefore, each participant will undergo additional tract based analyses.

and then thinned (skeletonized) to include only the tracts common across the group (See Figure 7.6).

Projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. This type of analysis extends analysis to the whole brain and mitigates the concern about interoperator reliability, because it is operator-independent. In this fashion, it is possible to interrogate the differences between mTBI patients and demographically matched controls using image-

The main advantage of tractography is that the whole fiber bundle, instead of just a fragment, as with ROI methods, can be evaluated. Furthermore, small branches that otherwise would be cut off during ROI drawing, or registered incorrectly during normalization in a voxel-based morphometry (VBM) study, can now be followed and quantified.

Additionally, fiber crossings can be solved with advanced fiber tracking algorithms, where voxels that do not belong to the fiber bundle (even if characterized by high FA values) can be excluded from analysis.³¹

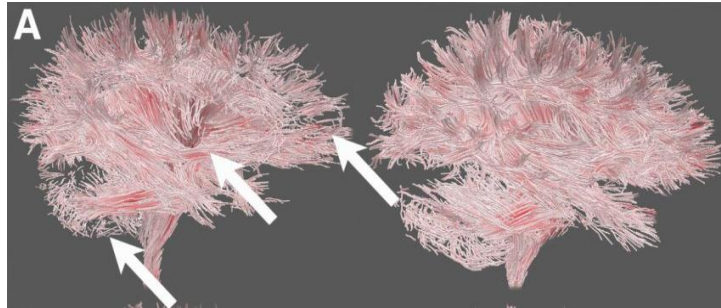


Figure 7.7. Global tractography maps illustrating the difference between TBI and control participants. Arrows point to areas where tractography algorithms fail, indicating white matter abnormalities

This method provides three-dimensional reconstruction of WM pathways (see Figure 7.7), and has been used to measure tracts of interest across a range of patient populations. There are multiple algorithms and software solutions (e.g., 3D Slicer, TrackVis, DTI Studio, etc.) that have been validated for examining tract-based statistics among several important tracts

of interest, including the cingulate bundle, arcuate fasciculus, fornix, corpus callosum, uncinate fasciculus, and the cerebellar peduncles. Average FA along the length of tracts, number of tracts, and average length of tracts are examples of various quantitative features in tractography analyses. More specifically, probabilistic or stochastic tractography methods that estimate the probability of connectivity distribution using morphometric and/or functional imaging activation sites will be used to constrain the generation of tracts.

Functional magnetic resonance imaging

fMRI has been shown to be sensitive to differential blood flow activation abnormalities in the context of TBI, including persistent default network and inhibition task abnormalities. Analysis of both task-related and resting-state data will be performed within subject across time points and between subjects relative to treatment outcome and task performance. Analyses of critical clinical covariates (i.e., CRT type, SOE, cognitive testing results) can also be examined to determine the effects of CRT on task-related brain activations.

Analysis of the acquired fMRI data for localization of cortical regions modulating their activity due to the different experimental conditions as well as for parametric modulations of the hemodynamic response characteristics by these conditions will be performed using SPM8 software. First, data will be pre-processed using a standard protocol. This will include a robust, two-pass image realignment procedure, spatial normalization to the MNI templates (using the unified segmentation approach on the mean functional images to optimize the registration of functional volume space into standardized coordinates) and smoothing by an 8 mm full width/half max Gaussian.

Subsequently, single subject responses to the individual experimental conditions will be modeled in the context of a general linear model. The individual effect size (beta) estimates for all conditions and subjects will then be fed into a second-level analysis of variance including appropriate corrections for data non-sphericity. In this framework of a multi-subject analysis of variance (ANOVA), activations evoked by the different conditions and applying the appropriate voxel-level contrasts will test for differences between the conditions. Treatment-related effects and performance on the effort tasks will be tested by introducing linear and second order covariates reflecting

subjects' response to treatment into this ANOVA model. Inference will be performed at $p < 0.05$, corrected for multiple comparisons by the theory of Gaussian random fields.³² Finally, location of significant effects will be compared with probabilistic cytoarchitectonic maps of the human cerebral cortex, which provide details about its histological organization of the human brain and are available as three-dimensional maps in the same reference space,³³ thereby allowing quantitative analyses of structure-function relationships.³⁴

Dynamic causal modeling

Any connectivity or treatment regulated network properties will be assessed by modeling effective connectivity using dynamic causal modeling (DCM).³⁵ This approach motivated from general systems theory treats the brain as a dynamic input-output system. The inputs are presented by the experimental conditions that are transferred to hidden neuronal states, and finally, an output corresponding to the measured hemodynamic responses is observed. By setting up a factorial model space covering competing hypotheses on the network implementation of predictive coding mechanisms and applying Bayesian model selection procedures, inference on the connectivity architecture of such systems becomes feasible.

Because within DCM the hidden neuronal layer is explicitly modeled via the fitted model parameters, investigation into the effective connectivity within a neural system and the context-dependent changes thereof induced by stimuli or task can be examined. Importantly, explicit modeling of hemodynamic responses robust to changes in neurovascular coupling can be reasonably expected to be sensitive to CRT effects on the functional imaging signal.

DCM will be performed on the fMRI data to examine the effective connectivity between brain regions during task execution. DCM models the brain as a deterministic non-linear system whose inputs (perturbations) are the experimental manipulations and the outputs are the measured signals.

In the standard form, changes in neuronal states **x over time** are represented in the following equation forming the generative model of the neuronal layer. In the formulation of effective connectivity architecture, the intrinsic connectivity matrix **A** represents the task- or process-

$$\frac{dx}{dt} = (A + \sum_{j=1}^m u_j B^{(j)} + xD)x + Cu$$

independent component of inter-regional interactions while the task- dependent modulations in **B** represent the changes in coupling strength brought upon by a particular stimulus or task **u**. The non-linear effects in **D** model the modulatory influence of a particular region on the coupling strength between two other regions (i.e., gating). Finally, the driving inputs **C** reflect direct effects of experimental conditions on the different regions.

The described neuronal model is then augmented by an observation model, which for fMRI consists of the hemodynamic response function based on the biophysically validated balloon model. Based on the acquired experimental data, the model is then fitted using Bayesian inversion, yielding estimated model parameters for the modeled system as well as the model evidence. The latter can be used to infer the most plausible among several competing models, given the observed data.

The posterior estimates of the model parameters as obtained for all subjects in turn may be used for additional assessment of inter-subject reliability of parameter magnitude using a one-sample inference (T-test or Wilcoxon sign test). Likewise, comparison of connection strength between conditions and as a function of time (pre- and post-treatment) is feasible by the corresponding two-

sample inference procedure. Finally, parameter expression also may be analyzed as a function of an external covariate that will be employed to test for a relationship between the individual connectivity parameters and experimental conditions.

Resting state analysis

Group independent component analysis (ICA),³⁶ will be used to analyze the resting state fMRI data, using GIFT software. GIFT software results in the detection of consistent resting state networks across multiple sessions at least over a period of several weeks,³⁸ a strategy we have used before.³⁹ Using the ICA, we will analyze the resting state fMRI data for each test point (pre-post treatment). Prior to ICA analysis, principal component analysis (PCA) will be used to reduce data. The number of ICA components will be set to 20 because a previous study has shown that 20 components can yield robust ICA results for various brain networks with a moderate computation load. Spatially independent components will be back-reconstructed^{40,41} for all participants and all test points.

One of the challenges in ICA analysis is the selection of components of interest among several identified independent components.³⁸ Proposed ICA algorithms^{42,43} are able to deal with this challenge. These algorithms use some prior temporal⁴² or spatial information⁴³ on the fMRI data to search the components of interest, and are therefore referred to as “semi-blind” ICA algorithms. Here the focus is on the default mode network nodes and the attention network regions as priors to constrain the two different resting state analyses. All independent components will be converted to **z** maps.³⁷ Each **z**-score represents the fit of a specific voxel BOLD time course to the time course of the group averaged component.⁴⁴ The **z** maps will be tested for the strength of the connectivity (i.e., signal synchronization) of each voxel to the entire spatial component using standard SPM statistical analysis package.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure concentrations of different chemical components within brain tissue. MRS has the potential to elucidate various metabolic abnormalities that might reflect degenerative and/or reparative processes in TBI patients. There are many techniques for performing MRS, each with its own inherent advantages and disadvantages. In this study MRS data will be acquired using two separate techniques, single voxel proton MRS (1H-MRS) and multi-voxel chemical shift imaging (CSI).

The most commonly performed method of spectroscopy involves using single-voxel acquisition with either point resolved excitation or stimulated echo acquisition mode. The three main variables that are adjusted using single voxel methods are the echo time (TE), voxel placement, and voxel size. Another benefit is the slightly greater signal to noise ratio, which is seen with this acquisition with better peak homogeneity and water suppression in general.

For this clinical trial, a single voxel will be placed in the pons of each patient, as this appears to be a focal point for blast injury and a point of leverage for traumatic injury. Output data will be scaled based on the single-voxel unsuppressed water reference spectrum and then converted into the spectroscopy format acceptable to LCModel software.

The following metabolites will be fitted and quantified by LCModel for analysis: creatine, choline, myoinositol, *N*-acetylaspartate (NAA), glutamate/glutamine (Glx), and lactate. Utilizing the values from these various metabolites, we will examine the differences between the TBI patients and controls as well as how well any abnormalities in these values predict response to CRT (Aim 1). Changes over time can be used to determine any metabolic benefits of CRT (Aim 2), although these

data will need to be interpreted cautiously in the context of several quality control efforts, including the acquisition of prospective phantom data.

There is a major disadvantage to the single voxel method: Only a single voxel can be placed, limiting the analysis to a single location in the brain. Multiple acquisitions must be obtained, which is not a problem when evaluating a single patient, but in a large trial, evaluating large numbers of patients at different time points, assuring that the voxel placement and analysis are in the same location, can be very difficult. Even though the location is likely to demonstrate metabolite changes in response to common traumatic injuries in military service members, there may be additional areas of the brain demonstrating changes.

One solution for the spatial limits of single voxel spectroscopy is CSI, or multivoxel spectroscopy. Multivoxel methods employ an interrogation of a slab of voxels in either two or three dimensions. These methods are very similar in technique utilizing a slab acquired and then divided into smaller voxels (see Figure 7.8) that can then be analyzed evaluating individual spectra, a map of relative metabolite levels, or a map of metabolite ratios. The major benefit of improved area of coverage is slightly offset in these techniques by an increase in the noise of each individual spectrum and a propensity to encounter more water suppression difficulties. However, this type of imaging may capture the potentially unique spatial distribution of metabolite changes resulting from a head injury, which could better inform clinical decisions regarding TBI.

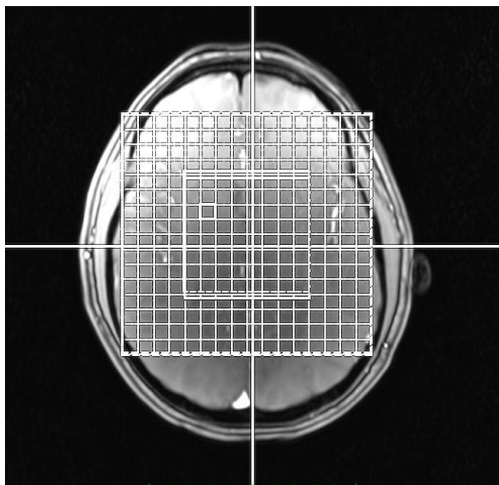


Figure 7.8. Illustration depicting the grid approach of CSI that will be utilized

Therefore, CSI will be acquired through the middle of brain using a short echo time to monitor more metabolites that could not be seen at long TE. In each subject, a single-voxel unsuppressed water spectrum also will be obtained in the gray matter at the occipital region as an internal reference, based on the assumption that the water content of that region is relatively constant (approximately 78 percent). Similar to the single voxel data, data will be scaled based on the signal-voxel unsuppressed water reference spectrum and then converted into the spectroscopy format acceptable to LCModel.

The following metabolites will be fitted and quantified: creatine, choline, myoinositol, NAA, Glx, and lactate. Similar to the single voxel analyses, we will utilize the values for each of the metabolites to examine the

differences between the TBI patients and controls as well as how well any abnormalities in these values predict response to CRT (Aim 1). Changes over time can be used to determine any metabolic benefits of CRT (Aim 2).

Data Analysis

Aim 1

To determine and characterize baseline structural and functional differences between mTBI patients and extra-cranial trauma control participants requires a mix of traditional and image based statistical procedures. The image-based statistical approaches are described earlier in the image processing methods. These methods use regression and general linear modeling to interrogate the brain at a voxel level for differences between groups and/or examine the effect of various demographic,

clinical, cognitive, or behavioral measures on image measurements (i.e., volume, thickness, DTI scalar values, or functional activation). Results are often presented as a heat map, where varying colors indicate the significance of the relationship at that particular location (see Figure 7.5).

In addition, the metrics derived from various post-processing methods can also be examined using more traditional statistical approaches including multivariate analysis of covariance and regression methods. At the simplest level, an analysis of covariance with five groups (four CRT groups and one control) with age and gender as covariates will be utilized to determine whether or not groups have similar brain volume, DTI metric, and metabolites at baseline. Furthermore, differences in imaging variables can be examined between the mTBI patients as a group and the demographically matched controls.

When determining the significant baseline structural and functional biomarkers that can predict positive CRT response, we will use logistical regression methods with imaging variables as the independent variables and treatment response as the dependent variable.

Aim 2

In addition to the image-based statistical approach described above, the general approach for investigating hypotheses in Aim 2 will involve models of multivariate imaging and cognitive/behavioral data. Models will be formulated that capture both within- and between-marker variation over time, with a correlation function that relates the contemporaneous values of the two markers and relates lagged values of one marker to current values of the other.

Models of this type have two levels. The first level characterizes within-marker variation over time using a longitudinal model. The second level introduces correlation between two markers using a between-marker correlation matrix. The correlation functions can then be parameterized explicitly as regression functions.⁴⁰ Then, using multivariate models, specific hypotheses about associations between imaging, cognitive, and behavioral variables can be examined. To investigate the effect of treatment, a possibly time-varying treatment indicator can be added to the regression part of the relevant marker model.

Aim 3

To address Aim 3, this data will then be tested using a series of generalized estimating equations in Statistical Package for the Social Sciences testing for the main effects of probability, reward magnitude and 1) trait anhedonia as measured by the Revised Physical and Social Anhedonia Scales, 2) depression as measured by the Centers for Epidemiological Studies-Depression inventory, and 3) behavioral activation as measured by the Behavioral Inhibition/Activation Scale. These data will be analyzed with repeated-measures multivariate analysis of variance, commonly known as MANOVA, with group, structure, and trial as within-subjects factors. Group is defined as a within-subjects factor to allow for paired comparisons of matched participants.

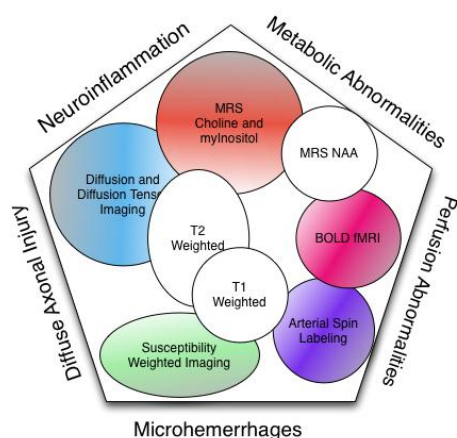


Figure 7.9: Ven diagram illustrating the pathological sensitivity of various MRI sequences

Rationale of multimodal imaging

What is emerging from the current neuroimaging research literature is that MRI variables examined in isolation

provide limited pathological specificity. Future studies of mTBI would benefit from the use of multi-modal imaging methods that exploit the complimentary and unique sensitivities of different imaging modalities (see Figure 7.9). For example, the combination of MRS and structural MRI has the potential to distinguish between two different pathways of injury, inflammatory and non-inflammatory. Studies designed to maximize the dissociative qualities of different imaging modalities have the best potential of establishing pathological specificity not afforded by clinical and/or cognitive variables.

Quality control monitoring

Given the large-scale prospective nature of the study, MRI quality control in such a large study requires several important steps.

First, sequence parameters will be rigorously instituted from the beginning of the study and monitored throughout using automated procedures implemented within the previously described upload system. This will help ensure the use of consistent scan parameters across the subjects.

Second, both an MRS and DTI phantom will be used. Phantom data will determine the consistency of the scanner over time, across patients, and after software upgrades.

Third, a trained rater to determine the quality of each scan will visually examine each scan. Raters will examine each scan for artifacts, complete anatomical coverage, and other issues that might influence automated processes.

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Appendix A: Acronyms and Initialisms

ADNI	Alzheimer’s Disease Neuroimaging Initiative
ANOVA	analysis of variance
BAMC	Brooke Army Medical Center
BOLD	blood oxygen level dependent
CBT	cognitive-behavioral psychotherapy
CE	constant effort
CRT	cognitive rehabilitation therapy
CSI	computed spectral imaging or chemical shift imaging
DCM	dynamic causal modeling
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EEfRT	Effort Expenditure for Rewards Task
FA	fractional anisotropy
FDT	FSL Diffusion Toolkit
FFE	fast field echo
FLAIR	fluid attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FMRIB	Functional MRI of the Brain (group, Oxford, United Kingdom)
FNIRT	FMRIB’s nonlinear image registration tool
FSL	FMRIB Software Library
Glx	glutamate/glutamine (metabolites)
GM	gray matter
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz, or cycles per second
ICA	independent component analysis
IOPI	Iowa Oral Performance Instrument
iSCORE	Imaging Support for the Study of Cognitive Rehabilitation Effectiveness

kPa	kilopascal
LED	light-emitting diode
MANOVA	multivariate analysis of variance
MD	mean diffusivity
MNI	Montreal Neurological Institute
MPRAGE	magnetization prepared gradient-echo
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
Ms	milliseconds
mTBI	mild traumatic brain injury
NAA	<i>N</i> -acetylaspartate (amino acid)
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PACS	picture archiving and communication system
PCA	principal component analysis
PD	proton density
P _{max}	participant's maximum strength
ROI	region of interest
SOE	sense of effort
SWI	susceptibility weighted image
TBSS	Tract Based Spatial Statistics
TC	time constant
TE	echo time
WM	white matter

Appendix B: Resources

Iowa Oral Performance Instrument (IOPI), tool that measures tongue and lip strength. Blaise Medical. www.IOPImedical.com

FreeSurfer, software tools for analysis and visualization of structural and functional brain imaging (MRI) data. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts. <http://surfer.nmr.mgh.harvard.edu/>

LCModel, software for quantitation of proton MRS data. Stephen Provencher Inc., Oakville, Canada. <http://lcmodel.ca>

FMRIB software library, (FSL), a comprehensive library of analysis tools for fMRI, MRI and DTI brain imaging data. <http://www.fmrib.ox.ac.uk/fsl>

SPM8, software for MATLAB for analysis of brain imaging data sequences. www.fil.ion.ucl.ac.uk/spm

GIFT software. <http://icatb.sourceforge.net/>