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Neural and Behavioral Sequelae of Blast-Related Traumatic Brain Injury

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Blast-related traumatic brain injury (TBI), fMRI, DTI, cognition

Traumatic brain injuries (TBI) are a common occurrence from roadside blasts of improvised explosive devices (IEDs). In the proposed cross-sectional study, we aim to apply neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related MTBI. We will accomplish this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients who have experienced blast injuries, 15 civilian MTBI patients with mechanical closed head injuries, 15 military and 15 civilian patients with orthopedic injuries. Year one of the project has been devoted to the development of the necessary infrastructure for the execution of this complex multisite study. A number of development tasks have been undertaken, including hiring and training staff and personnel for the study, developing the cognitive and computational neuropsychological tasks, developing the functional imaging tasks and scanning protocols, and developing the avenues for recruitment of subjects. All of these goals have been accomplished and the accrual of subjects is beginning. We are satisfied that we are beginning the accrual of data that will be of high reliability and integrity. Over the next two years, we will enroll the planned 120 subjects across the two study sites.
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Introduction

Traumatic brain injuries (TBI) are a common occurrence from roadside blasts of improvised explosive devices (IEDs). Like civilian TBI, blast-related TBI can result from mechanical forces in which objects in motion strike the head or the head is forcefully put into motion and strikes an object. TBI from exposure to an explosive blast may also result from a third cause: barotrauma. Blasts produce wave-induced changes in atmospheric pressure, which in turn produce characteristic injuries to vulnerable bodily regions at air-fluid interfaces, such as the middle ear. It is unknown whether the neural and cognitive sequelae of blast-related TBI differ from those resulting from mechanically-induced TBI commonly observed in civilian accidents. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions.

In the proposed cross-sectional study, we aim to apply neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related MTBI. This will be accomplished by comparing neurobehavioral and neuroimaging findings obtained from military personnel who have experienced a blast injury with those obtained from civilians who have experienced TBI from motor vehicle accidents and from military and civilian control participants with orthopedic injuries. We will accomplish this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients who have experienced blast injuries, 15 civilian MTBI patients with mechanical closed head injuries, 15 military and 15 civilian patients with orthopedic injuries.

Body

Year one of the project was devoted to the development of the necessary infrastructure for the execution of this complex multisite study. A number of development tasks have been undertaken to develop the staff and personnel for the study, develop the cognitive and computational tasks, and to establish and validate the reliability of the imaging infrastructure to conduct the study. All of these goals have been accomplished and the accrual of subjects is beginning. While there have been problems over the year, each of them has been successfully managed to the exacting standards of the Principal Investigators. This meticulous work has laid the groundwork for high integrity in data collection. Details regarding each of these tasks are provided below, broken down by category.

Staff recruitment, employment, organization, training. We have hired all required personnel and general orientation and human subjects training was completed for all hired employees at the Cleveland and Houston sites. Christine Reece (Cleveland Clinic Program Coordinator) traveled to Baylor to complete her training on the administration of screening and behavioral tasks. Staff who will administer neuropsychological tests at the two sites have conversed regularly in monthly phone conferences and during visits to develop consistency in test administration procedures.
Neuropsychological and Neurobehavioral procedures

- All tasks were readily identified and purchased, with the exception of the PDA task – ANAM (see below for details). A task manual, including instructions, procedures, scoring materials and data dictionary was created and standardized between the two sites. Christine Reece, site coordinator and research assistant at the Cleveland clinic completed online training to become certified to administer the Stroke Scale which is very similar to the Neurophysical Exam in this study.

- In order to ensure standardization of the performance of neuropsychological measures and neurobehavioral procedures, Ms. Reece underwent training side-by-side with her Houston counterparts on March 10th and 11th. The two sites designed a standardized order of neuropsychological test administration, integrated with other study procedures, to ensure consistency between datasets collected at the two sites.

- The computerized version of the Structured Clinical Interview for the DSM-IV (SCID) was ordered. Unfortunately, the vendor sent the wrong version of the SCID which required the program to be returned and then the correct version was sent. The SCID-IV required presence of a floppy disc drive in the laptop computer used for the study, which was then ordered and installed, allowing the SCID software to be installed and tested. The SCID is now fully functional.

- The Houston site initiated the development of a comprehensive database for the recording of neurobehavioral and neuropsychological data at both sites. Through the process of telephone conferences and visits, the forms and entry fields were developed and standardized. At the August 25 conference call, the final two forms were completed in the database.

Computerized Neuropsychological test development

- In January, 2009, a task manual, including instructions, procedures, and data dictionary, were drafted and provided to the ANAM test developer (Dennis Reeves) and tasks were programmed. The PDA was shipped to the Cleveland Clinic in early March. It was noted that a task was omitted, one was incorrectly programmed, and another was prone to crashing. A test version of the ANAM battery was shipped to the Cleveland Clinic and after collecting a few sets of pilot data decided to request several changes on two of the tasks in the battery. The PDA has been sent back to Dr. Reeves for additional programming. The reprogrammed ANAM was received by CCF in April and all tasks were tested on several pilot subjects. The results were discussed in a conference call between the CCF and Houston sites on 4/30 and it was determined that details of timing and sensitivity of the “Running Memory” task were inadequate. A conference call with Dennis Reeves was conducted on 5/7 and it was suggested that the Running Memory task be changed to allow for a longer stimulus presentation. It was also noted that touch sensitivity seemed to be inconsistent, as the Houston site in particular was noting a large number of “no response” indications to the stimuli. All of the ANAM Palm Pilot devices were returned to Dennis Reeves for these changes. They were returned in mid-June and underwent repeat pilot testing on June 23rd. The results were satisfactory.
MRI
- **FMRI Task Development:**
  - The two FMRI cognitive tasks for this project, the Stop Signal Task and the Sternberg Item Recognition Task were programmed for use in the scanner by the Cleveland group using the Presentation software platform. The Houston group uses the E-Prime software with an Invivo Eloquence system connected to the Philips scanner console through a coaxial cable. The Integrated Functional Imaging System (IFIS) permits communication between stimulus presentation and scanner computers. Both tasks needed to be reprogrammed into E-Prime 1.1.
  - In late 2008 the Sternberg task was programmed by Cleveland staff, and both the Cleveland and Houston groups reviewed and edited the task parameters for consistency.
  - By early 2009 the Stop Signal task was programmed in E-Prime 1.1, and was piloted on a participant in Cleveland. In order to be run in Houston the task had to be modified to work with fMRI data acquisition equipment at that site, including the IFIS software system. This task required the input of Invivo technical support. On April 30th a final version of the Stop Signal Task, modified for IFIS, was verified as consistent with the intended parameters and sent to Houston.
  - A test of both fMRI cognitive paradigms and the scanner in Houston was conducted the evening of 5/4/2009 using a healthy volunteer subject. Acquisition of sample fMRI data was attempted using the modified versions of the Stop Signal and the Sternberg Item Recognition Tasks. While running these paradigms the Eloquence system did not recognize sync signals transmitted through the coaxial cable and, consequently, the programs did not start at the correct time. However, it was possible to start the programs manually and the paradigms then appeared to run with the correct timing parameters. Testing of the Eloquence system indicated that the hardware was recognizing the sync signals properly and that the problem involved the programs, themselves.
  - Additionally, the test of the fMRI cognitive paradigms in Houston noted that the auditory stop cue for the stop signal task might not be perceived by military personnel due to hearing loss resulting from blast exposure. This issue was discussed between groups during a conference call on 5/7/2009 and, based upon technical limitations and our expectation that some subjects are likely to have hearing impairment, a decision was made to have the Stop Signal task reprogrammed to use a visual “Stop” cue.
  - The task was reprogrammed to integrate the visual “Stop” cue by Cleveland staff in mid-May and was sent to Invivo for modification for the IFIS system (required for use on the Houston Phillips scanner) on May 22nd.
  - The Stop signal task with visual “Stop” cue was tested on a healthy volunteer on the scanner in Cleveland on June 2nd, 2009. Results were …
  - Invivo returned the reprogrammed Stop Signal Task for use on the Houston scanner in early July, and a test on the scanner was run on July 7. The Sternberg Item Recognition Task ran successfully but the Stop Signal Task was noted to have several problems: it did not record responses correctly, and was failing to wait for a scanner pulse to trigger each trial. In a series of conference calls and emails, the problems were identified and solutions were suggested. The task was
sent back to Invivo for further programming.

- On July 14th, the Stop Signal Task was returned to the Houston group. In a test run, it was apparent that the “correct response” settings were not correct. The task was returned to Invivo and received back with corrected “correct response” settings on July 17th.

- Cleveland staff traveled to Houston July 20th-July 22nd for final testing of the fMRI tasks and imaging parameters. On the night of July 20th Cleveland staff identified additional timing problems with the Stop Signal Task and reprogrammed a new Stop Signal task for use in Houston. The following evening both the Stop Signal and the Sternberg Item Recognition paradigm (see Figure 1) were successfully run on a test subject with no additional problems. At that time both the Cleveland and the Houston tasks were complete.

![Figure 1](image_url)

**Figure 1.** FMRI activation images from the Sternberg Item Recognition paradigm run on a single test subject at the Cleveland site. The images show brain activation when items in the task were correctly identified. Activation maps are superimposed on a standardized/idealized anatomical brain image showing the right lateral surface (A), the left lateral surface (B), the right medial surface (C) and the left medial surface (D).

- **Brain Imaging Protocols:** Combining brain imaging data across two research sites, with different scanners and staff at each site, is a considerable technical challenge. Extensive work has been done to establish a good matching of the scan parameters for the Cleveland Clinic (Siemens 3T Trio) and Houston VAMC (Philips 3T Achieva) scanners.
  - The initial challenge was to obtain access to scanner console software features on
the Philips system through the use of a temporary research key. This was accomplished through a research contract between the Philips Healthcare and the Houston VAMC (a comparable license was already available for the Siemens scanner at the Cleveland Clinic).

- During the March 10-11 imaging workshop, Dr. Mark Lowe (Cleveland Clinic MR physicist) traveled to the Houston VAMC to begin the process of identifying scan parameters to produce nearly equivalent fMRI and DTI scans across platforms. Imaging protocols for structural MRI scans, fMRI and DTI were conducted using a phantom to assess and minimize differences in signal-to-noise ratio (SNR) between the two scanners.

- Several problems were identified:
  - The reconstruction on the Phillips scanner (Houston) limits the number of slices acquired within the specified repetition time (TR). The parameters for the brain imaging acquisition had to be modified to maximize the brain coverage/time of acquisition trade-off. A scanning protocol was developed for each site, including a printed sheet to ensure reliability of scanning parameters.
  - During the July 20-22 imaging workshop in Houston, a subject was scanned using the protocol as implemented, it was noted that larger coverage by the anatomic volumes was needed. This was subsequently implemented.
  - Imaging artifacts/differences - considerable eddy current artifact was observed in initial DTI data from Houston. Cleveland staff suggested a re-run of eddy current calibration by service engineer for the Phillips scanner. Subsequent data acquired showed reduction of the eddy current artifact to satisfactory levels.
  - Slow drift of central frequency observed was also observed in DTI data obtained on the Houston scanner (see Figure 2. Image drift over time (due to drift in central frequency of the main magnet of the scanner) accumulated to a total of 5.5 voxels or 11mm by the time the 71st direction was acquired (10 minutes of scanning).

![Figure 2. Images of one slice, three volumes throughout a DTI scan - 1st volume, 36th volume and 71st volume, showing a gradual drift in the phase-encoding direction (note the apparent movement of the phantom along the x-axis of the crosshairs – shown by yellow bar). Image drift over the course of the scan accumulated to a total of 5.5 voxels or 11mm.](image)
  - This was corrected by a change in sequence to calculate the central frequency for every volume, requiring a frequency adjust with relaxation
time of ~ 3 sec every volume, adding several minutes to scan time (see Figure 3).

Figure 3. Images show no drift after the development and implementation of a modified sequence which measures the central frequency during scanning.

- A protocol for managing the imaging data as it is collected was established (see Table 1, below), identifying the staff involved in each step of data analysis, agreeing upon integrity checks for the imaging data, and outlining a timeline for the processing of data.

Table 1. Flow chart for imaging data analysis

<table>
<thead>
<tr>
<th>tasks to complete</th>
<th>person responsible</th>
<th>when to complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>copy from scanner to server</td>
<td>MR technologist</td>
<td>immediately after scanning</td>
</tr>
<tr>
<td>verify data integrity (all scans &amp; data present)</td>
<td>Study coordinator</td>
<td>same day as retrieving data</td>
</tr>
<tr>
<td>Generate README file with description of data</td>
<td>Study coordinator</td>
<td>same day as retrieving data</td>
</tr>
<tr>
<td>backup onto DVD</td>
<td>Study coordinator</td>
<td>same day as retrieving data</td>
</tr>
<tr>
<td>Generate behavioral data logfiles and send to analysts</td>
<td>Study coordinator</td>
<td>same day as retrieving data</td>
</tr>
<tr>
<td>check logfiles for behavioral performance criteria</td>
<td>Study coordinator</td>
<td>within a week of sending logfile</td>
</tr>
<tr>
<td>E-mail study status to analysis specialists</td>
<td>Study coordinator</td>
<td>immediately after checking</td>
</tr>
<tr>
<td>transfer demographic, behavioral data to access database</td>
<td>Study coordinator</td>
<td>weekly</td>
</tr>
<tr>
<td>check server for new data</td>
<td>Analysis specialist 1</td>
<td>within a day of receiving new stimfiles</td>
</tr>
<tr>
<td>generate “stimfiles”</td>
<td>Analysis specialist 2</td>
<td>within the week</td>
</tr>
<tr>
<td>preprocess fMRI data</td>
<td>Analysis specialist 1</td>
<td>within a week</td>
</tr>
<tr>
<td>run individual subject fMRI analysis</td>
<td>Analysis specialist 1</td>
<td>within a week</td>
</tr>
<tr>
<td>copy processed data to server and notify faculty/staff researcher</td>
<td>Analysis specialist 1</td>
<td>within a week</td>
</tr>
<tr>
<td>email Jan that data are copied</td>
<td>Analysis specialist 1</td>
<td>same day data copied to server</td>
</tr>
<tr>
<td>check processed data</td>
<td>faculty/staff</td>
<td>within a week of receiving processed data</td>
</tr>
<tr>
<td>run advanced/group fMRI analyses</td>
<td>faculty/staff</td>
<td>after all subjects preprocessed</td>
</tr>
<tr>
<td>analyze behavioral data</td>
<td>faculty/staff</td>
<td>after all subjects preprocessed</td>
</tr>
<tr>
<td>complete subject checklist spreadsheet that monitors data processing</td>
<td>Study coordinator</td>
<td>weekly</td>
</tr>
</tbody>
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Institutional Review Board approval

- Baylor College of Medicine and Michael E. DeBakey Medical Center Office of Research
- Memorial Hermann Hospital Office of Research
- Cleveland Clinic
- Cleveland VAMC
- MetroHealth Hospital (Cleveland)

Subject recruitment

The detailed flow chart of recruitment procedures has been completed. The final version of the procedural manual for the screening and outcome measures is completed. Challenges to the project have been identified and a number of solutions proposed, pending additional information.

- **Cleveland recruitment:** The two primary venues for subject recruitment in the Cleveland area have been established and a great deal of work has gone into building relationships with referral sources at those sites.
  - **The Carl Stokes Veterans Administration Medical Center:** Neurologists at the VAMC have been involved in meetings and calls with the PI and Ms. Reece. Due to busy clinic schedules, allowing the neurologists little time to discuss the study with potential subjects, it was determined that we would be more successful if our group were physically present in the neurologists’ clinics. In May of 2009, Ms. Reece began the process of obtaining a ‘without compensation’ appointment to the VAMC. This process (including background checks, paperwork, orientations) began on May 5th and was completed on July 16th. On this date we were able to begin the process of submitting an IRB amendment to add Ms. Reece to the VA protocol, which was approved in late summer, 2009. Since that time, Ms. Reece has been attending neurology clinics on a weekly basis and making contact with many potential subjects. This led us to decide that eligibility criteria for the study should be altered to allow inclusion of veterans who have been exposed to more than one blast during combat. Since beginning this recruitment method, we have pre-screened 2 military TBI subjects who have agreed to participate in the study and are currently being scheduled for the study.
  - **Cleveland’s MetroHealth Hospital:** This is the site for recruitment of civilian TBI and orthopedic injury subjects. Initial contacts were made with neurologists and physiatrists at Metro and led to commitments to assist in subject recruitment. However, we have identified that the clinicians at Metro are also overwhelmed with patients and have little time for study recruitment. We are currently considering initiating a similar process to that we have set up at the VA for subject recruitment at Metro.

- **Houston recruitment:** The last test scan for the Houston center was completed on July 22nd, 2009. The first study subject (military TBI, 23 y/o White male) was tested and scanned in Houston on August 4th, 2009. Imaging data were sent to the co-investigators in Cleveland for analysis. All screening and outcome data have been scored and entered into the study database. A second subject has been scheduled for October 2nd, 2009. We also have two more prospective subjects who will be tested and scanned after October 15th. All of these subjects have sustained military TBI. Preparations have also been completed to start the screening of potential civilian subjects at Hermann Hospital.
Key Research Accomplishments

At this point in the project, the key accomplishments have been the development of the infrastructure for conducting the research with the highest possible degree of consistency and integrity between the two sites. This significant accomplishment has taken the work of the entire staff supported on the project and many others. With this solid foundation, we are in position to begin data collection and analysis. The subjects we recruit for the study will be extremely well characterized and matched across groups, based on the integrated involvement of our staff in the recruitment clinics. We anticipate a productive and efficient process based on the painstaking and meticulous work that has been put in to this point. To summarize, the key accomplishments have been:

- Recruiting and training staff to conduct the study
- Development of neuropsychological test battery and training on neurobehavioral examination methods
- Development of computerized cognitive assessment battery, including the production of new computerized tests and the modification of others
- Development of fMRI activation tasks and overcoming numerous obstacles to the seamless synchronization of the tasks at two sites.
- Coordination of brain imaging protocols across the sites despite different manufacturers of the machines.
- Institutional review board approval at multiple locations
- Development of a recruitment infrastructure to support accurate subject identification and characterization.

Reportable outcomes

Given that the initial goals have been to develop the mechanisms by which we will conduct the project, the products of our labor are not yet tangible. The data from this project will be flowing in over the next two years, generating reportable outcomes. We have spent the time over this carefully attending to detail, ensuring the integrity and reliability of the data we will use to arrive at those outcomes.

Conclusion

The first year of the project has been devoted to creating a viable infrastructure to support the collection of data across multiple sites. We have dealt with numerous challenges, some anticipated, some unanticipated. In each case, through the dedicated work of project staff, we have successfully resolved the problems and achieved our goals. We are satisfied that we are beginning the accrual of data that will be of high reliability and integrity. Over the next two years, we will enroll the planned 120 subjects across the two study sites.

References

Given that we are not yet reporting data, we have no references at this time.

Appendices: None at this time