Relationship between attention and emotional function after traumatic brain injury (TBI): probing neural circuitry with transcranial direct current stimulation (tDCS)

I. PURPOSE OF THE STUDY AND BACKGROUND

1. Purpose of the study

The purpose of this pilot study is to investigate the relationship between attention and emotional function post-TBI in an effort to better understand the cognitive mechanisms of emotional processing in patients with TBI, and explore novel treatment strategies to improve emotional regulation using tDCS to modulate activity in the dysfunctional prefrontal-limbic circuits. This project will provide pilot data for extramural funding to expand on this topic.

The specific aims are:

1) To examine the relationship between alerting, orienting and executive attention and emotional recognition, reactivity and regulation in patients with TBI and controls. Hypothesis: Patients with TBI will show clear patterns of attentional and emotional impairment compared with controls. Deficits in executive attention will be related to deficits in emotional appraisal in patients.

2) To determine whether anodal tDCS applied over the dorsolateral prefrontal cortex in conjunction with computer assisted cognitive re-training of attention will lead to greater improvement in attention and/or emotional regulation compared with sham-tDCS + cognitive re-training. Hypothesis: Patients receiving tDCS + cognitive re-training will show greater improvement in post-intervention measures of attention and emotional regulation.

3) To determine whether resting-state activation patterns in the fronto-limbic connections of patients receiving tDCS + cognitive re-training show greater improvement compared with sham-tDCS + cognitive re-training, using functional connectivity MRI (fMRI). Hypothesis: Patients receiving tDCS + cognitive re-training will show higher temporal correlation between the frontal and limbic areas compared to baseline than patients receiving sham tDCS + cognitive re-training.

2. Background and Significance

2.1 Cognitive, emotional and behavioral sequelae of Traumatic Brain Injury (TBI)

According to the CDC/National Center for Injury Prevention and Control, approximately 1.4 million individuals sustain a TBI annually in the United States, of which 235,000 are hospitalized and a large proportion become long-term survivors (Brown, Elovic et al. 2008). Key behavioral disturbances that impact life after TBI include inattention, impulsivity, unawareness of problems, apathy, interpersonal difficulties, communication problems, somatic difficulties, and difficulty with emotional adjustment (Kolitz, Vanderploeg et al. 2003). The mechanisms of these behavioral difficulties and the interrelationships between them are not fully understood, but are crucial for planning appropriate treatments to improve quality of life and reduce the societal burden of TBI. Cognitive disturbances following TBI have been shown to occur in the domains of attention, memory, and other aspects of executive functioning, and patients usually undergo

detailed neuropsychological testing to define the extent of these deficits (Brown, Elovic et al. 2008). However, one recent study examined subjective and objective reports of cognitive and behavioral problems in fifty-four individuals 10 years after TBI and found no strong relationships between subjective reports of cognitive problems and test performances; much stronger relationships were found between subjective reports of cognitive change and emotional state (Draper and Ponsford 2009). The results suggest that improved understanding of the interaction between aspects of cognition and emotion is needed to understand and treat behavioral disturbances post-TBI.

Accurate interpretation of emotion in oneself and others is critical for the successful negotiation of social interactions. Several studies have found that a significant proportion of individuals with TBI are unable to recognize and understand affective information from the face, voice, bodily movement, and posture of others, suggesting that they are impaired in emotional appraisal (Bornhofen and McDonald 2008; McDonald, Bornhofen et al. 2009). Lack of response to emotional stimuli is more prevalent for negative emotions, which may further accentuate the impact of the emotional processing deficit in social situations and contribute significantly to the behavioral dysfunction (Saunders, McDonald et al. 2006). In fact, difficulty identifying emotions has been associated with poorer quality of life, even when depression and anxiety are controlled for, and has also been uniquely associated with executive function deficits (Henry, Phillips et al. 2006).

It has also been suggested that the inability to recognize emotions may be related to deficits in error processing during sustained attention to response tasks (O'Keeffe, Dockree et al. 2004), even when controlled for severity of injury (McAvinue, O'Keeffe et al. 2005). Error feedback has been shown to lead to improvement in emotional recognition (McAvinue, O'Keeffe et al. 2005), but training in focused attention and mimicry have not (McDonald, Bornhofen et al. 2009). One recent study in a group of healthy volunteers found that individuals who had difficulty understanding, processing, or describing emotions (alexithymics) on the Toronto Alexithymia Scale (TAS-20) showed less efficient voluntary control of executive attention (Gu, Liu et al. 2008). Elucidating the relationships between specific aspects of attention and emotional processing inform the development of more effective, clinically translatable treatment strategies for behavioral dysfunction post-TBI.

Behavioral assessments have been used to quantify neurobehavioral outcomes in TBI, among which the Neurobehavioral Rating Scale-Revised (NRS-R) has shown subsets of symptoms that tend to present together (Vanier, Mazaux et al. 2000; McCauley, Levin et al. 2001). These subsets support two broadly defined clinical profiles in TBI (Zappala, Thiebaut de Schotten et al. 2012) - disinhibition, difficulty coping, and social inappropriateness arising from damage to the orbitofrontal networks of the prefrontal cortex (PFC) (Berlin, Rolls et al. 2004; Beer, John et al. 2006); and disinterested, unmotivated pseudo-depression arising from damage to the ventromedial networks of the PFC (Shamay-Tsoory, Tomer et al. 2003; Hornak, O'Doherty et al. 2004; Jorge, Robinson et al. 2004; Leopold, Krueger et al. 2011).The PFC is a crucial region for sophisticated information processing involved in social cognition and emotional intelligence (Forbes and Grafman 2010), and is particularly vulnerable to diffuse axonal injury (DAI) in TBI. While symptom classification with the NRS-R supports this paradigm, there is a gap in our understanding of mechanisms of emotional dysfunction after TBI to link recurrent patterns of behavioral symptoms to specific treatments.

2.2 Diffuse Axonal Injury (DAI) leads to shearing of limbic-prefrontal circuits

TBI is caused by rapid acceleration-deceleration of the brain inside the skull, which causes DAI, or disruption of axonal connections between widespread regions of the brain. However, the extent of DAI is difficult to quantify (Inglese, Makani et al. 2005) as it requires sophisticated imaging techniques that are not widely available (Cohen, Inglese et al. 2007). Realistic in vivo and in vitro models of TBI have been able to demonstrate that DAI, marked by bead-like pattern of beta-amyloid precursor protein (beta-APP) in damaged axons, leads to early degeneration particularly in axons of the cingulum bundle and external capsule leading to disconnection between the cortical and thalamic neurons with delayed apoptotic death in the nuclei of the limbic cortex, the seat of emotions (Dikranian, Cohen et al. 2008; Kilbourne, Kuehn et al. 2009). Similarly, a functional magnetic resonance imaging (fMRI) study that compared patterns of cortical activation in patients with cognitive impairment after TBI and controls during a Stroop task, showed that TBI patients showed decreased activity in the anterior cingulate cortex which may reflect cortical disinhibition attributable to disconnection or compensation for an inefficient cognitive process (Soeda, Nakashima et al. 2005). Many of the behavioral symptoms of TBI such as prominent impulsivity, affective instability, disinhibition, difficulties with substance use, sexual expression, and aggression (McAllister 1992) stem from perseverative behavior that can be explained by damage to the prefrontal cortex and/or disconnection between limbic and prefrontal circuits (Morgan, Romanski et al. 1993; Neave, Nagle et al. 1997; Sotres-Bayon, Cain et al. 2006; Hartley and Phelps 2010). Detailed electrophysiologic and functional neuroimaging studies on the emotion of fear have revealed that interactions between the amygdala and hippocampus in the limbic system and the ventromedial prefrontal cortex (VMPFC) and dorsolateral prefrontal cortex (DLPFC) support the acquisition, storage, retrieval, and regulation of emotional memory (Sotres-Bayon, Cain et al. 2006; Hartley and Phelps 2010).

2.3 Stimulation of dorsolateral prefrontal cortex (DLPFC) and prefrontal-limbic circuit plasticity

A primary goal of cognitive therapy is to enable the patient to more accurately assess a situation, using cognitive strategies such as emotional reappraisal, selective attention and reframing (Gross 1998; Gross and John 1998), in order to regulate the associated emotional responses (Allen, McHugh et al. 2008). In turn, successful treatment of emotional dysregulation (altering the emotional response) after TBI involves the employment of cognitive strategies that require the patient's active engagement and cognitive reappraisal of the event (Olsson and Ochsner 2008; Macnamara, Ochsner et al. 2010). Functional neuroimaging studies on reappraisal of negative affect have consistently reported increased activation of the DLPFC and/or VLPFC and decreased amygdala activation (Wager, Davidson et al. 2008; Ochsner, Hughes et al. 2009; McRae, Hughes et al. 2010). The cognitive regulation of emotion model (Ochsner, Bunge et al. 2002; Delgado, Nearing et al. 2008; Schiller and Delgado 2010) proposes that the DLPFC is involved in the effortful manipulation or interpretation of the emotional stimulus and the VLPFC may have a function in the selection of emotional interpretation (Wager, Davidson et al. 2008). The changes observed in the amygdala are thought to result from top-down modulation of the emotional meaning of the stimulus.

However, patients with TBI show reduced responsiveness to these cognitive strategies (McDonald, Bornhofen et al. 2009). It is possible that stimulation of the residual prefrontal-limbic circuits may increase the efficacy of cognitive interventions for emotional regulation post-TBI. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), particularly anodal tDCS, have been shown to increase excitability and induce long-lasting changes in motor (Bolognini, Pascual-Leone et al. 2009; Edwards, Krebs et al. 2009; Reis, Schambra et al. 2009) and cognitive systems (Miniussi, Cappa et al. 2008). In one study that used cranial electrotherapy for emotional control post-TBI, improvement was seen on all negative mood factors on the Profile Of Mood States on pre-post analysis with alternating current cranial electrotherapy compared with sham-treated and placebo controls, with good tolerance and no significant adverse effects (Smith, Tiberi et al. 1994). TDCS is promising as a relatively simple, non-invasive and safe modality to probe the mechanisms behind cognitive regulation of emotion and investigate whether increasing excitability in prefrontal-limbic pathways, that show reduced excitability post-TBI, will enhance the responsiveness of patients to cognitive strategies that mediate emotional regulation.

The rationale for neuromodulatory effects of tDCS is that at the cellular level, the effect of applied electricity can be considered on three levels (Gross 2007). The applied electric currents may (1) change the electrical state of neurons by triggering or blocking action potentials); (2) change neurotransmitter (e.g. glutamate, dopamine, serotonin) activity or neuromodulator (e.g. endogenous opioids) levels; (3) alter electrical activity within neuronal circuits and networks (e.g., in the complex "mood/affects/emotion regulating" network). All devices delivering non-invasive electrical brain stimulation consist of two components: a unit generating the current and at least two electrodes that enable the current to enter and to leave the brain. The clinical effects of brain stimulation depend on the dose of electricity delivered to the brain and on brain structures that are targeted (Kleiman 2004).

2.4 We will use resting state functional connectivity MRI (fMRI) to directly test the hypothesis that tDCS strengthens fronto-limbic connections involved in emotional processing. Resting state functional connectivity MRI (fMRI) is a recently evolving method from which functional connectivity between distant brain regions is extracted based on low-frequency fluctuations. It allows for the identification of discrete functional networks in the brain. Distributed networks of brains regions have been shown to display temporally correlated patterns of spontaneous activation. This temporal coherence tends to occur in the brain regions that are anatomically connected (Zhang and Raichle 2010). Furthermore, functionally connected networks derived using resting state approaches mirror activation patterns found in task-based functional imaging studies. For clinical purposes, the strength and nature of network connections can be compared in clinical and healthy populations, or resting state can be used in a repeated measures fashion to assess changes within clinical groups. Resting state fMRI had been employed in a small number of studies of TBI patients to examine how network connectivity changes with recovery (Nakamura, Hillary et al. 2009; Hillary, Slocomb et al. 2011).

3. Study Design.

Forty (40) individuals status post TBI with complaints of emotional dysfunction 6 months post-brain injury and twenty-five (25) healthy controls will participate in the study. We expect a

total of 65 subjects to enroll. After obtaining informed consent, they will be screened to ensure that they meet inclusion-exclusion criteria at Visit 1. At visit 1 subjects also will be tested on chemosensory performance evaluation using Sniffin' sticks test and occulomotor movement evaluation using King-Devick test Subjects meeting criteria will then be tested at baseline on neuropsychological assessments, tests of attention (at Visit 2), and the emotional function battery (at Visit 3). The TBI subjects will also undergo resting-state MRI (at Visit 4).

There will be a total of 4 testing visits (visits 1, 2 3 and 4 as described above) prior to starting the study, after which, subjects will receive treatment for visits 5-16). After completion of treatment, the subjects will then be re-tested on the baseline assessments and resting state MRI (Post-intervention Visits 17, 18, 19 and 20the total amount of visits for TBI subjects will be 20.). Healthy Control Subjects will have a total of three testing visits (1-3) only.

The subjects with TBI will then be randomly assigned to one of two groups, each consisting of 10 subjects. Subjects will be randomized by a simple randomization method. They will have a 50/50 chance of being in either group by flipping of a coin. Randomization will be carried out by the PI. Subjects and study personnel performing assessments and data analysis will be blind to group assignment. Only the PI will be unblinded.

The experimental group will receive active tDCS for 20 minutes and computerized cognitive training twice a week for 30-45 minutes for 6 weeks as described below. The control group will receive sham-tDCS 20 minutes and computerized cognitive training for 30-45 minutes twice a week for 6 weeks (12 training sessions). The sham group will not receive real tDCS after completion of the study.

In addition, we will conduct a qualitative interview with each of the subjects. Giorgi's phenomenology (Giorgi 1985; Kleiman 2004) is the method that will be used to describe the experiences of persons undergoing tDCS for treatment of TBI. In-person audio-taped interviews will be conducted at the completion visit by an experienced qualitative interviewer and immediately transcribed verbatim. Interviews are expected to range from 30 minutes to 1 hour. Each of the subjects will be asked the open-ended question, "Please tell me about your experience undergoing tDCS for the treatment of traumatic brain injury." Probes included the following questions: "What was the experience like for you? What should we continue to do and what should we change to make the experience better for patients?" Themes will be derived using the constant comparative method (Sandelowski 1995; Thorne 2000).

II. CHARACTERSTICS OF THE RESEARCH POPULATION

1. **Number of Subjects.** Forty (40) patients with complaints of emotional dysfunction 6 months post-brain injury between 18 and 85 years of age, and twenty-five (25) healthy control subjects will participate. The patients will be referred after discharge from the inpatient brain injury units of Bellevue Hospital and Hospital for Joint Diseases and from their outpatient TBI clinics, and will meet the inclusion-exclusion criteria listed below.

2. **Gender of Subjects.** Both male and female subjects will be included. We will attempt to recruit 50% of male and 50% female subjects. There will be no gender based enrollment restrictions.

3. **Age of Subjects.** The age range of subjects is between 18 and 85 years. The goal of this study is to understand emotional dysfunction in adult patients. Individuals below the age of 18 will be excluded from this study since pediatric TBI is relatively rare and the mechanisms of recovery may differ. Adults over 85 will be excluded to rule out possible confound of co-morbid medical conditions.

4. **Racial and Ethnic Origin.** There are no exclusions based on gender or ethnic group.

5. **Inclusion Criteria.**
   (1) Brain Injury at least 6 months prior.
   (2) Family or self-identification of cognitive or emotional difficulties.
   (3) Unchanged and stabilized medical treatment in the three weeks prior to the screening.

6. **Exclusion Criteria.**
   (1) Any social or medical problem that precludes completion of the protocol.
   (2) Presence of focal motor deficits in the upper extremities.
   (3) Comorbid psychiatric disease such as schizophrenia, or active substance abusers (except nicotine).
   (4) History of craniectomy, active infection, or seizure activity beyond 1 week post-TBI.
   (5) Complicating medical problems such as uncontrolled hypertension, diabetes with signs of neuropathy, and previous neurological illness such as head trauma, prior stroke, epilepsy or demyelinating disease, implanted neuromodulatory or electronic device, metal in head
   (6) Pregnancy

7. **Vulnerable Subjects.** Although TBI patients have some cognitive impairment, we will only consent patients who have been determined to have the capacity to give consent. This determination will be made by Dr. Preeti Raghavan, Dr. Brian Im or Dr. Joseph Rath who are specialists in Brain Injury and will screen patients to determine if they are in a stable cognitive state, whose capacity to give consent is not expected to fluctuate. Only such patients will be enrolled in the study. We will provide information to the subjects in terms that they can fully understand, and capacity to consent will be determined by the subject's verbal understanding of the protocol as determined by the PI. We will not exert any overt or covert coercion, and no financial incentive will be offered. The consent document that each potential subject will be asked to sign will be written in the language that he or she understands, and will be approved by the IRB.

III. METHODS AND PROCEDURES

1. Methods and Procedures.

Patients will sign informed consent and be required to undergo self-assessment (using the TIRR symptom checklist), caregiver assessment (using the Neurobehavioral Functioning Inventory/NFI), and clinician assessment (using NRS-R) to determine neurobehavioral status on study entry. Screening procedures will also include medical history and interview, review of medications and imaging records to ensure that participants meet inclusion/exclusion criteria. Screening procedures will take place at the Motor Recovery Laboratory. The following outcome measures will be administered at baseline and at the end of the 6-week tDCS intervention.

1.1 NeuroCognitive Testing

Neurocognitive Domains	Neurocognitive Measures
Premorbid Functioning	Wechsler Test of Adult Reading (Wechsler 2001) n = 60, a = .95 Time = 10 min
Attention/Working Memory	Trails A (Reitan and Wolfson 1985) n = 25, a = .73 Time = 3 min WAIS Subtest: Digit Span (Wechsler 2008) n ~ 16, a = .94 Time = 4 min Auditory Consonant Trigrams (Peterson and Peterson 1959) n = 20, a = .85 Time = 10 min
Executive Function	Trails B (Reitan and Wolfson 1985) n = 25, a = .87 Time = 5 min Stroop Color-Word (Golden 1978) n ~ 300, a = .83-.91 Time = 5 min
Information Processing Speed	Symbol Digit Modalities Test (Smith 1993) n ~ 110, a = .80 Time = 5 min

n = # items; a = alpha; Time = time to administer

Premorbid Neurocognitive Functioning:
Wechsler Test of Adult Reading (Wechsler 2001). The WTAR estimates pre-morbid intellectual functioning for adults (16-89 years old). Thus, it allows for the identification of relative impairments by detecting discrepancies between levels of premorbid functioning and current functioning. This is particularly important for detecting impairment in higher functioning individuals, who may currently have average performance where they performed in the superior range premorbidly.

Attention/Working Memory:
Trails A (Reitan and Wolfson 1985) is a test of attention and complex visual scanning with a psychomotor speed component. Trails A requires individuals to connect randomly arranged numbers sequentially from lowest to highest number. Like many attention and motor speed measures, Trails A is sensitive to cognitive decline.
Digit Span (Tulsky, Zhu et al. 1997) requires the respondent to recall digits forward and backward and is used to measure working memory. Although forward span usually remains stable and resistant to brain disorders (Lezak, Howieson et al. 2004), individuals with diffuse

damage (e.g., mild TBI) can have mental tracking difficulties and those with more severe TBI can perseverate from previous items (Ruff, Evans et al. 1986). However, backward span is more sensitive to brain disorders, particularly diffuse damage which is characteristic of TBI (Fork, Bartels et al. 2005).

Auditory Consonant Trigrams (Peterson and Peterson 1959) is a test of information processing and divided attention. Three consonants are presented to the individual, who must remember them after intervals of 0, 9, 18 and 36 seconds. During intervals, the person is required to count backwards aloud by threes from different starting points. The task captures everyday experience of momentary distraction and subsequent loss of recently learned information and can identify dysfunction following mild neurological changes (Boone 1999).

Executive Function:

Stroop Color-Word Test (Golden 1978) is a measure of selective attention, verbal processing speed, cognitive flexibility and response inhibition. Poor performance on the Stroop has been found to be associated with frontal systems dysfunction secondary to closed head injury (Trenerry, Crosson et al. 1989). The test is a good discriminator between individuals with TBI and controls (Asikainen, Nybo et al. 1999; Bate, Mathias et al. 2001; Wallesch, Curio et al. 2001).

Trails B (Reitan and Wolfson 1985) is a speeded test of attention, sequencing, mental flexibility, visual search and psychomotor speed. The participant draws lines connecting alternating circles with numbers and letters in sequence. Speed of performance on Trails B is considered to be vulnerable to the subtle cognitive effects of TBI (Lezak 1995; Rasmusson, Carson et al. 1996) . Test-retest reliability over two weeks was reported as .44 in a non-disabled sample and .67 in people with disabilities. Trails B errors are considered valid measures of dorsolateral prefrontal dysfunction (Stuss and Levine 2002).

Information Processing Speed:

Symbol Digit Modalities Test (Smith 1993) is used to measure visual scanning, tracking and motor speed, and it is sensitive to subtle cognitive impairment. A score below 1.5 standard deviations below the mean is indicative of cerebral dysfunction. Performance declines are observed with increasing age, demonstrating that cognitive changes could be detected with this measure. This test is sensitive to brain injury (Lezak 1995; Spreen and Strauss 1998).

Attention Network Test-Revised (ANT-R): The ANT-R is a computerized half-hour test that provides a measure of the efficiency of the attentional networks involved in *alerting, orienting and executive attention*, three aspects of attention that have been shown activate anatomically distinct networks in the brain and are differentially innervated by neuromodulatory systems (Fan, McCandliss et al. 2005). The components of attention described by the ANT encompass the clinical modules such as focused, sustained, selective, alternating, and divided attention (Sohlberg and Mateer 1989), but are better suited to understand the underlying mechanisms. **Alerting** describes the function of tonically maintaining the alert state and physically responding to a warning signal (similar to sustained attention or vigilance), and activates thalamo-cortical networks involving anterior and posterior cortical sites. Efficiency of the alerting network is

examined by changes in reaction time (RT) resulting from a warning signal. **Automatic and voluntary orienting** are involved in the selection of information among multiple sensory inputs (similar to focused attention), and activate the parietal cortex and frontal eye fields. Efficiency of orienting is examined by changes in RT that accompany cues indicating where the target will occur. **Executive attention** describes a set of more complex operations that include detecting and resolving conflicts in order to control thoughts or behaviors (encompasses selective, alternating and divided attention), and activates the anterior cingulate along with several other brain areas. The efficiency of the executive network is examined by requiring the subject to respond by pressing two keys indicating the direction (left or right) of a central arrow surrounded by congruent, incongruent or neutral flankers. However, the three networks are also integrated and interact during functional tasks (Fan, Gu et al. 2009).

Moss Attention Rating Scale (MARS): The Moss Attention Rating Scale (MARS) is a recently developed clinical measure of attention deficits for patients with TBI in the acute inpatient rehabilitation setting (Whyte, Hart et al. 2008). It involves ratings of observed patient behavior by rehabilitation professionals such as nursing staff, occupational therapists, speech therapists etc. The items on the MARS measure deficits in three distinct subcomponents of attention: restlessness/distractibility, sustained/consistent attention, and initiation. *Restlessness/ distractibility* is defined as the ability to inhibit preservative, restless, or irrelevant responses (similar to executive attention on the ANT-R), *sustained/consistent attention* is defined as the ability to sustain attention and persist on tasks (similar to alerting on the ANT-R), and *initiation* is defined as the ability to initiate a task without cueing (similar to orienting on the ANT-R). This scale will be completed by the PI or her delegates during the visit.

Sniffin' Stick test: Sniffin' sticks is a nasal chemosensory performance evaluation test using pen like odor dispensing devices which was introduced by Kobal et al. It comprised three subsets namely an odor identification test, an odor discrimination test, and a test for olfactory threshold. The screening 12 test used in our experiment is a smell identification test with 12 different everyday smells. The patients will name the smells using a multiple choice form which offers four definitions for each pen, among which only one choice would be correct. Chemosensory impairments are common after traumatic brain injury occurring in about 20 percent of patients depending on the mechanism of injury. This test can be used to estimate whether a TBI subject has normal or reduced olfactory capacity and also can be used to understand the relationship between olfactory dysfunction and emotional dysregulation.

King-Devick Test: King-Devick test is an objective way of measuring visual tracking and saccadic eye movements. It is based on the identification of impaired eye movements and saccades which indicates a suboptimal brain function. The subjects are asked to read out the numbers aloud on three different cards from left to right as quickly as possible without making any errors. The final score is the sum of the three test card scores. The charts become progressively difficult form the first to the third. It can be used as a good visual screening test in addition to other test in patients with traumatic brain injury. Deficiency of saccadic eye movements can be an indicator of mild traumatic brain injury or concussion injury.

1.2 Emotional Function Testing

Toronto Alexythimia Scale (TAS): Alexithymia refers to the condition of having trouble identifying and describing emotions, and minimizing emotional experience while focusing attention externally. The TAS is a well-validated and commonly used 20-item instrument to measure alexithymia. It is a self-reported scale with 3 subscales: describing emotions, identifying emotions, and externally-oriented thinking; each item is rated using a 5-point Likert scale whereby 1 = strongly disagree and 5 = strongly agree. The total alexithymia score is the sum of responses to all 20 items, while the score for each subscale factor is the sum of the responses to that subscale: equal to or less than 51 indicates non-alexithymia, equal to or greater than 61 indicates alexithymia. Scores of 52 to 60 indicate possible alexithymia. The scale demonstrates good internal consistency (Cronbach's alpha = .81) and test-retest reliability (.77, $p<.01$). Research using the TAS-20 demonstrates adequate levels of convergent and concurrent validity. The 3 factor structure was found to be theoretically congruent with the alexithymia construct. In addition, it has been found to be stable and replicable across clinical and nonclinical populations (Bagby, Parker et al. 1994; Bagby, Taylor et al. 1994).

Emotional Function Battery

For a comprehensive objective measurement of emotional function, we will employ paradigms from basic affective science to comprehensively assess multiple aspects of emotional function, including emotional recognition, reactivity, and regulation in an ecologically valid manner using film clips (Werner, Roberts et al. 2007; Goodkind, Gyurak et al. 2010).

a. Emotional Reactivity: Patients will view a series of short (~3 min.) film clips that have been selected for their ability to produce particular positive and negative emotions (Gross and Levenson 1993; Gross 2007). During each film, physiological responses will be measured and facial behavior will be coded. Following each film clip patients will be asked to provide subjective ratings of the nature and intensity of their emotional responses to the film clips. **Film clips intended to induce happiness, sadness, fear, and neutral emotion will be used.**

b. Emotion Recognition: Following each of the reactivity film clips described above, participants will also be asked to identify how the characters in the clips were feeling. Answers will be scored based on predetermined correct responses. We will also use picture stimuli to sample a broader range of positive and negative emotions for patients to identify.

c. Emotional Regulation. Both instructed and uninstructed (or spontaneous) emotion regulation will be assessed. Physiological, behavioral and subject responses will be measured under several conditions. Patients will watch films that are known to produce the emotion of disgust under three different instructional conditions: suppress, amplify, no regulation (Gyurak, Goodkind et al. 2012). The emotion of disgust will be used because it is highly arousing and one of the easiest emotions to elicit in the laboratory context. The instructions for each condition are based on previous research, are as follows: *"We will now be showing you a short film clip. It is important to us that you watch the film clip carefully. (***Suppress***: "Watch the film clip carefully. If you have any feelings as you watch the film clip, please try your best not to let those feelings show."*

Amplify*: "Watch the film clip carefully. If you have any feelings as you watch the film clip, try your best to let those feelings show."* **No regulation***: "Watch the clip carefully").*

Startle responses
Startle probes have been used previously as reliable indicators of emotional reactivity and regulation. At the end of the experimental session, we will administer the following startle probes:

a. Unwarned Startle. Emotional reactivity will also be assessed in response to an unwarned, high intensity (115 dB, 100ms) acoustic startle that sounds like a gunshot going off behind the head. The response to this probe consists of two reactions, starting with the primary defensive response, which includes a sequence of motor responses to protect the body(eye closure, shoulder raise) as well as increased electrodermal activity (Ekman, Levenson et al. 1983). The secondary response involves an emotional reaction to the primary startle. The high intensity acoustic startle taps into very basic, low-level aspects of defensive reactivity that are largely brain-stem mediated, as well as more complex aspects of emotion response as individuals reflect on their primary reaction (a typical secondary response includes behavioral displays and self-reports of embarrassment/amusement) (Sturm, Rosen et al. 2006). The simple startle probe also offers the advantage of being a reliable elicitor of response across individuals and being a highly controlled and easily standardized stimulus. Physiological, behavioral, and subjective responses to the unwarned startle will be assessed.

b. Uninstructed Emotion Regulation (anticipated startle). The startle task described above will be repeated, but this time participants will be warned that they will be startled again. A 20-second countdown will signify exactly when the startle will occur. Previous research has shown that people typically "brace" themselves during the countdown and spontaneously recruit regulatory strategies to control their reactions.

1.3 Quality of Life Measurements

Quality of Life will be measured with the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q – SF), a 16-item scale that measures general well-being and, is among the most frequently used outcome measures in psychiatry research (Endicott, Nee et al. 1993). The internal consistency and test–retest coefficients were 0.9 and 0.93, respectfully. Almost all items significantly correlate to the total score and other measures used in the study, with the correlations ranging 0.41–0.81. The responsiveness parameters indicate Q-LES-Q – SF is 80% sensitive and 100% specific. The psychometric properties of the questionnaire indicate that it can produce reliable and valid clinical assessments of quality of life (Stevanovic 2011).

1.4 Resting functional connectivity MRI

T1- and T2-weighted anatomic images will first be obtained to identify focal lesions. 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) will be used to produce reference images of overlying resting state fMRI activation maps. To capture resting state images, subjects will be instructed to keep their eyes closed and to remain motionless in the scanner. Whole-brain images will be collected using a T2-weighted gradientech echoplanar

imaging sequence (repetition time_3000 ms, echo time_35 ms, number of slices_35, slice thickness_4 mm, matrix size_128_128, and field of view_220_220 mm) on a 3T scanner.

1.5 Intervention with active and sham tDCS and computerized cognitive re-training

After providing informed consent approved by the IRB of New York University School of Medicine (NYUSoM), all patients will undergo testing with the above listed outcome measures. They will then be randomized into the two intervention groups, the groups being (1) tDCS + cognitive re-training, and (2) sham tDCS + cognitive re-training. The intervention will be carried out for 20 minutes twice a week for 6 weeks during which the subjects in each group will be engaged in re-training using visual cognitive re-training software programs for 30-45 minutes during each session (www.positscience.com). These re-training programs have been used in patients with TBI and have been shown to be effective (Fisk, Novack et al. 2002; Calvanio, Williams et al. 2004; Novack, Banos et al. 2006). Cognitive re-training will thus be individualized to each patient's cognitive level, but still be systematic, and will not need direct one-on-one supervision by a neuropsychologist.

Transcranial direct current stimulation will be delivered by trained study personnel using the saline-soaked pair of surface sponge electrodes (35 cm2) delivered by a specially developed, battery-driven, constant direct current stimulator (Fisher Wallace Cranial Stimulator, Fisher Wallace Laboratories, New York) with a maximum output of 4 mA (**Fig. 1**). FDA approval: The Cranial Stimulator is an FDA cleared device indicated for application of electrical stimulation to a patient's head to treat insomnia, depression, or anxiety. TBI subjects experience insomnia, depression and anxiety and all subjects enrolled in this study will have some combination of these problems. The purpose of this study is to understand the mechanisms behind the depression, anxiety and insomnia that patients with TBI experience. The hypothesis is that emotional dysregulation contributes to the symptoms. This device will therefore be used in alignment with FDA clearance indications. To stimulate the DLPFC, the anode electrode will be placed over F3 according to the 10–20 international system for EEG electrode placement (Fregni, Boggio et al. 2005) (**Fig.2**). The cathode will be placed over the contralateral supraorbital area.

Fig.1. FDA approved Fisher Wallace Cranial Stimulator.

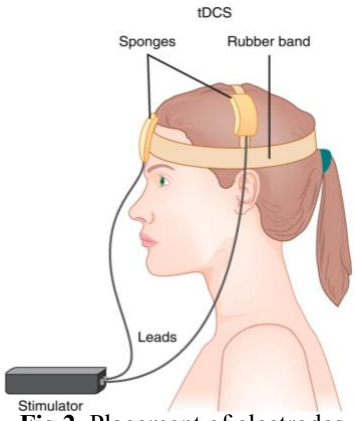

Fig.2. Placement of electrodes (Rosa and Lisanby 2012).

We will focus our investigations on the left DLPFC, as modulation of this area by tDCS has been shown to enhance working memory (Fregni, Boggio et al. 2005) which also demands similar attentional resources as emotional control (Anderson and Knight 2010). A constant current of 2 mA intensity will be applied for 20 min. Patients will feel the current as an itching sensation at both electrodes at the beginning of the stimulation. For sham stimulation, the electrodes will be placed in the same position; however, the stimulator will be turned off after 5 seconds (Siebner, Lang et al. 2004) so that patients will feel the initial itching sensation in the beginning, but receive no current for the rest of the stimulation period; this procedure has

been used to blind patients to the stimulation condition (Nitsche, Liebetanz et al. 2003; Nitsche, Schauenburg et al. 2003).

2. Data Analysis and Data Monitoring.

Power Analysis: This is a pilot feasibility study hence sample size is small and arbitrary. Power analysis from these pilot data will be used to determine sample size in future studies. Subjects with TBI will be randomized to the 2 treatment groups n=10 in each group.

Data Analysis:

1) To examine the relationship between alerting, orienting and executive attention and emotional recognition, reactivity and regulation in patients with TBI and controls.
Hypothesis: Patients with TBI will show clear patterns of attentional and emotional impairment compared with controls. Deficits in executive attention will be related to deficits in emotional appraisal in patients.

Scoring of emotional recognition, reactivity and regulation:

1) **Emotional reactivity film clips:** Physiological responses (cardiac inter-beat, finger pulse amplitude, finger pulse transmission time, ear pulse transmission time, and respiration period) will be recorded, and input from baseline will be subtracted from input across the most intense segment of the clip. Data will be combined into a single aggregate score for each diagnostic group to increase reliability and reduce noise; aggregate scores of patients and controls will then be compared. Facial behavior will be recorded and coded for displays of the target emotion across the most intense segment of the clip; data from patients and controls will then be compared.
2) **Emotional recognition:** Responses to emotion recognition questions, using both the reactivity film clips described above and picture stimuli will be recorded and coded; coded data from patients and controls will be compared.
3) **Emotional regulation with disgust videos:** For the three conditions, physiological responses (as described above) will be recorded, and input from baseline will be subtracted from input across the most intense segment of the clip. Facial behavior will be recorded and coded. Data from patients and controls will be compared.

For coding facial behavior, coders will be blind to the diagnostic status of the participant and code videos with sound muted; coding will be assessed for inter-rater reliability

Pearson's correlation analysis will be performed to examine the relationship between reaction time (RT) scores indicating alerting, orienting and executive attention on the ANT-R and emotional recognition, reactivity and regulation scores. Differences in patients and controls will be computed. We will also correlate the clinical scores on the MARS with the ANT-R and the TAS-20 scores with the emotional battery scores. We expect that deficits in selective or executive attention will be related to deficits in emotional appraisal in the patients.

2) To determine whether anodal tDCS applied over the dorsolateral prefrontal cortex in conjunction with computer assisted cognitive re-training of attention will lead to greater improvement in attention and/or emotional regulation compared with sham-tDCS + cognitive re-training. Hypothesis: Patients receiving tDCS + cognitive re-training will show greater improvement in post-intervention measures of attention and emotional regulation.

A 2 (condition) x 2 (pre and post session) repeated measures ANOVA with a priori orthogonal contrasts will be performed on the variables related to executive attention and emotional appraisal to determine whether there is a difference both within and between groups. This analysis will also provide data for power analysis to determine the sample size for subsequent interventional studies. We expect that patients receiving tDCS + cognitive re-training will show greater improvement in post-intervention measures of attention and emotional regulation.

3) To determine whether the tDCS intervention produces stronger functional connectivity between fronto-limbic networks compared with sham-tDCS. Hypothesis: Patients receiving tDCS + cognitive re-training will show higher temporal correlation between the frontal and limbic areas compared to baseline than patients receiving sham tDCS + cognitive re-training.

Analyses of the resting state fMRI images will be performed using AFNI and FSL software packages (www.fmrib.ox.ac.uk/**fsl**/) using standard procedures. The images will be slice-time corrected, despiked, and motion corrected using AFNI, and time series detrending will be performed. The Brain Extraction Tool (Smith 2002; Smith, Jenkinson et al. 2004; Woolrich, Jbabdi et al. 2009) (BET) will be used to skull strip the images, which will be spatially smoothed using a Gaussian kernel. In the first stage analysis, data from each subject will be individually modeled. The stimulus time course will be convolved with a gamma function and the general linear model (GLM) will be employed with motion parameters as covariates. Additionally we will use temporal bandpass filtering (0.01 Hz < f < 0.1Hz), regression of the six motion parameters and of white matter and cerebrospinal fluid signals. Average resting state time series will be obtained for all the seeds of interest, particularly in the **cingulate motor cortex, and dorsolateral premotor cortex** based on prior studies.(Marshall, Zarahn et al. 2009) FSL FEAT will be employed to find the brain voxels that correlate with the seed time series in each subject. Individual functional connectivity maps will be registered to the MNI space and entered into group-level analyses. Higher level analyses will be carried out using FEAT. Connectivity patterns pre- and post-treatment will be compared for all the seeds of interest. Gaussian random field theory will be used for cluster-level multiple comparisons correction (minimum $Z > 2.3$; $p < .05$, corrected) for the resting state analyses.

Data Monitoring: The PI will be overall responsible for data monitoring.
(1) Types of Data or Events: All accumulated outcome data, enrollment numbers, reportable event data (including adverse reactions and unanticipated problems) and overall compliance with the protocol will be monitored.

(2) Responsibilities and roles for gathering, evaluating, and monitoring the data: The PI will be responsible for monitoring the data collected, including data related to adverse events and

unanticipated problems. Accuracy of data collection from assessments at the Motor Recovery Laboratory will be verified on an ongoing basis and at weekly lab meetings. Compliance with the protocol will be verified by the PI and co-investigators. Independence of judgment will be assured by using independent assessors for outcomes.

(3) Reporting adverse events and unanticipated problems to the monitoring entity: Any adverse reaction to the assessment procedures or intervention procedures, although expected to be minimal, will be reported to and compiled by the PI and Co-PI jointly on an ongoing basis. Reportable events will be reported by the PI to the IRB at NYU Medical Center within 5 business days.

(4) Assessments: Assessments will be performed on a quarterly basis to review and assess all the data or events captured under the Data Monitoring Plan to examine any "unanticipated problems involving risks to participants or others" (i.e., as to whether they are unexpected, related to the research, or harmful).

(5) Criteria for action: If significant research-related and harmful adverse events are found at the quarterly assessments, the study will be terminated.

(6) Procedures for communicating; dissemination of safety information: Outcomes of monitoring entity reviews will be communicated to the IRB at NYU Medical Center annually unless there are reportable adverse events or criteria for action.

3. Data Storage and Confidentiality. Data from assessments at the Motor Recovery Laboratory will be stored securely in the PI's office,, at the Rusk Institute of Rehabilitation Medicine, NYU Medical Center. All data will be labeled by subject codes only, and stored on password-protected computers and/or in locked filing cabinets in the secure offices of the PI. Videotapes of the assessments will be stored on password-protected computers and servers, and backed up on DVDs stored in locked cabinets, in the secure offices of the PI. Videotapes will be stored for at least 3 years following the conclusion of the study, and may be stored indefinitely thereafter. Data collection computers will be in locked, fixed locations (no mobile laptops), password protected, and on local networks. Only the PI and her HIPAA certified delegates will have access to the data.

4. Data Stored for Future use: Data will be labeled with unique codes. Only the PI and the study coordinator will have access to the code. This information will be stored in a password protected shared network drive. There are currently no plans for future research. However new questions may come up from this study that may be addressed by reanalyzing the collected data. If patients specifically request to withdraw their data from the data stored for future use, they must do so in writing, which will be kept on file. Their data will be segregated from the rest of the data and not used for future analysis. However it will be stored for analysis of the present study and as per rules of publication, for at least 7 years post-publication.

IV. RISK/BENEFIT ASSESSMENT

1. **Risk.** TBI subjects may fatigue easily. We will ensure that subjects are given adequate rest breaks to prevent them from becoming fatigued during the experimental protocol. Each testing session will not last longer than 3 hours on a single day. The assessments and videotapes may pose risks to confidentiality which will be minimized by following the protections below. The emotional function videos will assess physiological responses to neutral, happiness, sadness, fear and disgust-inducing video clips which mimic everyday experiences which may produce these emotions. The unwarned startle probe may be emotionally distressing. If a previously undetected, potentially significant medical problem is observed, the subject will be informed of it by the-PI by phone so that the matter may be investigated further with the subject's regular physician**.**

   Transcranial Direct Current Stimulation (tDCS), a non-invasive neuromodulatory technique that alters neuronal excitability using a low direct current delivered to the frontal cortex with saline-soaked sponge scalp electrodes. TDCS modulates the firing rates of individual neurons, and influences dopaminergic, adrenergic, and serotoninergic neural circuits (Boggio, Rigonatti et al. 2008; Nitsche, Boggio et al. 2009). tDCS utilizes low intensity direct current, which is known to have anti-seizure effects. Reversing the pathological alterations back to normal with tDCS presents a potential therapeutic option for persons with cognitive and emotional dysfunction post-TBI. Past research has demonstrated that tDCS safely improves depression in a general psychiatric population (Boggio, Rigonatti et al. 2008) and holds promise as a highly innovative therapy that may result in a substantial quality of life improvement in patients with TBI. Six weeks after the completion of tDCS treatment, its effects were still sustained and significant. Transcranial direct current stimulation will be provided by a saline-soaked pair of surface sponge electrodes (35 cm2) delivered by a FDA-approved battery-driven, constant current stimulator (Fisher Wallace Cranial Stimulator, Fisher Wallace Laboratories, New York). Major safety parameters of electrical stimulation utilizing direct current (as opposed to devices producing alternating current) are Current Density {A/cm2} = stimulation strength {A}/electrode size {cm2} X total stimulation durations(s) (Nitsche, Liebetanz et al. 2003). Therefore these major parameters of safety are determined by the size of the electrodes, the intensity of the current and the duration of the stimulation. A comprehensive review by Sundaram and colleagues (2009) evaluated ass existing tDCS protocols involving human subjects from the perspective of aforementioned safety limits. Potentially damaging value of Current Density is 25 mA/cm2, while existing tDCS protocols deliver Current Density ranging between 0.02-0.08 mA/cm2, well within safety limits. Potentially damaging value of Total Carge is 216C/cm2, while existing protocols deliver 0.002-0.068C/cm2, which is a well-within safety limit. The parameters of stimulation in our study will be: size of electrodes 36 cm2, intensity 2mA, stimulation time 20 min per sessions, which translates into Current Density 0.08 mA/cm2 and Current Density 0.08 mA/cm2 and Total Charge 0.068 C/cm2, which is in concordance with parameters of other tDCS studies and well within the safety limits.

   To stimulate the DLPFC, the anode electrode will be placed over F3 according to the 10–20 international system for EEG electrode placement (Fregni, Boggio et al. 2005). The cathode will be placed over the contralateral supraorbital area. We will focus our investigations on the left DLPFC, as modulation of this area by tDCS has been shown to

enhance working memory (Fregni, Boggio et al. 2005) which also demands similar attentional resources as emotional control (Anderson and Knight 2010). A constant current of 2 mA intensity will be applied for 20 min. These stimulation parameters have been used in other tDCS studies (Fregni, Boggio et al. 2006; Fregni, Boggio et al. 2006; Stevanovic 2011), and have been shown to produce effects outlasting the stimulation, well within safety limits [see detailed review in (Stevanovic 2011)]. To date**,** the above described stimulation parameters have not elicited any treatment-related serious adverse events. Non-serious adverse events infrequently occurring in tDCS studies (Poreisz, Boros et al. 2007) include short-term headache, transient fatigue or disturbed sensation under electrodes during the stimulation, such as mild tingling, itching or mild burning that is a natural sensation related to low-intensity current passing through the scalp. The sensation typically disappears immediately after the tDCS stimulation. Further, tDCS has not presented with any potentially harmful pharmacological interactions (Nitsche and Paulus 2001; Poreisz, Boros et al. 2007). Thus study participants receiving tDCS maintain their usual pharmacological regimen.

Patients having brain scans as part of the research study may feel claustrophobic from lying in the magnetic tube. There is risk of injury if there are metal objects in the body. Subjects will be required to fill out a questionnaire indicating if this is true. The subjects will be told that they may hear loud noises while in the MRI machine. The distress will be minimized by providing the subjects with ear plugs and limiting the duration of time in the MRI machine to less than 30 minutes. The research MRI scans will be read by the investigators within one week of the exam. If a previously undetected, clinically significant finding is observed the subject will be notified by the PI by phone so that the matter may be investigated further with the subject's regular physician.

Protection against Risks. Potential risks and discomfort will be minimized to the greatest extent possible through such procedures as appropriate training of personnel and monitoring of subjects. Subjects may take rest breaks as needed during therapy and assessment sessions so that the risk of fatigue is minimized.

In order to minimize any emotional distress, we will explain to the subjects that they may become upset so that they are forewarned. We will explain that the emotional stimuli are similar to everyday experiences that evoke emotional responses. The examination of emotional reactivity and the treatment included in the study will examine how well they cope with real-life situations that may be upsetting to them. In case of any adverse event or difficulty, including events unrelated to the study that make it difficult to continue with the protocol, the subject will be withdrawn from the study and referred for treatment, counseling, or other necessary follow-up. Physicians (Dr. Preeti Raghavan and Dr. Brian Im) and a neuropsychologist (Dr. Joseph Rath) who specializes in treating patients with TBI are included on the team, and will be available to counsel, treat and provide other necessary follow-up in such an event. This study does not provide financial assistance for medical or other injury-related costs.

Risks to confidentiality will be minimized by maintaining a secure, immobile computer database. Subjects will be identified by code rather than by name.

Potential Benefits to the Subjects. As this is a treatment study, tDCS and cognitive training intervention will be provided to participants. This intervention is intended to benefit participants by improving their attentional and emotional function. TDCS modulates the firing rates of individual neurons, and influences dopaminergic, adrenergic, and serotoninergic neural circuits (Boggio, Rigonatti et al. 2008; Nitsche, Boggio et al. 2009). Reversing the pathological alterations back to normal with tDCS presents a potential therapeutic option for persons with cognitive and emotional dysfunction post-TBI. Past research has demonstrated that tDCS safely improves depression in a general psychiatric population (Boggio, Rigonatti et al. 2008) and holds promise as a highly innovative therapy that may result in a substantial quality of life improvement in patients with TBI. TDCS treatment offers several potential advantages, including: i) faster onset of action than antidepressants, ii) non-systemic treatment that can be used in patients who cannot tolerate antidepressants or psycho stimulants due to side-effects, medication interactions, and co-morbidities; iii) no observed adverse interactions between pharmacological agents and tDCS; iv) usefulness for patients with low performance status, because it does not require patients' focused attention or physical effort; and v) it is well-tolerated, brief, safe, and easy to administer . In addition, because no adverse interactions have been observed between pharmacological agents and tDCS, it can be used as adjuvant therapy in patients who report partial relief from pharmacological treatment.

V. INVESTIGATORS' QUALIFICATIONS AND EXPERIENCE (CVs attached)

Preeti Raghavan, MD is the original Principal Investigator and Director of the Motor Recovery Research Laboratory at the Rusk Institute of Rehabilitation Medicine. She and her delegates will be responsible for administering the assessments, the tDCS intervention, and data analysis.
Prin Amorapanth, MD will be continuing the role of PI once Dr. Raghavan leaves.
Brian Im, MD is an Attending Physician in the inpatient brain injury unit. He will refer patients with TBI eligible for the study to the PI.
Joseph Rath, PhD is the Director of Psychology Research at the Rusk Institute of Rehabilitation Medicine. She will be responsible for supervising neuropsychological testing and training.
Anita Madan, PhD is a researcher in the Department of Psychiatry at the NYUSOM. She is an expert in the testing of emotional function using film clips and physiological recordings. She will assist with the set up for testing of emotional function.
Mariana Lazar, MD is a neuroradiologist at the NYUSOM. She is an expert in Resting state fMRI and will assist in the collection and analysis of resting-state connectivity.
Mary Rosedale, PhD, PMHNP is researcher in the NYU College of Nursing, and Department of Psychiatry, NYSOM., board-certified psychiatric nurse practitioner and expert in the use of tDCS She will serve as a co-investigator on this project for issues related to the tDCS intervention.
Viswanath Aluru, MD will be the research assistant on the project and will be responsible for the recruitment, data collection, training and data analysis under the supervision of the PI.
Iain Jeffrey will be a medical student on the project and will assist Viswanath in data collection, training and data analysis under the supervision of the PI.
Zena Moore will be the data associate on the project and will be responsible for subject recruitment, and data management and reporting under the supervision of the PI.

VI. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT/ASSENT

1. **Method of Subject Identification and Recruitment.** Dr. Brain Im will refer patients with TBI with symptoms of emotional dysfunction to the Motor Recovery Laboratory, at NYU Medical Center's Rusk Institute of Rehabilitation Medicine. Attending physicians, physical therapists, and occupational therapists from the outpatient facility at the Rusk Institute will also refer patients to the study by providing them with contact information for the PI if they meet study criteria. Also, subjects will be recruited by advertisement in the New York metropolitan area. Subjects who contact the PI and are found eligible for the study will be required to provide informed consent prior to participation in the study. The study protocol and informed consent forms will be approved by the IRB at NYU Medical Center. Subjects will be informed that they can discontinue the study or its procedures at any time, and that further evaluation or treatment will not be withheld. The identification and recruitment of subjects will protect the privacy of subjects and be free of undue influence.

   We will also place an Ad on Craigslist in the volunteer section to aid in recruitment. The Ad will be listed at: http://newyork.craigslist.org/search/vol

2. **Process of Consent.** Consent will be obtained from subjects by the PI or her HIPAA-certified delegates in the PI's office, which is a private area, at the Rusk Rehabilitation Institute, NYU Medical Center, prior to participation in the study. The consent document will be discussed at a convenient time, free of time constraints, and each potential subject will be allowed time to think about his or her decision. The study and the consent form will be thoroughly discussed with each subject, section by section. Subjects will be asked to provide a statement of their understanding of the procedures, risks, and general concept of the study. All subjects will be given a copy of the written consent form and encouraged to contact the PI if they have further questions about the protocol.

   All subjects will also provide separate consent for videotaping of functional task assessments at the Motor Recovery Laboratory. Videotapes of emotional function battery will be scored to understand deficits in emotional recognition, reactivity and regulation. Videotapes of therapy sessions and functional task assessments may be used for instruction and training purposes.

3. **Subject Capacity.** While TBI leads to cognitive impairments, the subjects recruited for this study will be community-dwelling individuals with capacity to provide consent. Only subjects who have the capacity to consent will be enrolled.

4. **Subject/Representative Comprehension.** Capacity will be determined by a general conversation between the subject or authorized representative and the PI to assess the subject's verbal understanding of the protocol, including the nature and purpose of the study, the procedures involved, and the risks and benefits of participating vs. not participating; appreciation of the significance of disclosed information, and the potential risks and benefits of disclosure for the subject's own situation and condition; the ability to engage in a reasoning

process about the risks and benefits of participating vs. not participating; and the ability to express a choice about whether or not to participate.

5. **Debriefing Procedures.** No information will be purposely withheld from subjects.

6. **Consent Forms.** The IRB Standard Consent Form will be used (please see attached).

7. **Documentation of Consent.** The study and the consent form will be thoroughly discussed with each subject, section by section. Subjects will be asked to provide a statement of their understanding of the procedures, risks, and general concept of the study. The consent document, and documentation of the process, will be stored in the PI's office at the Rusk Institute of Rehabilitation Medicine, NYU Medical Center, on a password protected computer and/or in a locked filing cabinet. The computer will be in a locked, fixed location (no mobile laptop), password protected, and on a local network.

8. **Costs to the Subject.** Subjects will not incur any costs for the therapy.

9. **Payment for Participation.** TBI Participants will be compensated a total of $100.00 for participating in the study. The first compensation will occur after the subjects complete baseline assessments. At this point they will be compensated $50.00. The TBI subjects will be compensated the remaining $50.00 after they complete the post testing assessments. Healthy Control Subjects will be not be compensated for participating in the study.

References:

Allen, L. B., R. K. McHugh, et al. (2008). Emotional disorders: a unified protocol. Clinical Handbook of Psychological Disorders. D. H. Barlow. New York, Guilford Press.

Anderson, T. M. and R. G. Knight (2010). "The long-term effects of traumatic brain injury on the coordinative function of the central executive." Journal of Clinical and Experimental Neuropsychology: 1-9.

Asikainen, I., T. Nybo, et al. (1999). "Speed performance and long-term functional and vocational outcome in a group of young patients with moderate or severe traumatic brain injury." Eur J Neurol **6**(2): 179-185.

Bagby, R. M., J. D. Parker, et al. (1994). "The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure." J Psychosom Res **38**(1): 23-32.

Bagby, R. M., G. J. Taylor, et al. (1994). "The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity." J Psychosom Res **38**(1): 33-40.

Bate, A. J., J. L. Mathias, et al. (2001). "Performance on the Test of Everyday Attention and standard tests of attention following severe traumatic brain injury." Clin Neuropsychol **15**(3): 405-422.

Beer, J. S., O. P. John, et al. (2006). "Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions." J Cogn Neurosci **18**(6): 871-879.

Berlin, H. A., E. T. Rolls, et al. (2004). "Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions." Brain **127**(Pt 5): 1108-1126.

Boggio, P. S., S. P. Rigonatti, et al. (2008). "A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression." Int J Neuropsychopharmacol **11**(2): 249-254.

Bolognini, N., A. Pascual-Leone, et al. (2009). "Using non-invasive brain stimulation to augment motor training-induced plasticity." J Neuroeng Rehabil **6**: 8.

Boone, K. B. (1999). Neuropsychological assessment of executive functions: Impact of age, education, gender, intellectual level, and vascular status on executive test scores. The human frontal lobes: Functions and

disorders. The science and practice of neuropsychology series. . B. L. Miller and J. L. Cummings. New York, Guilford Press**:** 247-260.

Bornhofen, C. and S. McDonald (2008). "Emotion perception deficits following traumatic brain injury: a review of the evidence and rationale for intervention." Journal of the International Neuropsychological Society **14**(4): 511-525.

Brown, A. W., E. P. Elovic, et al. (2008). "Congenital and acquired brain injury. 1. Epidemiology, pathophysiology, prognostication, innovative treatments, and prevention." Archives of Physical Medicine and Rehabilitation **89**(3 Suppl 1): S3-8.

Calvanio, R., R. Williams, et al. (2004). "Acquired brain injury, visual attention, and the useful field of view test: A pilot study." Archives of Physical Medicine and Rehabilitation **85**(3): 474-478.

Cohen, B. A., M. Inglese, et al. (2007). "Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury." AJNR. American Journal of Neuroradiology **28**(5): 907-913.

Delgado, M. R., K. I. Nearing, et al. (2008). "Neural circuitry underlying the regulation of conditioned fear and its relation to extinction." Neuron **59**(5): 829-838.

Dikranian, K., R. Cohen, et al. (2008). "Mild traumatic brain injury to the infant mouse causes robust white matter axonal degeneration which precedes apoptotic death of cortical and thalamic neurons." Experimental Neurology **211**(2): 551-560.

Draper, K. and J. Ponsford (2009). "Long-term outcome following traumatic brain injury: a comparison of subjective reports by those injured and their relatives." Neuropsychol Rehabil **19**(5): 645-661.

Edwards, D. J., H. I. Krebs, et al. (2009). "Raised corticomotor excitability of M1 forearm area following anodal tDCS is sustained during robotic wrist therapy in chronic stroke." Restor Neurol Neurosci **27**(3): 199-207.

Ekman, P., R. W. Levenson, et al. (1983). "Autonomic nervous system activity distinguishes among emotions." Science **221**(4616): 1208-1210.

Endicott, J., J. Nee, et al. (1993). "Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure." Psychopharmacology Bulletin **29**: 321-326.

Fan, J., X. Gu, et al. (2009). "Testing the behavioral interaction and integration of attentional networks." Brain and Cognition **70**(2): 209-220.

Fan, J., B. D. McCandliss, et al. (2005). "The activation of attentional networks." Neuroimage **26**(2): 471-479.

Fisk, G. D., T. Novack, et al. (2002). "Useful field of view after traumatic brain injury." Journal of Head Trauma Rehabilitation **17**(1): 16-25.

Forbes, C. E. and J. Grafman (2010). "The role of the human prefrontal cortex in social cognition and moral judgment." Annu Rev Neurosci **33**: 299-324.

Fork, M., C. Bartels, et al. (2005). "Neuropsychological sequelae of diffuse traumatic brain injury." Brain Inj **19**(2): 101-108.

Fregni, F., P. S. Boggio, et al. (2006). "A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury." Pain **122**(1-2): 197-209.

Fregni, F., P. S. Boggio, et al. (2005). "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory." Experimental Brain Research **166**(1): 23-30.

Fregni, F., P. S. Boggio, et al. (2006). "Treatment of major depression with transcranial direct current stimulation." Bipolar Disord **8**(2): 203-204.

Giorgi, A. (1985). Phenomenology and psychological research. Philadelphia, PA, Duquesne University Press.

Golden, C. (1978). Stroop Color and Word Test: Manual for Clinical and Experimental Uses. . Chicago, IL, Stoelting.

Goodkind, M. S., A. Gyurak, et al. (2010). "Emotion regulation deficits in frontotemporal lobar degeneration and Alzheimer's disease." Psychol Aging **25**(1): 30-37.

Gross, J. J. (1998). "Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology." Journal of Personality and Social Psychology **74**(1): 224-237.

Gross, J. J. (2007). Handbook of emotion regulation. New York, London Guilford.

Gross, J. J. and O. P. John (1998). "Mapping the domain of expressivity: multimethod evidence for a hierarchical model." Journal of Personality and Social Psychology **74**(1): 170-191.

Gross, J. J. and R. W. Levenson (1993). "Emotional suppression: physiology, self-report, and expressive behavior." J Pers Soc Psychol **64**(6): 970-986.

Gu, X., X. Liu, et al. (2008). "Alexithymic trait and voluntary control in healthy adults." PLoS One **3**(11): e3702.

Gyurak, A., M. S. Goodkind, et al. (2012). "Executive functions and the down-regulation and up-regulation of emotion." Cogn Emot **26**(1): 103-118.
Hartley, C. A. and E. A. Phelps (2010). "Changing fear: the neurocircuitry of emotion regulation." Neuropsychopharmacology **35**(1): 136-146.
Henry, J. D., L. H. Phillips, et al. (2006). "Cognitive and psychosocial correlates of alexithymia following traumatic brain injury." Neuropsychologia **44**(1): 62-72.
Hillary, F. G., J. Slocomb, et al. (2011). "Changes in resting connectivity during recovery from severe traumatic brain injury." Int J Psychophysiol **82**(1): 115-123.
Hornak, J., J. O'Doherty, et al. (2004). "Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans." J Cogn Neurosci **16**(3): 463-478.
Inglese, M., S. Makani, et al. (2005). "Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study." Journal of Neurosurgery **103**(2): 298-303.
Jorge, R. E., R. G. Robinson, et al. (2004). "Major depression following traumatic brain injury." Arch Gen Psychiatry **61**(1): 42-50.
Kilbourne, M., R. Kuehn, et al. (2009). "Novel model of frontal impact closed head injury in the rat." Journal of Neurotrauma **26**(12): 2233-2243.
Kleiman, S. (2004). "Phenomenology: to wonder and search for meanings." Nurse Res **11**(4): 7-19.
Kolitz, B. P., R. D. Vanderploeg, et al. (2003). "Development of the Key Behaviors Change Inventory: a traumatic brain injury behavioral outcome assessment instrument." Archives of Physical Medicine and Rehabilitation **84**(2): 277-284.
Leopold, A., F. Krueger, et al. (2011). "Damage to the left ventromedial prefrontal cortex impacts affective theory of mind." Soc Cogn Affect Neurosci.
Lezak, M. D. (1995). Neuropsychological Assessment. New York, Oxford University Press.
Lezak, M. D., D. B. Howieson, et al. (2004). Neuropsychological Assessment. Oxford, Oxford University Press.
Macnamara, A., K. N. Ochsner, et al. (2010). "Previously reappraised: the lasting effect of description type on picture-elicited electrocortical activity." Soc Cogn Affect Neurosci.
Marshall, R. S., E. Zarahn, et al. (2009). "Early imaging correlates of subsequent motor recovery after stroke." Annals of neurology **65**(5): 596-602.
McAllister, T. W. (1992). "Neuropsychiatric sequelae of head injuries." Psychiatric Clinics of North America **15**(2): 395-413.
McAvinue, L., F. O'Keeffe, et al. (2005). "Impaired sustained attention and error awareness in traumatic brain injury: implications for insight." Neuropsychol Rehabil **15**(5): 569-587.
McCauley, S. R., H. S. Levin, et al. (2001). "The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment." J Neurol Neurosurg Psychiatry **71**(5): 643-651.
McDonald, S., C. Bornhofen, et al. (2009). "Addressing deficits in emotion recognition after severe traumatic brain injury: the role of focused attention and mimicry." Neuropsychol Rehabil **19**(3): 321-339.
McRae, K., B. Hughes, et al. (2010). "The neural bases of distraction and reappraisal." Journal of Cognitive Neuroscience **22**(2): 248-262.
Miniussi, C., S. F. Cappa, et al. (2008). "Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation." Brain Stimul **1**(4): 326-336.
Morgan, M. A., L. M. Romanski, et al. (1993). "Extinction of emotional learning: contribution of medial prefrontal cortex." Neuroscience Letters **163**(1): 109-113.
Nakamura, T., F. G. Hillary, et al. (2009). "Resting network plasticity following brain injury." PLoS One **4**(12): e8220.
Neave, N., S. Nagle, et al. (1997). "Evidence for the involvement of the mammillary bodies and cingulum bundle in allocentric spatial processing by rats." European Journal of Neuroscience **9**(5): 941-955.
Nitsche, M. A., P. S. Boggio, et al. (2009). "Treatment of depression with transcranial direct current stimulation (tDCS): a review." Exp Neurol **219**(1): 14-19.
Nitsche, M. A., D. Liebetanz, et al. (2003). "Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects." Suppl Clin Neurophysiol **56**: 255-276.
Nitsche, M. A. and W. Paulus (2001). "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans." Neurology **57**(10): 1899-1901.

Nitsche, M. A., A. Schauenburg, et al. (2003). "Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human." Journal of Cognitive Neuroscience **15**(4): 619-626.

Novack, T. A., J. H. Banos, et al. (2006). "UFOV performance and driving ability following traumatic brain injury." Brain Injury **20**(5): 455-461.

O'Keeffe, F. M., P. M. Dockree, et al. (2004). "Poor insight in traumatic brain injury mediated by impaired error processing? Evidence from electrodermal activity." Brain Research. Cognitive Brain Research **22**(1): 101-112.

Ochsner, K. N., S. A. Bunge, et al. (2002). "Rethinking feelings: an FMRI study of the cognitive regulation of emotion." Journal of Cognitive Neuroscience **14**(8): 1215-1229.

Ochsner, K. N., B. Hughes, et al. (2009). "Neural systems supporting the control of affective and cognitive conflicts." Journal of Cognitive Neuroscience **21**(9): 1842-1855.

Olsson, A. and K. N. Ochsner (2008). "The role of social cognition in emotion." Trends Cogn Sci **12**(2): 65-71.

Peterson, L. R. and M. J. Peterson (1959). "Short-term retention of individual verbal items." J Exp Psychol (58): 193-198.

Poreisz, C., K. Boros, et al. (2007). "Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients." Brain Res Bull **72**(4-6): 208-214.

Rasmusson, D. X., K. A. Carson, et al. (1996). "Predicting rate of cognitive decline in probable Alzheimer's disease." Brain Cogn **31**(2): 133-147.

Reis, J., H. M. Schambra, et al. (2009). "Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation." Proceedings of the National Academy of Sciences of the United States of America **106**(5): 1590-1595.

Reitan, R. M. and D. Wolfson (1985). The Halstead-Reitan Neuropsychological Test Battery. Theory & Clinical Interpretation. Tucson, Neuropsychology Press.

Rosa, M. A. and S. H. Lisanby (2012). "Somatic treatments for mood disorders." Neuropsychopharmacology **37**(1): 102-116.

Ruff, R. M., R. Evans, et al. (1986). "Impaired verbal and figural fluency after head injury." Arch Clin Neuropsychol **1**(2): 87-101.

Sandelowski, M. (1995). "Qualitative analysis: what it is and how to begin." Res Nurs Health **18**(4): 371-375.

Saunders, J. C., S. McDonald, et al. (2006). "Loss of emotional experience after traumatic brain injury: findings with the startle probe procedure." Neuropsychology **20**(2): 224-231.

Schiller, D. and M. R. Delgado (2010). "Overlapping neural systems mediating extinction, reversal and regulation of fear." Trends Cogn Sci.

Shamay-Tsoory, S. G., R. Tomer, et al. (2003). "Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex." J Cogn Neurosci **15**(3): 324-337.

Siebner, H. R., N. Lang, et al. (2004). "Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex." Journal of Neuroscience **24**(13): 3379-3385.

Smith, A. (1993). A Symbol Digit Modalities Test. A Manual., Western Psychological Services.

Smith, R. B., A. Tiberi, et al. (1994). "The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients." Brain Injury **8**(4): 357-361.

Smith, S. M. (2002). "Fast robust automated brain extraction." Human brain mapping **17**(3): 143-155.

Smith, S. M., M. Jenkinson, et al. (2004). "Advances in functional and structural MR image analysis and implementation as FSL." Neuroimage **23 Suppl 1**: S208-219.

Soeda, A., T. Nakashima, et al. (2005). "Cognitive impairment after traumatic brain injury: a functional magnetic resonance imaging study using the Stroop task." Neuroradiology **47**(7): 501-506.

Sohlberg, M. M. and C. A. Mateer (1989). Introduction to cognitive rehabilitation: theory and practice. New York, Guilford Press.

Sotres-Bayon, F., C. K. Cain, et al. (2006). "Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex." Biological Psychiatry **60**(4): 329-336.

Spreen, O. and E. Strauss (1998). A Compendium of Neuropsychological Measures. . New York, Oxford Press.

Stevanovic, D. (2011). "Quality of Life Enjoyment and Satisfaction Questionnaire-short form for quality of life assessments in clinical practice: a psychometric study." J Psychiatr Ment Health Nurs **18**(8): 744-750.

Sturm, V. E., H. J. Rosen, et al. (2006). "Self-conscious emotion deficits in frontotemporal lobar degeneration." Brain **129**(Pt 9): 2508-2516.
Stuss, D. T. and B. Levine (2002). "Adult clinical neuropsychology: lessons from studies of the frontal lobes." Annu Rev Psychol **53**: 401-433.
Thorne, S. (2000). "Data analysis in qualitative research." Evidence-Based Nursing **3**(3): 68.
Trenerry, M., B. Crosson, et al. (1989). Stroop Neuropsychological Screening Test Manual. . Odessa, FL, Psychological Assessment Resources.
Tulsky, D. S., J. Zhu, et al. (1997). WAIS-III WMS-III Technical Manual. San Antonio, TX, Psychological Corporation.
Vanier, M., J. M. Mazaux, et al. (2000). "Assessment of neuropsychologic impairments after head injury: interrater reliability and factorial and criterion validity of the Neurobehavioral Rating Scale-Revised." Arch Phys Med Rehabil **81**(6): 796-806.
Wager, T. D., M. L. Davidson, et al. (2008). "Prefrontal-subcortical pathways mediating successful emotion regulation." Neuron **59**(6): 1037-1050.
Wallesch, C. W., N. Curio, et al. (2001). "Outcome after mild-to-moderate blunt head injury: effects of focal lesions and diffuse axonal injury." Brain Inj **15**(5): 401-412.
Wechsler, D. (2001). Wechsler Test of Adult Reading WTAR Manual. San Antonio, TX, The Psychological Corporation.
Wechsler, D. (2008). Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV). San Antonio, TX, The Psychological Corporation.
Werner, K. H., N. A. Roberts, et al. (2007). "Emotional reactivity and emotion recognition in frontotemporal lobar degeneration." Neurology **69**(2): 148-155.
Whyte, J., T. Hart, et al. (2008). "The Moss Attention Rating Scale for traumatic brain injury: further explorations of reliability and sensitivity to change." Arch Phys Med Rehabil **89**(5): 966-973.
Woolrich, M. W., S. Jbabdi, et al. (2009). "Bayesian analysis of neuroimaging data in FSL." Neuroimage **45**(1 Suppl): S173-186.
Zappala, G., M. Thiebaut de Schotten, et al. (2012). "Traumatic brain injury and the frontal lobes: what can we gain with diffusion tensor imaging?" Cortex **48**(2): 156-165.
Zhang, D. and M. E. Raichle (2010). "Disease and the brain's dark energy." Nat Rev Neurol **6**(1): 15-28.