COGNITIVE AND EMOTIONAL FUNCTIONING AFTER TRAUMATIC BRAIN INJURY: AN FMRI INVESTIGATION

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Master's Thesis Project

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DEDICATION

I dedicate this thesis to my family for their tireless encouragement, and for inspiring my scientific curiosity and passion for helping others. I also dedicate this thesis to my friends for lightening the journey with laughter and hugs and for always believing in me, and also to all the other members of the Armed Forces past and present for their dedicated service to our country.

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ABSTRACT

Title of Thesis: COGNITIVE AND EMOTIONAL FUNCTIONING AFTER TRAUMATIC BRAIN INJURY: AN FMRI INVESTIGATION

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Background: Traumatic Brain Injury (TBI) may result from physiological disruption of normal brain functioning and occurs in an estimated 20% of combat veterans. TBI severity classification is based on observable patient characteristics following the injury including length of time of Loss of Consciousness (LOC), length of Posttraumatic Amnesia (PTA) and Glasgow Coma Scale (GCS) scores. Postconcussive symptoms (e.g. headache, irritability, fatigue, trouble with concentration/memory) following a TBI may cause functional impairment. However, TBI severity does not consistently predict the intensity or duration of post-concussive symptoms. Because working memory and emotional reactivity problems are often reported following many TBIs, it is important to better understand factors which may impact these domains and related symptoms.

Methods: Demographic, medical, behavioral and neuroimaging data were collected from 110 TBI patients and 12 healthy controls as part of a retrospective exploratory analysis using an emotional working memory fMRI task. Aim 1 explored

differential effects of an emotional faces N-back task in TBI subjects vs. healthy controls. Aim 2 investigated the contributions of patient and injury characteristics (including LOC and prior blast exposure) toward differential activation patterns within the TBI group. Also within the TBI subsample, Aim 3 explored correlations between activation patterns of components of the emotional N-back task and reported neurobehavioral symptoms.

Results: fMRI was used to detect changes in regional blood oxygenation associated with the hemodynamic response to brain function. Differences between the TBI and control groups were seen in interactions with emotional aspects of the task. Within the TBI group, greater performance variability and LOC correlated with differential patterns of activation. Additionally increased symptoms, particularly in the somatic subdomain, correlated with altered activation.

Discussion: Models incorporating patient and injury characteristics may better help elucidate the complex relationships among pre-injury, TBI, and psychosocial support factors in predicting symptoms, outcomes, and targets for treatment. Specifically, profiles of patient and injury characteristics and symptom clusters, for example TBI with LOC, or TBI with PTSD or somatic symptoms may provide meaningful ways of categorizing patients who have suffered a TBI into more homogeneous groups. In addition these results suggest that individual patient performance variability may be in an important marker to examine in future studies of TBI.

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CHAPTER 1: Introduction

TRAUMATIC BRAIN INJURY: BACKGROUND

Traumatic Brain Injury (TBI) is a physiological disruption of normal brain functioning occurring from biomechanical and/or inertial forces to the skull, which may result in diffuse and/or focal damage to the brain (Rao & Lyketsos, 2000). An estimated 3.5 million TBIs occur annually in the U.S. (Coronado et al., 2012). Moreover, U.S. military personnel returning from deployment are increasingly being diagnosed with related behavioral health issues, most notably TBI and Posttraumatic Stress Disorder (PTSD), recognized as "signature wounds" of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (Tanielian & Jaycox, 2008; Vanderploeg, Belanger & Curtiss, 2009). Prevalence rates of TBI in OEF/OIF combat veterans are estimated to be around 20% (Hoge et al., 2008; Terrio et al., 2009; Tanielian & Jaycox, 2008). In addition to the direct effects of sustaining such an injury, which include the possibilities of permanent disability or even death (CDC, 2013; Belanger, Curtiss, Demery, Lebowitz & Vanderploeg, 2005), there are also direct and indirect medical costs, significant patient distress, and lost productivity costs that can affect the nation as a whole (CDC, 2013; Finkelstein et al., 2006).

Classification of TBI severity is typically based on observable patient characteristics following the injury including duration or presence of Loss of Consciousness (LOC), Posttraumatic Amnesia (PTA), and the patient's verbal motor and eye-opening responses measured by the Glasgow Coma Scale (GCS) (see Figure 1). Mild TBI (mTBI) is commonly defined as a GCS ranging from 13-15, LOC duration

from 0-30 minutes, PTA ranging from 0-24 hours post injury, and frequently normal clinical imaging findings. Moderate TBI is characterized by a confused/disoriented state lasting greater than 24 hours or LOC greater than 30 minutes but less than 24 hours, PTA lasting greater than a day but less than a week, GCS 9-12, and structural brain imaging that may be either normal or abnormal. Severe TBI is classified by a confused or altered state lasting greater than 24 hours, LOC greater than 24 hours, PTA lasting longer than 7 days, GCS 3-8, and imaging findings that may be normal or abnormal (Fischer, 2010; Jackson, Hamilton & Tupler, 2008; VA/DoD, 2010). While crucial in helping to determine immediate injury treatment, the TBI classifications made from these measures are typically unhelpful in predicting long term symptoms and prognosis (Belanger et al., 2005). For patients with mild TBI as classified by LOC, PTA and GCS scores TBI severity can be further classified as uncomplicated (no abnormal findings on neuroimaging), or complicated (complicated by brain lesion or depressed skull fracture) (Williams, Levin & Eisenberg, 1990).

TBI Injury Characteristics

In addition to possible damage from the initial trauma, a pathophysiological cascade is set into motion which may continue to propagate neuronal injury during the acute recovery process (LaPlaca, Simon, Prado & Cullen, 2007; Rao & Lyketsos, 2000; Silver, McAllister & Arciniegas, 2009). Since differential pathophysiological sequelae from TBIs of varying impact and inertial forces may lead to differential outcomes, inclusion of injury and post-injury pathology processes in predictive models for TBI has been suggested (LaPlaca et al., 2007). For instance, there is preliminary evidence that

direction and mechanism of impact influence the development of specific postconcussive symptoms (Silver et al., 2009), although the literature has not defined clear relationships between mechanism of injury and neuronal damage (LaPlaca et al., 2007; Silver et al., 2009).

A number of studies have begun to report patterns of worsened symptoms following a concussion with LOC (McCrea, Kelly, Randolph, Cisler & Berger, 2002; Matthews, Simmons & Strigo 2010), and some studies have noted that the direction of impact on the head may influence the length of LOC (Hannay, Howieson, Loring, Fischer & Lezak, 2004) as well as functional outcomes (Silver et al., 2009). For example, Rassovsky and colleagues noted that neurotrauma to the frontal systems specifically appears to play a key role in information processing speeds and patients' difficulties with social and occupational functioning (2006b). While direction of impact may be difficult to determine post-injury from self-reports, damage to specific areas is one factor that may be helpful in predicting expected symptoms.

Specifically regarding mechanism of injury, a large number of TBIs sustained by military personnel in OIF/OEF are due to a blast mechanism. While some previous studies have found blasts to cause a differentially distinct pattern of injury and functional impairment from non-blast TBI (Davenport, Lim, Armstrong, & Sponheim, 2012; Mendez, Owens, Reza Berenji, Peppers, Liang & Licht, 2013), symptom report differences in a number of other studies show limited or no correlation with this specific mechanism of injury (Levin et al., 2010; Luethcke, Bryan, Morrow & Isler, 2010). Interestingly, other studies show that TBIs involving LOC have been associated with a

subsequent increased vulnerability to the development of psychiatric symptoms, most prominently depression (Matthews et al., 2010).

Post-Concussive Neurobehavioral Symptoms

Frequently following a TBI, patients report postconcussive symptoms (PCSx) which can be variously grouped by cognitive, emotional, and physical domains, and are frequently associated with decreased quality of life and psychosocial challenges (Bagiella et al., 2010; Potter, Leigh, Wade & Fleminger, 2006). In addition to typical postconcussive symptom complaints such as headaches, nausea, dizziness and balance problems, distractibility, concentration/memory problems, impulsivity, irritability or anger management problems, fatigue, light/noise sensitivity, and emotional disturbances, functional deficits in executive and attentional domains, as well as symptoms of psychiatric disorders including depression and anxiety may also be reported (Brenner et al., 2010; Cook, Chapman & Levin, 2008; Walker et al., 2010; Whelan-Goodinson, Ponsford, Schonberger & Johnston, 2010). These symptoms can last for up to several months and in a small minority of cases longer (Brewer, Metzger & Therrien, 2002; Brooks, Fos, Greve & Hammond, 1999; Cicerone & Azulay, 2002; Hammond-Tooke, Goei, du Plessis & Franz, 2010; Lundin, de Boussard, Edman & Borg, 2006). Patients with persistent symptoms beyond the normally anticipated time-frame of recovery may be referred to as having “chronic TBI,” persistent symptoms for a “remote” TBI (especially in the case of mild TBI), or possibly diagnosed with postconcussive syndrome. Moreover, these postconcussive symptoms can cause significant distress, and in many cases have been seen to affect neuropsychological functioning well beyond the

anticipated acute injury time-frame (Vanderploeg, Curtiss & Belanger, 2005). Currently there is little understanding of the intensity or duration of these deficits or why certain patients suffer from specific symptoms.

Despite the fact that severity of TBI does not appear to correlate directly with many postconcussive symptoms (Brown et al., 2010), prior research has shown that certain factors are helpful in characterizing the functional outcomes and recovery time course of TBI in some circumstances. Most prominently, a history of multiple prior TBIs has been associated with worsened measures of delayed memory and executive functioning (Belanger, Spiegel & Vanderploeg, 2010). A number of studies have also begun to report patterns of worsened symptoms following a concussion causing LOC (McCrea et al., 2002; Matthews et al., 2010).

Early conceptualizations of TBI predicted a pattern of fairly limited acute post-concussive symptoms, followed by a post-acute spontaneous resolution. For mild TBI this recovery time course is usually within 10 days (Macciocchi, Barth, Alves, Rimel & Jane, 1996). For moderate and especially severe TBIs, typically fewer postconcussive symptoms are reported, however recovery time is often longer, and post-acute symptoms and deficits may be prolonged or even permanent. Subsequent research, however, has shown that even mild TBI can have effects on neuropsychological functioning beyond the acute injury time-frame of varying length and lead to unpredictable postconcussive symptoms (Belanger et al., 2005; Vanderploeg et al., 2005).

Specifically, although there is evidence of various stages of recovery from TBI typified by improvement of symptoms in several domains (Hammond-Tooke et al., 2010), difficulties are frequently reported up to 3 months post-injury (Lundin et al.,

2006). Significantly adverse outcomes have been noted not just in moderate or severe TBI, but also in mild TBI cases (Slobounov et al., 2010). Furthermore, there is a small but important subset of TBI patients that experience prolonged symptoms well beyond the anticipated acute injury time-frame, as well as partial or otherwise complicated recoveries resulting in worse outcomes than their severity classification would have predicted (Mooney & Speed, 2001; Belanger et al., 2005; Vanderploeg et al., 2005). Additionally, such organismic and psychosocial factors as age at time of injury, gender, social support, and psychiatric comorbidities including PTSD and depression have shown some relationship to postconcussive symptoms (Luis, Vanderploeg & Curtiss, 2003). While additional psychosocial factors (such as psychiatric comorbidity, social support, stress) are often implicated in these "chronic" or "complicated" mTBI cases, no clear pattern has emerged in terms of specific correlations with predictable outcomes (McCauley, Boake, Levin, Contant & Song, 2001; Rassovsky , 2006a; Rassovsky et al., 2006b).

Differences in Neuropathology and Symptom Reports for TBI and Healthy Controls

TBI is characterized by an evolving symptomatology. Currently, the timing and diagnostic sequence of the recovery process, as well as developmental aspects of the injury, are imprecisely understood, making it difficult to predict outcome and optimal treatments (Kou et al., 2010). Neuroimaging has been used to investigate both diffuse axonal injury (DAI) and specific sites of contusions/lesions to help assess acute and post-acute effects of TBI. As with symptom reports, there appear to be variable differences in brain activity patterns between TBI and control subjects (Hammond-Tooke et al., 2010).

TBI resulting in damage to the corpus callosum (CC) as detected by DTI, appears to correlate with increased postconcussive symptom expression and distress (Wilde et al., 2008). Higher symptom reports of depression have also been found to be associated with decreased fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF), a white matter tract known to connect dorsolateral prefrontal cortex (dlPFC) with several essential areas in the temporal parietal and occipital lobes (Matthews et al., 2011).

Working Memory and TBI

Impairment in working memory has been associated with TBI (Perlstein et al., 2004) and is a frequent symptom complaint among patients. Damage either to structures involved with working memory or white matter connections supporting this network have been implicated in these symptoms (Kasahara et al., 2011). While overall performance may not be clearly different between patients and controls, a distributed network of brain regions involved in supporting working memory have shown alterations in activation patterns (Sanchez-Carrion et al., 2008; Kasahara et al., 2011), for example in the dlPFC (Perlstein et al., 2004).

Specifically, TBI patients' working memory impairments appear to reflect both changes in activation pattern during increased workload (especially increased activation in bilateral frontal-parietal regions (McAllister, Flashman, McDonald, & Saykin, 2006)), as well as poorer performance including slower reaction times (RT; Hammond-Tooke et al., 2010), and problems with attention and memory (Ashman et al., 2008) relative to controls. For working memory tasks for which TBI subjects do not show higher error rates, it is likely that efficiency is reduced, requiring TBI patients to work harder to

maintain performance (McAllister et al., 2006). The term "Cognitive Load" refers to the "load imposed on working memory while performing a particular task" (p. 730, Chen & Chang, 2009). Emotional processing can serve as a cognitive load; for example in Chen & Chang's study they found that increased anxiety created an increased cognitive load during task performance (2009). Tasks to assess working memory frequently utilize an "N-back" paradigm, for which the participant matches the current presented stimulus with another "N" number of steps earlier in the sequence. Incrementally larger N-back steps represent increasing cognitive load demands, resulting in higher degrees of difficulty.

TBI and Emotional Attention

TBI patients have also demonstrated deficits in attention and reactivity to emotional stimuli (McDonald et al., 2011). Specifically, brain imaging studies have found altered functional activation patterns in emotion-processing and control regions of patients with TBI (Gosselin et al., 2011; Lipton et al., 2009; Matthews et al, 2011). These altered activation patterns appear to potentially correlate with post-consussive symptom severity (Gosselin et al., 2011).

Given that neurocognitive subdomains may cluster, such as into cognitive and affective symptoms (Ettenhofer & Barry, 2012), targeted investigations of altered brain activation patterns could look at specific symptom subdomains to improve specificity.

Additionally, higher rates of diagnosed comorbid emotional disorders (e.g. Major Depressive Disorder (MDD), PTSD) are frequently seen following TBI relative to healthy controls. Interestingly, non-TBI patients with a history of mood/anxiety

disorders exhibit altered emotional and cognitive neural processing (Demenescu et al., 2011; Simmons & Matthews, 2011), in some brain regions that overlap with areas commonly showing altered activation patterns in patients with TBI, such as frontal and limbic regions including dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), hippocampus, and insula. There is preliminary evidence that tasks combining emotion processing and working memory may represent a more challenging cognitive load in general (Chiew & Braver, 2011), and especially in patients with a history of depression (Bertocci et al., 2011). It is possible that this difficulty may be further exacerbated in patients with a history of TBI.

Interestingly, there is also evidence that there may be more variability in performance associated with TBI patients relative to controls (Stuss, Pogue, Buckle & Bondar 1994; Stuss, Stethem, Hugenholtz, Picton et al., 1989). Measuring variability has been found helpful in contextualization and characterization of some of the deficits seen in other disorders (Ettenhofer et al., 2010). Moreover, frontal lobe lesions on MRI have been associated with increased reaction time (RT) variability (Stuss, Murphy, Binns & Alexander, 2003).

TBI Literature on Neurocognitive Networks

Essential daily neurocognitive processes including orienting/alerting; perception; attention; memory encoding, storage and retrieval; social and emotional processing; and language motor and executive outputs rely on various brain regions and networks for proper execution. A number of TBI studies have pointed to differences in white matter integrity and functional activation patterns at various regions in connection with specific

patterns of neuropsychological disruptions and challenges (Hammond-Tooke et al., 2010). For example, various relationships with the dlPFC, dorsal and rostral ACC (dACC and rACC) in cognitive and emotional control of attention respectively have been identified (Mohanty et al., 2007). Due to the relatively high number of attention/memory and emotional problems reported by patients who have sustained a TBI, specific regions and networks involved in these tasks have been targeted for study. Although differences have been found in prior work, this study aims to better identify patient characteristics associated with these differences and better clarify the relationships among regional brain activation patterns, patient and injury characteristics, and neurobehavioral symptoms.

To best understand the complexity and interaction of factors which may impact outcomes from TBI, Silver & colleagues created a model of biopsychosocial factors (2009). According to their model, specifically, pre-injury factors including age, gender, neurogenetics, baseline cognitive function, psychiatric conditions, substance abuse, socioeconomic environment, and risk-taking behaviors may impact the initial brain state and, therefore, outcomes. Injury characteristics, such as location in the brain, as well as the type and severity of neural damage, may be predictive of problems across neuropsychiatric domains including cognitive, emotional, behavioral, and physical functioning. Finally, post-injury factors and environment including availability of social support, medical and rehabilitative treatments, and even socioeconomic status may further influence outcomes.

SIGNIFICANCE AND RATIONALE

Because injury factors and TBI severity do not directly predict postconcussive symptoms, Silver and colleagues suggest that additional pre/post- injury factors are helpful to best characterize and predict functional outcomes (2009). Given literature in the field, a history of multiple prior TBIs might predict worsened measures of delayed memory and executive functioning (Belanger et al., 2010). Additionally, age, gender, Post Traumatic Stress Disorder (PTSD) and other demographics may be valuable information to include in models predicting PCSx outcomes (Brown et al., 2010; Senathi-Raja, Ponsford & Schonberger, 2010; McCauley et al., 2001; Rassovsky et al., 2006a; Rassovsky et al., 2006b).

This model serves as a framework through which to approach the inclusion of additional variables in a neuroimaging analysis of task performance in TBI vs. healthy controls. While this framework and previous studies may suggest multiple individual factors which may help predict TBI symptoms, as an exploratory study of a retrospective data set additional considerations for available data must be taken into consideration in proposing aims and hypotheses. However, the current study presents a unique opportunity to explore interactions and relative contributions of a number of variables previously suggested in the literature in a large sample of active duty military personnel including combat-wounded patients who report persistent symptoms following a TBI.

AIMS AND HYPOTHESES

The overarching hypothesis is that in TBI patients with damaged neurocircuitry, brain plasticity may permit performance of a task with similar accuracy and/or efficacy as

a non-injured person. However, because previous studies have shown that increases in cognitive processing load can act as a sort of stressor to decrease performance efficiency even in healthy controls (Jansma, Ramsey, Coppola & Kahn, 2000), it is also hypothesized that performance of this emotional working memory task will result in an altered neuronal signal relative to the unstressed baseline state for patients with TBI. Analysis of this fMRI dataset will compare TBI and healthy control participant brain activation patterns on an emotional N-back task, as well as within TBI-group correlations between various pre-injury and injury-related variables and brain activation patterns on specific aspects of this task.

Aim 1:

To examine the differential effects of increasing emotional and cognitive load during an emotional N-back task in TBI subjects vs. healthy controls.

Hypothesis 1

Differences in voxel-wise activation patterns between TBI vs. controls will be found for working memory load (1 vs. 2 vs. 3 –back) as well as emotional valence of stimuli (happy vs. neutral) in accordance with previous literature (McAllister et al., 2006; Jansma et al., 2000). An interaction between these task types and patient group is also expected such that increased cognitive load will result in greater activation for TBI vs. healthy controls similar to previous findings (Chen & Chang, 2009; Chiew & Braver, 2011).

Aim 2:

To examine potential underlying brain structures and networks associated with increased cognitive and emotional processing (as evidenced by increased brain activation) following TBI, and their relationship to injury characteristics.

Hypothesis 2

Within the TBI group, differential activation patterns among N-back, emotion, and their interactions will correlate with specific injury characteristics (including presence/absence of LOC, and prior history of blasts) in accordance with prior literature (McCrea et al., 2002; Matthews et al., 2010; Belanger et al., 2010). Regression analysis with age as a covariate will help to determine whether these TBI characteristics provide additional predictive power beyond factors already identified in the literature. Additionally, differences in activation patterns related to task performance variability may enhance our knowledge of these cognitive and emotional processing networks. Variability in performance is therefore also expected to correlate with differences in activation patterns for varying levels of difficulty among task components (in keeping with Stuss et al., 1989).

Aim 3:

To examine the relationship of reported neurobehavioral symptoms to altered brain activation patterns in the TBI patient group.

Hypothesis 3a

Overall Neurobehavioral Symptom Inventory (NSI) score is additionally expected to be correlated with differences in whole brain activation patterns for number-back ((3-1)-back and (2-1)-back), and emotional valence (happy-neutral) task components, in accordance with previous findings (Hammond-Tooke et al., 2010; Wilde et al., 2008).

Hypothesis 3b

Differential patterns of activation for number-back ((3-1)-back and (2-1)-back), and emotional valence (happy-neutral) may also correlate more specifically with affective, cognitive and somatic symptom subdomain scores on the NSI following from previous literature (Matthews et al., 2011; Halbauer et al., 2009).

Aims Summary

Overall this project aims to identify differences between brain activation patterns of TBI and healthy control participants during a complex working memory task; to determine if certain TBI injury characteristics are predictive of identifiable differences in response patterns; and to establish whether activation patterns with larger variability or utilization in specific networks or structures are predictive of certain subdomain patterns of postconcussive symptoms.

CHAPTER 2: Methods

This study utilized a retrospective, between-subjects, cross-sectional, exploratory design.

PARTICIPANTS

De-identified data collected previously at the National Intrepid Center of Excellence (NICoE) at the Walter Reed National Military Medical Center (WRNMMC), from 203 subjects recruited as part of a larger comprehensive protocol ("National Capital Consortium TBI Neuroimaging Care Project – PT074437, Dr. Gerard Riedy PI) at NICoE/WRNMMC were used in the analysis. The participants included active duty military personnel and civilian Department of Defense health care beneficiaries either with a prior history of combat-related TBI or as healthy controls. For the control group, participants with a TBI diagnosis or history of prior brain injuries or severe neurologic or psychiatric conditions (such as psychosis, stroke, multiple sclerosis, or spinal cord injury) were excluded. Females in either group who were potentially pregnant were excluded from the imaging protocol. Additionally, participants in either group for whom physiological data were not recorded (respiratory and heart rate data to remove noise), task data were not correctly collected, or whose neuroimaging data contained too much movement for successful analysis were also excluded.

MEASURES AND MATERIALS

N-back task

An N-back fMRI task was developed to investigate the effects of presenting emotionally valenced faces in the context of a working memory task (see Fig. 2a-c). The task consisted of 12 blocks of trials, 2 each of 6 types: happy faces paired with a 1-back, a 2-back and a 3-back task; and neutral faces paired with a 1-back, a 2-back and a 3-back task. Participants were asked to respond as quickly as possible to each face presented, indicating whether the current face was the same as or different from the target face "N" pictures previous, where N could be 1, 2, or 3 faces "back". As N increased, there were more intervening faces between the current and the target face, so that the task difficulty increased. The N=3 task is considered quite difficult for most healthy subjects. Each of the twelve blocks contained 15 human face stimuli from the lifespan database of adult faces (Minear & Park, 2004) and was approximately 30 seconds long. Trial blocks were separated by a resting period of 18 seconds. Subjects responded to each picture using MRI-compatible hand paddles with finger and thumb buttons. Additionally Reaction Times (RT) for subject responses were recorded as auxiliary behavioral data, from which RT mean and standard deviation (RTSD) were calculated for each trial block.

Assessment of current symptoms

As part of the previously existing imaging protocol, TBI subjects also completed neuropsychological testing and patient interviews with the NICoE clinical team as well as self-report questionnaires including the NSI (for postconcussive symptom reporting), Combat Exposure Scale (CES; a standard measure to assess for severity of combat

experiences resulting in scores ranging from none to heavy combat exposure), and PTSD Checklist (PCL-C; to assess for symptoms of PTSD) with the research team. Brief medical history and neuropsychological examination (for TBI group) were either collected as part of routine care while at NICoE, or by the study team for any information not already available for participants in either group.

The NSI is a 22 item self-report measure of commonly reported postconcussive symptoms. Items use Likert-type scale ratings for each symptom experienced since the time of their injury, including "feeling dizzy," "headaches," "poor concentration, can't pay attention, easily distracted," "feeling depressed or sad" with ratings ranging from 0= "none" to 4= "very severe". NSI symptom subdomains include: cognitive (e.g., problems with concentration, memory, decision-making, speed), affective (e.g., depression, fatigue/insomnia, anxiety, irritability/frustration, headaches), and somatic (e.g., dizziness, numbness, poor balance/coordination, vision/hearing difficulty, light/noise sensitivity, changes in taste/smell or appetite). From this measure a postconcussive symptoms total score, as well as totals for each of the subscales (affective, cognitive, and somatic) are computed from raw scores of relevant items. Because PTSD is a frequently comorbid psychiatric condition with TBI, but not the focus of this study, the PCL-C, a standard 17 item screening questionnaire for PTSD symptoms, was also completed by participants.

Assessment of injury severity characteristics and patient demographics

Loss of Consciousness (LOC) and prior TBI history measures were obtained from the patients' medical records. LOC was recorded as either Yes or No specifically for the

most recent TBI and entered into the analyses. Prior TBI information was directly evaluated by the clinical team, but for purposes of the analysis was gathered from medical records as either a Yes or No for prior history of blast exposure as an analog for prior TBI. Additionally, to assess for potential confounding variables, participants' demographic information was gathered from the medical records and patient interviews.

NEUROIMAGING

fMRI Image Acquisition

This study used archival data previously collected as part of a larger neuroimaging protocol at NICoE. The IRB-approved study collected structural MRI and fMRI sequences, which were conducted using a GE 3.0 Tesla MR750 scanner within the NICoE neuroimaging suite. All subjects underwent a localizer scan to prescribe subsequent scans, followed by one or more high-resolution anatomical scans including T1-weighted structural images to provide a high-resolution spatial reference for other scans, and B0 field maps. Functional tasks utilized blood oxygenation level dependent (BOLD) imaging to detect changes in regional blood oxygenation associated with the hemodynamic response to brain function using an echo-planar imaging (EPI) sequence (40 sagittal slices, slice thickness at 3.75 x 3.75 x 4.0 mm^3 in-plane resolution, 64 x 64 voxel FOV, TR= 2000ms).

fMRI Analysis

Images for each subject were processed using standard scanner manufacturer software and software written either in-house or sourced from other institutions. After

initial scanner processing and data anonymization conducted as part of the original protocol, functional imaging sequences were pre-processed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Pre-processing of the EPI data for each subject included removal of the first 3 volumes (6 sec.) from each series, slice-time correction, motion correction, correction for B0 inhomogeneities, smoothing with an 8mm FWHM Gaussian kernel, alignment to the T1-weighted image using AFNI's registration software, and conversion to percent-of-mean rather than absolute intensity values. Standard censoring of time points for motion and noise were completed. Preliminary quality/integrity checks on the data were also performed for consistency and accuracy of automated processing.

Task analysis utilized a gamma variate function convolved with each of the paradigm blocks (12), for the data implementing a General Linear Model (GLM) to model variance in the observed fMRI time series at each voxel according to the following equation:

$$Y = x_1\beta_1 + x_2\beta_2 + \ldots + x_p\beta_p + \varepsilon$$

The GLM was used to find beta weight parameter estimates (β) for each regressor in the design matrix to determine which provided the best fit of factors contributing to the shape of Y (observed BOLD signal time series at each voxel). Optimal values for β minimized the sums of squares differences between the predicted model and observed data. Each x in the design matrix represents various factors in the model including task-related and nuisance regressors expected to help explain the observed data. Time course prediction included convolution of time series data with a gamma-variate hemodynamic response function. The ε term represents the residual differences between the predicted

model and observed data. Once all β values at each voxel were calculated, statistical tests to determine significance of task β weight contribution to changes in BOLD signal were conducted.

Specifically, preprocessed time series data for each participant were analyzed using a GLM in AFNI's 3dDeconvolve program (Cox, 1996). Task-related regressors for emotion (happy and neutral) and number-back (N=1, 2, and 3 -back), 2 drift parameters (baseline and drift polynomials), and 6 head motion regressors (X,Y, Z, roll, pitch, and yaw) were entered into a general linear model estimate for each subject using a gamma-variate function in 3dDeconvolve to estimate β weights for the hemodynamic response functions. Primary contrasts between β regression coefficients from 3dDeconvolve were then entered into 2-sample t-tests. Additional processing steps included integration of behavioral task data (ex. calculation of mean Reaction Times for event blocks) for each subject to identify regions of interest for group analysis. Data pre-processing steps included: concatenation of 2D DICOM images into single 3D+time datasets, removal of the first 3 time-points, voxel slice time correction, and sub-brick registration to base brick (dimon/to3d, 3dtcat, 3dtshift and 3dvolreg; AFNI); B0 field inhomogeneity corrections (in-house and FSL); application of spatial Gaussian blur, computation of alignment between fMRI EPI and anatomical T1 datasets, and transformation of EPI signal values to voxel-wise % of means (3dmerge with 8mm FWHM blur, alignepianat.py with transformation parameters to MNI, and 3dcalc; AFNI); and physiology corrections (McRETRO; AFNI). Data processing steps included: calculations of statistical parametric maps for the response to each block type as well as contrasts between block types for each subject, transformation to MNI space, masking, and clusterization

(3dDeconvolve, @auto_tlrc, 3drefit and 3dClustSim; AFNI). Finally processed imaging and behavioral data were examined for quality assurance.

fMRI Group Analysis

After post-processing of individual data as well as quality and data integrity checks, group functional image analyses were conducted. Each participant's T1 image underwent spatial normalization to the Montreal Neurological Institute (MNI152 brain) standard stereotactic space. The resulting transform was then applied to the fMRI data for functional-to-standard space transformation of co-registered functional images into standard space. Statistical parametric maps (SPM) of contrasts between the levels of N-back difficulty (2-back vs. 1-back, 3-back vs. 2-back, 3-back vs. 1-back) and face emotional valence (happy vs. neutral) for each subject were entered into group analysis. Differences in voxel activation were identified and thresholded for significant clusters of activation using family-wise error (FWE) correction. Family-wise error correction improves reliability and is a well-recognized conventional approach for correction for multiple comparisons in fMRI (Nichols & Hayasaka, 2003; Bennet, Wolford & Miller, 2009). The statistical analysis of fMRI data is characterized by individual voxel-wise p values, an assumed Gaussian random field typically achieved via explicit Gaussian smoothing, and the identification of spatially co-located clusters of "activation". FWE recognizes the spatial dependence of smoothing and incorporates measures of related neighboring brain areas, as well as using Monte Carlo simulations and Euclidean norms within the context of Random Field Theory to estimate the probability of achieving statistical significance given the smoothing level.

The use of a between-groups mixed-model ANOVA and within-group multiple regression analyses, allowed for assessment of the contributions of various factors to differences in brain activation patterns for each hypothesis and represent a strength of this study's statistical modeling approach. For participants with a history of TBI imaging findings were correlated with information from participants' medical histories, including demographic information such as age and gender as well as TBI characteristics, self-report questionnaires, and neuropsychological testing. These data were entered into the analysis models as covariates or nuisance regressors, in accordance with each aim. Further analyses were conducted according to identified specific aims (described below).

While the current study contained a relatively small control sample, previous literature suggests that a sample size of 12 should be sufficient for detection of sufficient effect sizes (Desmond & Glover, 2002). For groups with more intra-subject variability, larger sample sizes are required (Desmond & Glover, 2002). A larger number of control group participants would be ideal, however especially considering inclusion of within-subject factors in the proposed multi-level modeling (Beckmann, Jenkinson & Smith, 2003) the control sample size was determined to be adequate for the proposed analyses. Given the expected relatively homogeneity of the control group, and anticipated variability within the TBI group, however, differences in required sample sizes for each group were determined to be necessary. This imbalance in sample sizes, however, is not anticipated to adversely impact results because the statistical program utilized for the between-subjects comparison (aim 1; 3dMVM) utilized a program designed to hand unequal sample sizes across groups, as well as the capability to correct for sphericity

violations in within-subject variables with more than two levels (Chen, Saad, Britton, Pine & Cox, 2013).

Aim-Specific Neuroimaging Analysis Strategies

To summarize this exploratory project with multiple aims, the goals of this proposal were, broadly, to: 1) examine differences between TBI patients and controls on an emotional working memory task; 2) examine the impact and activation patterns associated with combined emotional and working memory loads specifically in TBI and their correlation with specific injury characteristics; and 3) investigate correlations between patterns of activation on the emotional working memory task and scores from specific neurocognitive domains of functioning in TBI patients.

Overall, this project aimed to help validate a task sensitive to differences between TBI patients and controls, while discriminating among comorbidities such as PTSD. Given the hypothesis that brain injury alters neural structure and function, this study aimed to identify and clarify the structures and networks most vulnerable, as mechanisms for performance degradation seen in TBI. To investigate differences in performance on components of the task, contrasts for emotional (happy vs. neutral) as well as N-back ((2-1)-back, (3-1)-back, and (3-2)-back) were calculated and utilized in most analyses. Significant results were defined as those which achieved a corrected $p<.05$ (with FWE voxel-wise p and cluster size corrections applied). Locations for clusters of activation were determined using Analysis of Functional NeuroImages (AFNI) (Cox, 1996).

Aim-specific Group Neuroimaging Analyses

Aim 1: Hypothesis 1 used a 3-way mixed model ANOVA (3dMVM from AFNI, 2012) with group, emotional valence, and N-back as the Independent Variables, and BOLD activation as the Dependent Variable. Specifically, group analysis for TBI vs. controls on this task involved creation of individual statistical parametric maps using AFNI followed by whole-brain group analyses. Voxel-wise regression coefficient (β) maps were created for each participant. A General Linear Model (GLM) approach calculated beta-weight regression coefficients for each individual for each voxel time-series. Average percent –signal changes in BOLD values for specific ROIs were compared between the control group and the TBI group using a 2 (group: between subjects) x 2 (emotional valence: within subject) x 3 (number-back: within subject) ANOVA using AFNI's 3dMVM for a Multi-Variate Modeling Approach to group analyses ANOVA.

Aim 2: Hypothesis 2 utilized multiple regression to examine the relationships between injury characteristics including LOC, performance variability, and prior blast TBIs, and their association with activation patterns using 3dRegAna (AFNI program for voxel-wise multiple linear regression group analysis). For TBI patients, β-weight maps were created using voxel-wise statistical analysis (over each voxel independently), then aligned into MNI152 space using the Montreal Neurological Institute (MNI) template. These β-weight maps for task contrasts were used as the Dependent Variables in multiple regression analyses with TBI characteristics as the Independent Variables (including LOC, multiple prior blast exposures, and performance variability with age as a covariate).

Aim 3: Hypothesis 3a utilized regression analysis (3dRegAna voxel-wise multiple linear regression group analysis program from AFNI) of whole brain activation with overall NSI score. Additionally, *a priori* covariates for age and PTSD diagnosis were included in the Hypothesis 3a model. Regression analyses using β-weight values for BOLD signal changes for each of 3 contrasts (happy – neutral, (2-1)-back, and (3-1)-back) were performed for overall NSI score (with age and PTSD as covariates). For Hypothesis 3b, multiple regression analyses (3dRegAna, AFNI) using β-weight values for BOLD signal changes tested the association of 3 within-subject contrasts analyses (for happy – neutral emotional valence, as well as (2-1)-back, and (3-1)-back Task contrasts), with reported postconcussive symptom subdomain scores as independent variables (one each for affective, cognitive and somatic symptoms) for TBI patients calculated from their responses on the NSI (in accordance with the CFA by Ettenhofer & Barry, 2012).

CHAPTER 3: Results

SAMPLE DESCRIPTION

Participants were DEERS-eligible (DoD beneficiaries enrolled in the Defense Enrollment Eligibility Reporting System) research volunteers at the National Intrepid Center of Excellence (NICoE), whose primary patient population comprises Active Duty military with mild TBI and psychological health conditions not responsive to current therapy (i.e. "chronic mTBI"). Patients at NICoE undergo comprehensive diagnostic and treatment planning (4 weeks, including neuroimaging), after which they return to their own Military Treatment Facility (MTF) with a personalized treatment plan, and additional skills and tools toward healing. After exclusions for task and equipment failure (n=28), lack of physiological correction data (n=20) and excessive movement (n=33), the final study sample consisted of TBI participants (n=110) and healthy controls (n=12) for whom complete fMRI task and anatomical image data were available from the larger research project. The study participants included in this analysis had a mean age of 34.53 years for the TBI group (SD=7.49, range 21-50) and 29.17 years for controls (SD=8.24, range 20-46), which was significantly different between groups (p=.02). Mean education level for the TBI group was 13.44 years (SD=1.95), and 14.25 years for controls (SD=2.92), which was not significantly different between groups (p=.28). Both groups consisted of more males (n=108 TBI group, n=8 control group) than females (n=2 TBI, and n=4 control), which was significantly different using Yates corrected χ^2 (1), p<.01. TBI group breakdown by branch consisted of USA= 42, USN= 30, MC= 21, AF= 9, NG/Reserves= 8, while controls comprised USA= 6, USN= 2,

Dependents/retired/unknown= 4. By rank, the TBI subsample included 17 Junior enlisted E1-E4, 45 participants at E5-E6, 36 participants at E7-E9, 11 Officers, and 1 Other/unknown. For the control group, there were 5 Junior enlisted E1-E4s, 1 subject at E5-E6, 0 participants at E7-E9, 2 Officers, and 4 Other/unknown. Mean combat exposure as captured by the Combat Exposure Scale (CES) in the TBI group (M=28.12, SD=7.57, equivalent to moderate-heavy combat exposure) was significantly different from the control group (M=4.82, SD=10.78, equivalent to light combat exposure with $p<.001$). Reported neurobehavioral symptoms for the TBI group (M=41.96, SD=16.01) were also significantly different from the controls (M=5.78, SD=7.89), with $p<.001$. Furthermore, reported PTSD symptoms for the TBI group on the PCL-C (M=53.46, SD=15.41) were significantly different from the control group (M=21.54, SD=5.61), with $p<.001$. Among the TBI group, medical records indicated that TBI severity was predominantly Mild (n=106) with 3 Moderate and 1 Severe TBI participants also included in the final sample (see Table 1 for sample description).

AIM-SPECIFIC RESULTS

Results for each aim are described below, with Tables and Figures of significant activation clusters included in the Tables and Figures sections respectively. Unless otherwise specified, for fMRI analyses "p" values represent the voxel-wise p threshold, and α represents cluster p value significance incorporating FWE correction. Due to the exploratory nature of the present study, clusters of activation in some brain areas which reveal bilateral trends (expected to represent decreased likelihood of Type I error) will be reported and marked as not statistically significant. These trends, although not

significant, will be indicated as such but included in the results and discussion for the purposes of generating potential areas of further investigation for future studies.

Aim 1

Aim 1 examined differences between TBI patients (n=110) and controls (n=12) (between-subjects Independent Variable) on an emotional working memory task with emotion (happy and neutral) and number-back (N=1, 2, and 3 -back) as within-subject Independent Variables. The ANOVA comprised three main effects (N-back level, emotional valence, and group), three 2-way interactions (N-back*emotion, N-back*group, and emotion*group) as well as one 3-way interaction (N-back*emotion*group), with results specified below. The F-test (across both groups) for N-back Task yielded significant clusters of activation at the ACC, dlPFC, supramarginal gyrus/SMA, cerebellum, cuneus, hippocampus, insula, and inferior/medial temporal regions ($p=1.3 \times 10^{-4}$, all FWE-corrected $\alpha<.01$, see Figure 3a and Table 2.1). Overall Emotion F-test across all groups revealed a significant cluster of voxels activated at the left lingual gyrus ($p=.0122$, $\alpha<.01$, see Figure 3b, Table 2.1) with a slight trend toward significance at bilateral pallidum (*$\alpha>.10$*). The Group F-test was not significant, although the analyses revealed a slight trend at bilateral inferior parietal lobules ($p=.0066$, *$\alpha>.10$, see Figure 3c and Table 2.1*). The N-back by Emotion interaction revealed significant activation at the left Superior Temporal gyrus ($p=.0052$, $\alpha<.05$, see Figure 3d and Table 2.1). The Group by Emotion interaction F was significant at the left Post-central gyrus ($p=.0091$, $\alpha<.02$, see Figure 3e and Table 2.1). The Group by N-back, and Group by N-back by Emotion F tests were not significant.

Follow-up post-hoc t-tests revealed significant clusters of activation for (2-1)-back contrast at ACC, dlPFC and bilateral superior frontal cortex, as well as significant deactivation in predominantly default mode network areas (across all groups, $p=1.2 \times 10^{-4}$, $\alpha<.001$, see Figure 3f, Table 2.2 for significant voxel locations/sizes). Significant clusters of activation were also seen in similar regions for the (3-1)-back contrast, with activation at ACC and dlPFC as well as cerebellum, and de-activation at bilateral insula, hippocampus and amygdala ($p=1.2 \times 10^{-4}$, $\alpha<.001$, see Figure 3g, Table 2.2). The difference between the 3-back and 2-back condition was significant for activation at the left superior medial gyrus ($p=1.2 \times 10^{-4}$, $\alpha<.001$, see Figure 3h, Table 2.2).

The happy-neutral contrast across all groups revealed a significant cluster of activation at the left lingual gyrus ($p=8.1 \times 10^{-4}$, $\alpha<.02$, see Figure 3i, Table 2.2), as well as deactivation in an area near the caudate, although this finding should be interpreted with caution for its partial overlap with MNI ventricle space ($\alpha<.01$).

For the simple effects of the interaction of Group and Emotion at (2-1)-back, the t-test revealed significant activation at left middle frontal gyrus ($p=.0108$, $\alpha<.05$, Figure 3j, Table 2.2). Simple effects for the interaction term for Group and Emotion at (3-1)-back contrast revealed a significant cluster of deactivation at the left precuneus ($p=.0196$, $\alpha<.01$, Figure 3k, Table 2.2).

Aim 2

Aim 2 examined TBI patient and injury characteristics (n=103), using multiple regression analysis with all β values thresholded by t-statistic for significance. For these analyses, injury characteristics (LOC, RTSD, and prior TBI) and task contrasts ((2-1)-

back, (3-1)-back, and happy-neutral) were analyzed for negative and positive correlations to better understand the associations between patient variables and changes in task difficulty. Significant clusters indicating a negative correlation between the behavioral variability factor (RTSD) and the (2-1)-back contrast were found at left dlPFC, left insula and ACC ($p=.0035$, all $\alpha<.05$, see Figure 4a, Table 3) with a bilateral trend at the right dlPFC ($\alpha<.10$). Additionally, similar areas of negative correlation were seen for the (3-1)- contrast for RTSD at right superior frontal and ACC regions ($p=.0050$, all $\alpha<.02$, see Figure 4b, Table 3). For the happy-neutral contrast, only the LOC analysis yielded significant results; with left hippocampus and ACC regions responding to a negative correlation with LOC ($p=.0210$, all $\alpha<.05$, see Figure 4c and Table 3), with a bilateral trend toward significance observed at right hippocampus ($\alpha<.10$).

Aim 3

Aim 3a examined TBI patient symptoms and demographics (n=95) using multiple regression, specifically for overall Neurobehavioral Symptom Inventory (NSI) score, covarying for age and PTSD severity measured by the PTSD CheckList (PCL-C). Again, all β values were thresholded by t-statistic for significance. For these analyses, reported neurobehavioral symptoms on the NSI (overall as well as subdomain scores, as well as covariates) and task contrasts ((2-1)-back, (3-1)-back, and happy-neutral) were analyzed for negative and positive correlations to better understand any associations between reported symptoms and task difficulty. Overall NSI scores were positively correlated with the (2-1)-back contrast, with a significant cluster at the cerebellar vermis and left cerebellum ($p=.0018$, $\alpha<.04$, see Figure 5a, Table 4). However, task activation for the

happy – neutral contrast was negatively correlated with overall symptoms on the NSI, with significant clusters identified at ACC as well as left caudate ($p=4.7 \times 10^{-4}$, all $\alpha<.01$, see Figure 5b, Table 4). For PCL-C scores, there was a positive correlation with happy – neutral contrast with significant clusters at bilateral cerebellum as well as left insula and left caudate ($p=3.0 \times 10^{-4}$, all $\alpha<.01$, see Figure 5c, Table 4). Analyses for PCL-C score and (3-1)-back contrast indicated a significant negative correlation in the right cerebellum ($p=.0238$, $\alpha<.05$, see Figure 5d, Table 4) with a trend toward significance at bilateral precuneus ($\alpha<.10$). For PCL-C scores at the (2-1)-back contrast, significant negative correlations were found at the right thalamus and right lingual gyrus ($p=.0069$, $\alpha<.05$, see Figure 5e, Table 4)

Aim 3b examined task activation contrast correlations for NSI symptom subdomain scores among TBI patients (n=105) using multiple regression with all β values thresholded by t-statistic for significance. For these analyses, reported neurobehavioral subdomain symptom scores on the NSI (cognitive, affective, and somatic) and task contrasts ((2-1)-back, (3-1)-back, and happy-neutral) were analyzed for negative and positive correlations to better understand any associations between reported symptoms and task difficulty.

Somatic subdomain scores were significantly positively correlated with the 2-1 contrast in the left cuneus ($p=.0097$, $\alpha<.02$, see Figure 6a, Table 5), trending bilaterally in the right cuneus ($\alpha<.10$). Somatic subdomain scores were also significantly positively correlated with happy-neutral contrast at the right middle frontal gyrus, and right cerebellum ($p=.0063$, $\alpha<.05$, see Figure 6b, Table 5).

CHAPTER 4: Discussion

SUMMARY

In the present study of TBI and healthy control participants, preliminary evidence suggests that while brain activation patterns for a working memory task may not differ for patients with predominantly chronic mild TBI, the addition of an emotional component begins to reveal significant differences between groups. These differential activation patterns may reflect the emotional aspect of the task acting as an increased cognitive load. Generally the results of this study lend support for a multivariate model of TBI such as suggested by Silver and colleagues (2009) to include pre-injury and injury characteristics effects on post-injury neuropsychiatric functioning (including task-related performance variables and brain activation patterns, as well as neurobehavioral symptoms), since factors including LOC and history of PTSD were able to add predictive power to the models tested.

The first aim examined differences in brain activation patterns between TBI and control participants on an emotional Working Memory task. To summarize, significant task effects were found for the N-back task in keeping with prior literature (Owen, McMillan, Laird & Bullmore, 2005; Nystrom et al., 2000; Ragland et al., 2002; Schendan, Searl, Melrose & Stern, 2003; Hampson, Driesen, Skudlarski, Gore & Constable, 2006). Additionally, significant effects for the emotional component of the task were found, however, no significant differences were found between groups for overall task performance nor for the interaction of group on performance of the N-back component of the task. An interaction between group and the emotion components of the

task was found to be significant in somatosensory, executive and default mode network areas, with simple effects revealing that the emotion component of the task may be acting as an additional cognitive load. While prior literature has demonstrated differences between TBI and control participants on working memory tasks (Perlstein et al., 2004; McAllister et al., 2006), it is possible that group characteristics (e.g. predominantly mild TBI with psychiatric comorbidity, high proportion of male gender, or longer time since injury) limit comparability of this sample. Potentially, heterogeneity within this sample may have reduced power to detect significant effects of TBI. However, the finding of non-significant results between the groups is still consistent with some prior literature (McAllister et al., 2006), and may be more related to differences in speed and accuracy variability.

To further elucidate the specific effects of TBI history on performance, Aims 2 and 3 examined individual patient and injury characteristics (demographics, prior TBIs, performance variability, LOC) as well as reported symptoms within the TBI group only. Assessing for correlations among these variables with altered brain activation patterns may increase predictive power for outcomes following TBI. Briefly within the TBI group, these multiple regression analyses revealed frontal and limbic region activation differences related to RTSD for N-back task performance as well as hippocampal and ACC activation differences in response to emotional task differences for participants who reported LOC during their TBI. Regarding reported symptoms on the NSI, differences in frontal activation patterns for the emotional task component and cerebellar activation patterns for N-back contrasts were also observed. An analysis including PTSD revealed increased reactivity to the emotional component in limbic brain regions, and decreased

reactivity to the cognitive component of the N-back task. Finally, reported somatic subdomain symptoms correlated with increased reactivity to both the emotional and cognitive components of the task across multiple brain regions.

AIM 1: TBI VS. HEALTHY CONTROLS

For TBI and control subjects, the N-back task across both groups showed expected effects at ACC and dlPFC as well as insula, SMA, posterior cingulate, and inferior/medial temporal areas (see Figure 3a) (Owen et al., 2005; Nystrom et al., 2000; Ragland et al., 2002; Schendan et al., 2003; Hampson et al., 2006). Follow-up t-test for the (2-1)-back contrast revealed a pattern of activation at the ACC, dlPFC, as well as bilateral superior frontal cortex, and decreased activation in a network of regions in the default mode network (including medial PFC, hippocampus, amygdala, and cerebellum) (see Figure 3f). Follow-up t-test for the (3-1)-back contrast revealed similar patterns of activation at ACC and dlPFC, and de-activation of left insula and default mode network areas (cerebellum and hippocampus) (see Figure 3g). Overall, participants were engaged in the N-back task; evidenced by increased activity in brain areas associated with attention and task processing, and decreased use of "resting state" areas of the brain.

Furthermore, significant activation for the emotion component of the task was seen in an area associated with visual memory (left lingual gyrus). Processing in this area is primarily associated with vision, and consistent with its role in encoding of complex images may reflect how the emotional aspect of the task acts as an increased cognitive load. Additionally, a trend toward significance was observed at bilateral pallidum (see Figure 3b). Given its dopaminergic inputs and primarily GABAergic neurotransmitter

composition, the pallidum plays an important role in reward pathways, which has been implicated for involvement in drug addiction (Pierce & Kumaresan, 2006). As an area associated with regulation of motivation, behavior and emotion, it is interesting to note its potential responsivity to emotional components of the task. Future studies that include a more homogenous TBI group or larger control group might be warranted to determine if the pattern remains.

There was no significant difference found in activation patterns between TBI and controls for the overall task. Interestingly, however, bilateral trends toward significance were observed at the inferior parietal lobule – an area associated with emotional face perception (see Figure 3c). While these results were not significant and therefore must be considered with extreme caution, prior literature has shown that patients with severe TBI may struggle with static facial processing (McDonald & Saunders, 2005). It is possible that these results may have been weakened by sample limitations (e.g. primarily remote mTBI with often complicated comorbidities), and thus future studies might consider further investigation of this region in an emotional face-processing task. A significant Group by Emotion interaction did emerge at the left post-central gyrus (see Figure 3e), an area associated with the Default Mode Network (DMN); which may reflect altered resting state and functional connectivity described in previous TBI literature (Mayer, Mannell, Ling, Gasparovic & Yeo, 2011). Specifically, for the Group by Emotion interaction at (3-1)-back, deactivation was observed at the left precuneus (see Figure 3k); a DMN area involved in self-awareness and implicated in creativity and latent inhibition (Takeuchi et al., 2011). Latent inhibition describes a type of mental "flexibility" related to distractibility as well as being associated more positively with daydreaming and

creativity. Previous literature has also identified suppression problems in working memory tasks at the precuneus related to other diagnoses (e.g. Schizophrenia; Schneider et al., 2007).

Furthermore, analysis of the Group by Emotion interaction at (2-1)-back contrast revealed a significant association with activation at the left orbitofrontal cortex, which is an area involved in executive functioning and particularly in reward-punishment expectations and decision-making. Interestingly, prior studies have shown increased rates of substance abuse reported following TBI (Corrigan, Bogner & Hollman, 2012). Taken together, these findings suggest targets for investigation in future studies which might further explore potentially overlapping neural circuitry pathways involved in observed Group by Emotion interaction differences.

AIM 2: TBI INJURY AND PATIENT CHARACTERISTICS

Aim 2 investigated correlations of TBI patient and injury characteristics (e.g. loss of consciousness (LOC), prior blast exposure (pTBI) and task reaction time variability (RTSD)), with differences in task activation patterns using multiple regression analyses. For the (2-1)-back contrast, performance variability (RTSD) was significantly negatively correlated in primarily frontal and limbic brain regions. Specifically, a smaller difference in activation between the 2-back and 1-back conditions was correlated with increased performance variability at the ACC, bilateral dlPFC, and left insula (see Figure 4a). Increased performance variability (RTSD) was also significantly correlated with reduced differences in activation for the 3-back and 1-back conditions in right PFC and bilateral ACC (see Figure 4b). Importantly these areas are associated with attention, error

detection, interoception, and executive control (Bush, Luu & Posner, 2000; Smith & Jonides, 1999; Miyake et al., 2000; Craig, 2003; Craig, 2009).

Reported LOC during the most recent TBI was associated with decreased differences in activation response to the happy – neutral contrast in hippocampus and the ACC – a frontal area known not only for cognitive processing but also involved in modulation of emotional responses (see Figure 4c). A previous study of neural processing found altered processing of positive events to be correlated with depression (Arnold et al., 2010). Affect and emotional expression have also been known to impact memory (Fitzgerald et al., 2011); especially prefrontal activity in the formation of memory (Sergerie, Lepage & Armony, 2005). The results of this study then are remarkable because prior literature has found that TBI with LOC is associated with a pattern of worsened symptoms, notably including increased vulnerability to Major Depressive Disorder (Matthews et al., 2011), and the ACC has been shown to be an integral part of processing emotional aspects of faces (Killgore & Yurgelun-Todd, 2004). These sites of increased performance variability and location-specific sensitivity to LOC disruption may offer glimpses into the mechanisms by which increased cognitive and affective dysfunction can occur following TBI. For example, if performance variability reflects inefficiency in allocation of neural resources, it could be speculated that networks already burdened with a cognitive load might be less responsive to increasing task demands.

AIM 3: TBI GROUP NEUROBEHAVIORAL SYMPTOMS CORRELATIONS

Neurobehavioral Symptoms Inventory (NSI) scores indicate a subject's overall reported symptoms, as well as division into subdomains for cognitive, affective and physical symptoms. Higher levels of reported neurobehavioral symptoms were correlated with decreased reactivity to the difference between happy and neutral faces at the ACC and left caudate (see Figure 5b). These areas are associated with attention, emotion processing, learning and memory which are highly interdependent. It is possible TBI performance may be characterized by cognitive inefficiency, and that once available resources are being utilized in response to somatic symptoms, the ability to respond consistently to emotional valence is diminished. Conversely, increased NSI scores were correlated with increased reactivity to the (2-1)-back contrast in the left cerebellum and at the cerebellar vermis. Damage to the cerebellum and particularly the cerebellar vermis has also been specifically associated with CCAS and affective dysregulation (Schmahmann, 2004; Schmahmann & Caplan, 2006). Interestingly, prior literature describing the cognitive and affective deficits associated with Cerebellar Cognitive Affective Syndrome (CCAS) resulting from damage to the cerebellum (Schmahmann, 2004; Schmahmann & Caplan, 2006) mirror some symptoms described by TBI patients.

Furthermore, increased somatic symptoms were also correlated with increased response to the difference between 2-back and 1-back at the left cuneus/mid-occipital region with a bilateral trend (see Figure 6a), such that increased difference in activation between N-back levels was correlated with increased reported somatic symptoms. The cuneus represents the start of visual processing for both the dorsal (visuo-spatial) and ventral (visual recognition and memory) streams of processing. In fact, differential activation patterns in this region are associated with inhibitory control disorders (Page et

al., 2009; Solanto, Schulz, Fan, Tang, & Newcorn, 2009) and PTSD (Falconer et al., 2008) while volumetric variations at the cuneus have been associated with bipolar disorder (Frangou, 2005; Haldane, Cunningham, Androutsos & Frangou, 2008). For somatic subdomain scores, significant activation was also seen in response to increased difference between happy and neutral faces at the right middle frontal gyrus and right cerebellum, with trends at the right caudate and precuneus (see Figure 6b), such that increased difference in activation between happy and neutral emotions was correlated with increased somatic symptoms reported. These areas are associated with attention, emotion processing and regulation, as well as learning and memory. Although the mechanisms by which increased responsivity to emotion is specifically related to somatic symptoms remains unclear, these findings are consistent with prior literature suggesting that a history of mild TBI may correlate most strongly with neurobehavioral symptoms in the somatic subdomain (Ettenhofer, Reinhardt & Barry, 2013). These findings highlight the necessity of further studies to better understand the role of the cerebellum in cognitive and emotional processing and regulation.

Although not the primary focus of the present study, considering the frequent comorbidity of PTSD with TBI it is worth reviewing interesting results from inclusion of a measure for PTSD from these exploratory analyses as well. For example, increased PTSD severity scores were correlated with decreased reactivity to the difference between 3-back and 1-back at the cerebellum (see Figure 5e), an area associated with cognitive and affective regulation. Volumetric changes in the cerebellum have been associated with PTSD symptoms and implicated in affect dysregulation previously in the literature (Baldaçara et al., 2011). If TBI results in changes in cerebellar volumes, this may help to

explain some of the frequently comorbid symptoms of PTSD. While results did not reach statistical significance for decreased reactivity at bilateral precuneus in this analysis, prior literature has found altered resting state activity in DMN regions in PTSD (Yan et al., 2013; Yin et al., 2011), and thus future studies should pursue this interesting possible connection. Combined with findings of decreased reactivity to the (2-1)-back contrast at the right thalamus, which is a central region essential in information processing and regulation of arousal, these findings suggest a potential pathway for some of the deficits and symptoms commonly associated with PTSD.

Conversely, increased PTSD symptom scores were correlated with increased activation response to the difference between happy and neutral faces at the cerebellum, as well as caudate and insula (see Figure 5d), such that higher level of PTSD symptoms was correlated with a greater reactivity to the difference between happy and neutral conditions. Taken together it seems that these findings suggest a dissociation between cognitive and emotional components, where reduced cognitive processing reactivity and higher emotional processing reactivity are associated with increased PTSD symptom burden. It is possible that cognitive and emotional processing might occur within different networks. However, these findings also suggest the possibility of additional brain regions involved in the neural circuitry of emotional dysregulation model of PTSD pathophysiology, in which hyporesponsivity in frontal executive regions including PFC result in hyperresponsivity of the amygdala and therefore inadequate inhibition of limbic system activity (McNally, 2006). While these findings for a measure of PTSD are interesting on their own, their inclusion highlights the importance of considering the effects of PTSD on neuroimaging results for TBI especially since it is unclear whether

there is any causal connection among them. Disruption at these areas involved in emotion and memory may be related to dysregulation observed in both TBI and PTSD and future studies might endeavor to better elucidate their relationships and potentially differential patterns of activation.

GENERAL DISCUSSION

Prior literature has demonstrated that severity of TBI alone does not adequately predict outcomes. These findings may be partially attributed to the fact that TBI often results in a complicated pattern of injury and sequelae. Variability in brain activation patterns and/or performance – even among those who have experienced a similar injury – suggests more complex analyses are warranted. Variables such as pre-existing patient factors and injury characteristics, as well as post-injury psychosocial environment are likely to contribute to outcome differences observed between patients with TBI and controls (Silver et al., 2009). While data for location of injury were not gathered in the present study, correlations between activation patterns at different brain area locations and various factors suggest that damage to those areas may be predictive of certain patterns of symptoms.

Although group differences were not observed on the overall emotional N-back task, an interaction between group and emotional valence revealed significant activation patterns in somatosensory, executive and default mode network areas, with follow-up analyses suggesting that the emotional component of the task may act as an additional cognitive load factor. Within the TBI group, activation differences at frontal and limbic regions were significantly associated with performance variability for both cognitive and

emotional components, while frontal regulatory and memory regions appeared especially sensitive to analyses for LOC. Neurobehavioral symptoms, and particularly those in the somatic subdomain, appeared to be correlated with increased reactivity to cognitive task elements at visual processing and cerebellar areas. In contrast, while somatic symptoms also correlated with increased reactivity in frontal and cerebellar regions, overall NSI scores appeared to correlate with decreased reactivity to emotional stimuli in executive and learning areas.

Regarding mechanism of injury (MOI), many of the participants included in the current study reported TBI related to an explosive blast (typically more diffuse pattern of injury) rather than blunt trauma (often more localized pattern of injury) (Davenport, Lim, Armstrong, & Sponheim, 2011). While in some studies blast vs. non-blast MOI has been associated with differences in reported symptoms (Mendez et al., 2013), other studies suggest that these differences may be primarily related to LOC (Luethcke et al., 2011).

Although not a focus of this study, inclusion of PTSD symptoms in the analyses revealed interesting cognitive and affective sensitivity differences. Specifically, increased reactivity to the emotional component and decreased reactivity to the cognitive component of the N-back task were observed. These differences were found not only in learning and emotion regulation areas, but also particularly in the cerebellum, an area noted in the literature to be especially sensitive to effects of trauma (Baldacara et al., 2011). In addition, decreased sensitivity to the difference among 2-back and 1-back was correlated with increased symptoms at the right thalamus, suggesting a potentially important link in the pathway responsible for altered levels of arousal and information processing in PTSD. It is also important to consider biopsychosocial context in

interpretation and potential application of the results of this study, since previous literature has noted differential effects of psychosocial environment on outcomes (Luis et al., 2003; Halbauer et al., 2009). While an initial brain injury may set into motion a subsequent pathophysiological cascade which continues to propagate neuronal injury acutely following an initial trauma (LaPlaca et al., 2007; Rao & Lyketsos, 2000; Silver et al., 2009), additional patient characteristics such as prior history of TBI, age, and psychiatric comorbidities should also be taken into account when predicting outcomes.

Limitations and Future Directions

Due to the nature of the study (in a clinical TBI population), it is important to consider that this dataset had a limited sample of healthy controls which may have affected the analyses. Although the sample does not appear to be biased, it is also important to consider whether there were any significant differences between those participants who were removed from the sample for movement or other errors and those participants who were not. Additionally, analyses were performed retrospectively so limited measures were available, many of which were self-report in nature. Regarding the significant difference in age between groups, results should be interpreted with caution. While it is expected that brain morphology in this participant sample should be relatively stable and unlikely to create a source of variability within the sample across the age range included (overall range= 20-50 years; with similar ranges among TBI group= 21-50 years and control group= 20-46 years), this restricted range may also suggest decreased generalizability to the greater TBI population. Specifically, while age was

controlled for in aims 2 and 3a, it was not included as a covariate in the analyses for aims 1 or 3b.

Moreover, differences in sample sizes between the TBI and control groups may have also affected the analyses. While the analysis methods used theoretically controlled for such differences, future studies should confirm whether more equivalent size and variability within each of these groups yield similar results. Also, a larger than usual number of patients were excluded for equipment and task failure, in addition to those excluded for movement. Unfortunately, because this study occurred in a clinical setting with a retrospective dataset, not all subjects completed all measures in order to respect patient care practices. Due to the TBI severity of this population being predominantly complicated or chronic mild TBI, generalizability to the U.S. population at large may be limited. However, as a clinical sample of the combat-wounded active duty military personnel population who have experienced a TBI and report persistent symptoms, the patients who participated in this study are highly representative.

Future studies should incorporate more sophisticated analyses such as multiple regression analyses with brain activation patterns adjusted for performance variability, as well as MANOVA and mixed linear effects modeling of within and between subjects factors analyses to incorporate additional covariates for more precise examination of the importance of pre-injury, injury and post-injury factors such as suggested by Silver and colleagues (2009) in pathophysiological sequelae and reported symptoms following TBI. Further examination of additional measures (e.g. for performance variability, as well as incorporating task interactions capitalizing on layered cognitive loading) should also be considered in order to best characterize the contributions of various factors to outcomes

following TBI. A follow-up analysis in which only mTBI patients are included could also eliminate the question of whether the small number of moderate and severe TBI patients included in this study skewed any of the findings. Although this sample is representative of a large proportion of TBIs classified as mild, it is possible that this group represents a different pathophysiological and/or functional category from more moderate and severe TBIs and should be analyzed as separate phenomena. Additional studies looking at the impact of TBI on brain areas including the cerebellum, as well as the default mode network, may help determine if a specific pattern of volumetric or connectivity changes are associated with this population of predominantly chronic mild TBI. Future research might also benefit from the use of a TBI-specific template for comparison of neuroimaging findings for more precise localization of functional variability without confounding any morphological differences caused by diffuse axonal injury or focal damage from TBI.

CONCLUSION

The involvement of frontal, limbic, and default mode networks in many of these results is consistent with literature describing cognitive and affective deficits in patients who have suffered a TBI (McAllister et al., 2006; Silver et al., 2009). The brain activation patterns observed for the emotional aspects of the N-back task on TBI vs. healthy control participants represents a novel finding. While in the present study only differences between happy and neutral emotional faces were investigated, these findings may be interpreted to be related to its distracting nature and subsequently increased cognitive load effect consistent with prior research (Chiew & Braver, 2011). The

inclusion of multiple patient and injury variables as well as the investigation of neurobehavioral symptoms within a large sample of TBI patients represents an important step in understanding how multiple factors contribute to a biopsychosocial model of recovery from TBI.

Together these results suggest the possibility of distinct brain activation patterns for differential reactivity to cognitive and emotional challenges. Increased reactivity to stimuli differences at brain structures responsible for interoception, coordination and planning of responses tended to be related to higher levels of symptoms. Conversely, decreased reactivity to changes in cognitive load at brain structures responsible to processing of information and executive control tended to be related to increased symptoms. LOC and performance variability factors showed a similar inverse relationship for brain areas associated with saliency and cognitive and affective decision making. Viewed another way, altered patterns of brain activation were found in brain areas involved in information processing, encoding and executive decisions for cognitive elements, while also in brain areas for memory, emotional-modulation and decision-making with respect to the emotional processing. The possibility of overlapping yet distinct networks of activation for cognitive and emotional stimuli is consistent with previous neuroimaging research (Chiew & Braver, 2011). Future studies combining structural and functional imaging will be important to help parse out the interactions among these networks under varying degrees of cognitive load.

Another recurring theme of the results from this study, is the potentially significant involvement of the cerebellum in cognitive and affective tasks. Prior research has alluded to altered patterns of cerebellar activity occurring in disorders including

PTSD and cerebellar cognitive affective syndrome (Schmahmann & Caplan, 2006; Baldacara et al., 2011) as well as TBI (Potts, Adwanikar & Noble-Haeusslein, 2009). While its role in these disorders is still incompletely understood, the results of this study suggest that differences in activation at the cerebellum may be associated with symptom complaints, especially for PTSD following TBI.

As in previous literature, the comparison of healthy controls with predominantly mild chronic TBI yielded weak predictive power for working memory performance. However, within-TBI group contrast analyses revealed differences in brain activation patterns which may highlight the role of additional patient and injury factors in performance. Specifically these analyses underscore the possible value of including LOC and RT variability in future models of TBI as predictive variables for outcomes and prognosis.

These results also support the possibility of identifying profiles of more homogeneous groups within TBI patient populations from these additional factors and symptoms. For example, patients reporting higher somatic symptoms tended to exhibit increased activation in cognitive information processing and inhibitory control regions, as well as brain structures responsible for attention, set-shifting, learning, and emotional-processing and regulation. The brain activation profile for patients with greater PTSD symptoms in this study appeared to comprise greater reactivity to emotional stimuli at coordination and saliency detection areas, while decreased reactivity to cognitive stimuli at input and information-processing structures. In line with previous research indicating poor frontal/executive modulation of affective limbic structures in PTSD (McNally, 2006), the results of this study point to brain areas which are potentially involved in the

input and information processing portions of these networks, and which may be particularly sensitive to brain injury. Subsequently, patients with damage to certain areas of the brain may be more or less likely to develop certain symptom profiles and future studies including structural white matter scans may better elucidate the mechanisms of altered patterns of activity within such networks. Perhaps most relevant to this idea of specific areas of damage relating to specific symptoms, the results from this study also indicate a role for the inclusion of injury factors in predicting outcomes following TBI.

Given that reported LOC appeared to be correlated with decreased reactivity to emotional aspects of the task in brain regions responsible for memory and emotional regulation, these results lend support to studies which suggest LOC may contribute to differential outcomes (Matthews et al., 2011; Halbauer et al., 2009). The inclusion of these additional patient and injury factors may provide important differentiation of potential risk factors in developing post-injury neurobehavioral symptoms and predictions for patient prognosis following a TBI. Furthermore, LOC, and possibly other factors including previous history of TBIs, may provide important predictive power to future models utilizing algorithms for identification of brain activation patterns which correlate with specific symptoms or prognosis. The possibility of using task performance on early neuroimaging measures to help determine potentially different avenues for treatment, would be highly beneficial in the implementation of individually-tailored medicine.

Lastly, given the high degree of heterogeneity found among TBI patients in prior literature (Silver et al., 2009; McAllister et al., 2006; Kou et al., 2010), this study emphasizes the utility of a measure of within-subject variability in examining brain

activation patterns. Specifically, decreased reactivity to the differences among various cognitive levels of difficulty was correlated with higher within-subject performance variability in primarily frontal attention, error-detection, and decision-making brain regions. Task performance variability may be an important marker for altered cognitive processing following TBI, especially given that overall achievement on neuropsychological examination may often be within normal limits for patients who have experienced a mild TBI (Belanger et al., 2005; Macciocchi et al., 1996). Future studies including measures of this performance variability may offer valuable perspective on difficulties reported by patients following a TBI.

Overall, the results of this study support the consideration of various profiles of patient and injury characteristics in creating more homogeneous groups of TBI patients, toward a better understanding of the brain networks and structures involved in various cognitive and affective tasks, as well as improved models for predicting outcomes and treatment planning.

Table 1. Sample Description and Demographics. ** TBI Severity: 106 mild, 3 moderate, 1 severe*

	TBI (n=110) **Mean (SD)**	**Controls (n=12)** **Mean (SD)**	**p (t or $\chi 2$)**
Age	34.53 (7.49)	29.17 (8.24)	*p=.02
Education	13.44 (1.95)	14.25 (2.92)	*p=.28.*
Gender (male)	98%	92%	* p<.001
PCL-C	53.46 (15.41)	21.54 (5.61)	* p<.001
NSI	41.96 (16.01)	5.78 (7.89)	* p<.001
CES	28.12 (7.57) *moderate - heavy*	4.82 (10.78) *light*	* p<.001
TBI severity (mild)	96%	---	---

Table 2.1. Aim 1 Regions of significant clusters of brain activation/deactivation (TBI n=110, CTL n=12)

Region/BA	X	Y	Z	Volume (mm3)	α	F-stat value	SD
Group F							
L Inf Parietal Lobule	*60*	*42*	*41*	*25*	*>.10*	*7.6*	*1.5*
R Inf Parietal Lobule	*-60*	*50*	*41*	*21*	*>.10*	*6.7*	*0.6*
N-back F							
L Sup Medial Gyrus	0	-29	44	278	<.001	14.9	4.7
R Parahippocampus	-32	37	-20	209	<.001	11.1	1.3
L Fusiform/Med Temp	40	61	-5	138	<.001	11.6	1.8
L Insula	36	5	22	89	<.001	11.3	1.8
R Inf Parietal	-48	50	56	78	<.001	11.8	1.8
L Supramarginal	52	35	26	71	<.001	10.7	1.1
L Amygdala	24	9	-12	69	<.001	12.4	2.9
L Sup Med	4	-55	26	65	<.001	11.7	2.0
R Middle Frontal	-36	-33	44	65	<.001	12.3	2.4
L Med Temp Pole	44	-14	-35	63	<.001	10.8	0.9
R Amygdala	-28	7	-12	57	<.001	13.7	3.7
R Post Cingulate	-20	39	22	45	<.001	13.1	2.8
L Mid Frontal	44	-25	37	38	<.001	10.8	1.4
R SMA	-8	12	63	38	<.001	12.8	2.2
L Cerebellum	36	69	-46	37	<.001	11.4	1.4
R Med Temporal Pole	-44	-6	-27	30	<.001	10.4	0.8
L Mid Frontal	28	-59	14	30	<.001	11.9	1.8
R Sup Temporal	-56	39	7	28	<.001	10.3	0.7
R Insula	-36	-3	18	23	<.001	11.6	1.9
R Cuneus/Sup Occ	-16	95	14	20	<.01	10.0	0.6
Emotion F							
L Lingual Gyrus	12	72	-5	122	<.01	9.3	2.3
L Pallidum	*28*	*12*	*7*	*34*	*>.10*	*8.8*	*1.8*
R Pallidum	*-28*	*8*	*-5*	*20*	*>.10*	*8.2*	*1.3*
Group*Emotion F							
L Post-Central Gyrus	48	16	33	70	<.02	8.9	1.6
N-back*Emotion F							
L Superior Temp	40	27	7	54	<.01	6.5	0.8
L Superior Temp	52	42	22	39	<.05	6.7	1.0

Table 2.2. Aim 1 Regions of significant clusters of brain activation/deactivation: contrasts (TBI n=110, CTL n=12).

Region/BA	X	Y	Z	Volume (mm3)	α	Coef. Estim.	t-stat
2-1 t							
L Fusiform/Cerebellum	44	46	-19	102	<.001	-0.1	-4.3
R Sup/Mid	-28	-10	66	85	<.001	0.1	4.8
L Sup Medial/ACC	8	-59	41	77	<.001	-0.1	-4.3
L Rolandic Opp	56	-3	3	67	<.001	-0.1	-4.3
R Frontal	-36	39	-23	58	<.001	-0.1	-4.3
L Mid Temp	44	-18	-35	54	<.001	-0.1	-4.4
L SMA	0	-29	44	54	<.001	0.1	4.7
R Mid Frontal	-40	-32	44	48	<.001	0.1	4.5
R Cuneus	-12	99	14	42	<.001	-0.1	-4.2
L Hippocampus	20	16	-12	40	<.001	-0.1	-4.2
L SupraMarginal	56	31	26	40	<.001	-0.1	-4.4
L Mid Frontal	28	-63	11	38	<.001	0.1	4.3
R Amygdala	-20	1	-16	34	<.001	-0.1	-4.5
L Mid Frontal	48	-25	37	32	<.001	0.1	4.4
R SMA	-4	12	59	27	<.001	-0.1	-4.2
R Sup Temp	-64	39	11	23	<.001	-0.1	-4.2
3-1 t							
L/R Sup Medial	0	-29	44	168	<.001	0.1	4.7
R Mid Temp	-60	61	14	115	<.001	-0.1	-4.3
L Inf Temp	44	69	-5	48	<.001	-0.1	-4.3
R Inf Parietal	-48	50	59	44	<.001	0.1	4.3
R Hippocampus	-20	5	-12	41	<.001	-0.1	-4.6
L Cerebellum	40	65	-46	36	<.001	0.1	4.5
R Fusiform	-40	42	-23	28	<.001	-0.1	-4.3
L Hippocampus	20	16	-12	28	<.001	-0.1	-4.5
L Insula	36	1	14	24	<.001	-0.05	-4.4
3-2 t							
L Sup Med	0	-40	29	25	<.001	0.1	4.3
Hap-Neu t							
L Lingual Gyrus	8	72	-5	20	<.02	0.1	3.7
Group*Emo @2-1 t							
L Mid Frontal	36	-59	-1	61	<.05	0.6	3.1
Group*Emo @3-1 t							
L Precuneus	20	87	41	130	<.01	-0.2	-2.7

Table 3. Aim 2 Regions of significant clusters of brain activation/deactivation (n=103 TBI). (+) = positive correlation between factors, (-) = negative correlation between factors.

Region/BA	X	Y	Z	Volume (mm3)	α	Coef. Estim.	t-stat
RTSD @2-1 (-)							
L Mid Frontal/dlPFC	32	-55	7	58	<.01	-12568.0	-3.7
L Sup Frontal	28	-10	67	38	<.03	-12720.9	-3.2
L Insula	28	-21	-5	36	<.03	-7499.5	-3.2
L/R Sup Med /ACC	0	-29	44	32	<.05	-13566.7	-3.3
R Sup Frontal	*-32*	*-55*	*22*	*27*	*<.10*	*-13513.2*	*-3.2*
RTSD @3-1 (-)							
R Sup Med	-4	-29	44	45	<.03	-13119.8	-2.9
R Sup Frontal	-32	-59	18	45	<.03	-6157.9	-3.0
LOC @Hap-Neu (-)							
L Hippocampus	12	24	-31	115	<.03	2507.8	0.8
L/R Sup Med /ACC	0	-51	-8	104	<.05	482.6	0.1
R Hippocampus	*-16*	*31*	*-5*	*24*	*>.10*	*824.9*	*0.5*

Table 4. Aim 3a Regions of significant clusters of brain activation/deactivation (n=95 TBI). (+) = positive correlation between factors, (-) = negative correlation between factors.

Region/BA	X	Y	Z	Volume (mm3)	α	Coef. Estim.	t-stat
NSI @Hap-Neu (-)							
L ACC	0	-36	-5	37	<.001	-74.7	-3.8
R ACC	-20	-33	-12	21	<.01	-49.5	-3.8
L Caudate	4	-10	-5	20	<.01	-32.7	-3.7
NSI @2-1back (+)							
Cerebellar Vermis	0	39	-16	26	<.03	37.6	3.8
L Cerebellum	28	46	-50	24	<.04	42.0	3.4
PTSD @Hap-Neu (+)							
R Cerebellum	-32	50	-53	89	<.001	40.4	4.1
R Cerebellum	-28	39	-31	55	<.001	22.2	4.1
L Cerebellum	20	35	-27	40	<.001	28.3	4.1
L Insula	52	-14	-8	22	<.01	54.0	3.9
L Caudate	20	-25	-1	21	<.01	22.2	4.0
PTSD @2-1 (-)							
R Thalamus	4	24	14	47	<.05	-29.8	-3.0
R Lingual	-12	91	-12	46	<.05	-112.5	-3.1
PTSD @3-1 (-)							
R Cerebellum	-28	80	-20	79	<.05	-76.5	-2.5
R Precuneus	*-16*	*76*	*59*	*38*	*<.10*	*-64.6*	*-2.7*
L Precuneus	*0*	*42*	*-23*	*38*	*<.10*	*-57.6*	*-2.7*

Table 5. Aim 3b Regions of significant clusters of brain activation/deactivation (n=105 TBI). (+) = positive correlation between factors, (-) = negative correlation between factors.

Region/BA	X	Y	Z	Volume (mm3)	α	Coef. Estim.	t-stat
Somatic @Hap-Neu (+)							
R Sup/Mid Frontal	-32	-48	41	54	<.02	70.0	3.3
R Cerebellum	-32	57	-57	44	<.05	43.8	3.2
Somatic @2-1 (+)							
L Cuneus/Mid Occip	44	84	3	72	<.02	60.9	3.1
R Cuneus/Mid Occip	*-40*	*76*	*7*	*21*	*>.10*	*51.5*	*2.8*

	Loss of Consciousness (LOC)	Posttraumatic Amnesia (PTA)	GCS
Mild	≤ 30 minutes	≤ 24 hours	13-15
Moderate	30 minutes - 24 hours	1-7 days	9-12
Severe	≥ 24 hours	≥ 7 days	3-8

Figure 1. Classification of TBI injury severity. *Adapted from VA, DoD and VA-DoD Deployment Health Working Group (2010)*

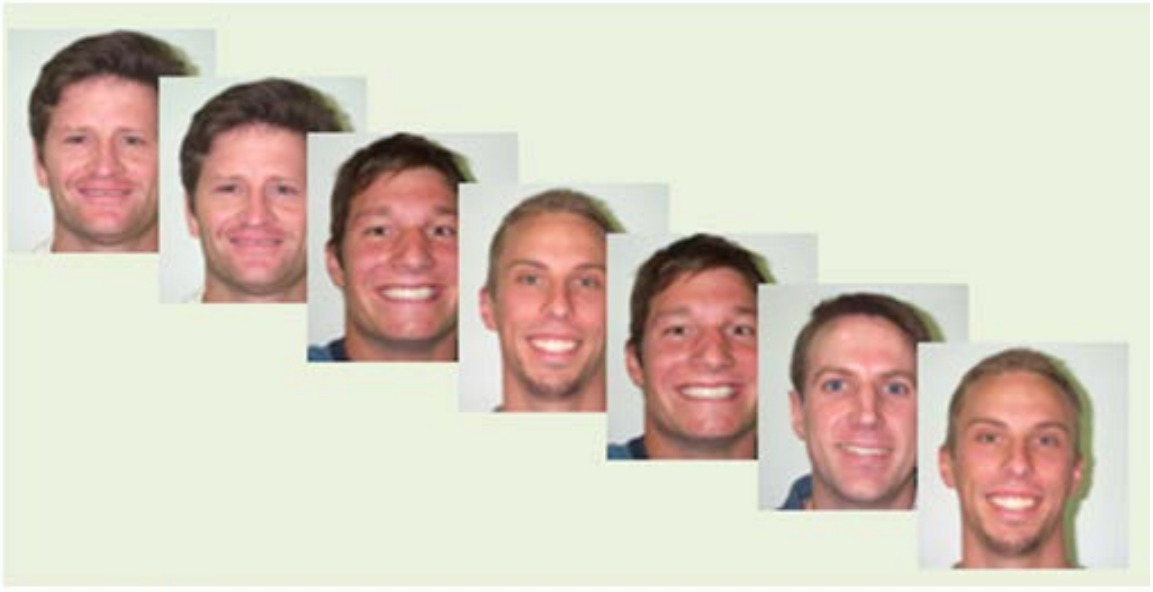

Figure 2a. Emotional N-back Task schematic representations of trial block sections (example of correct 1-back picture match for the 1-back trial blocks).

Figure 2b. Emotional N-back Task schematic representations of trial block sections (example of correct 2-back picture match for the 2-back trial blocks)

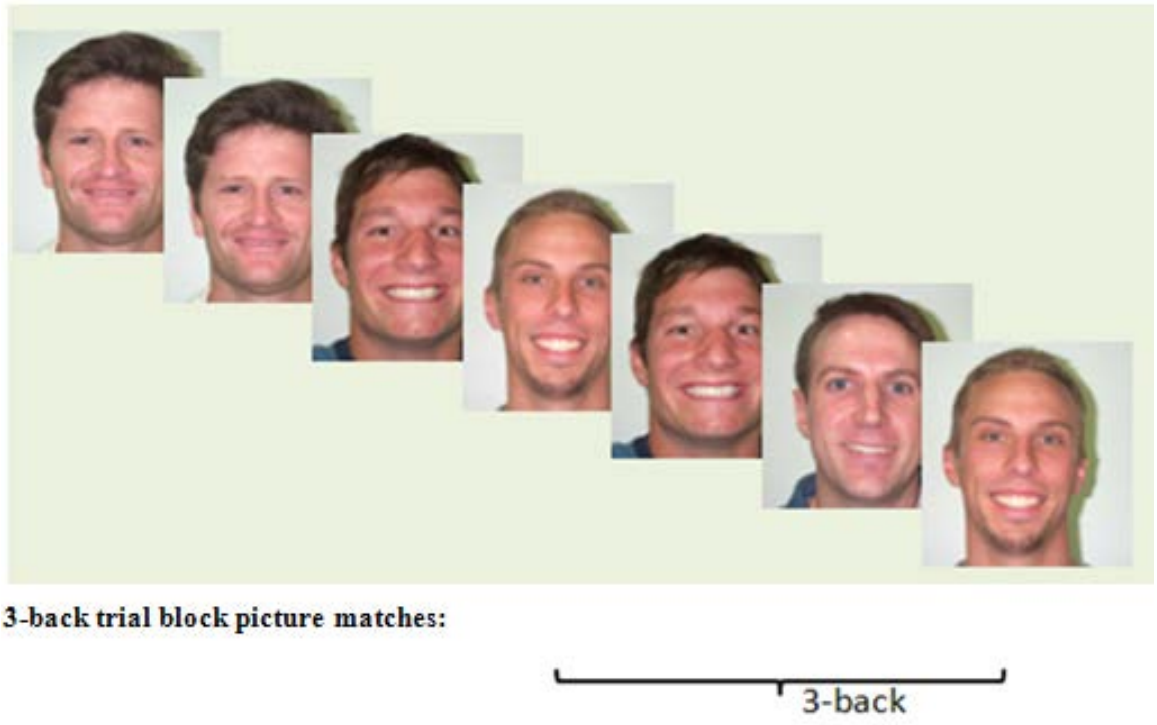

Figure 2c. Emotional N-back Task schematic representations of trial block sections (example of correct 3-back picture match for the 3-back trial blocks)

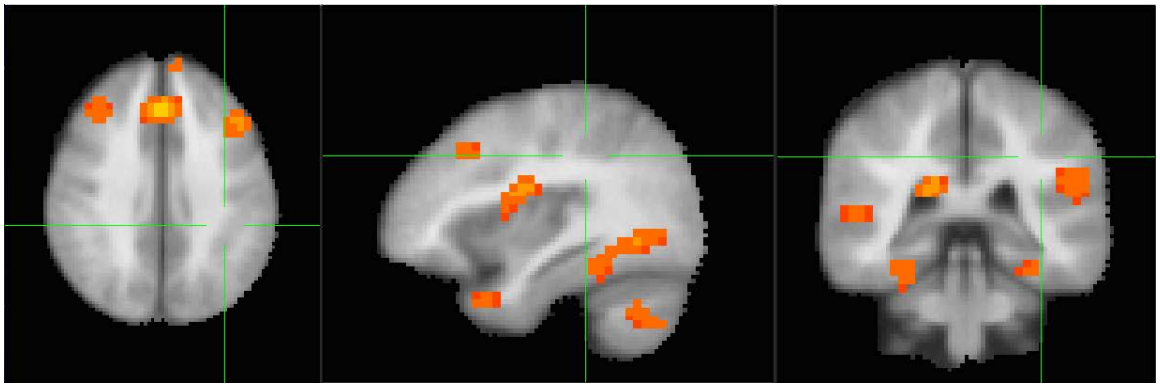

Figure 3a. Aim 1: Overall F-test for N-back Task activation (-36L -36P 36S)

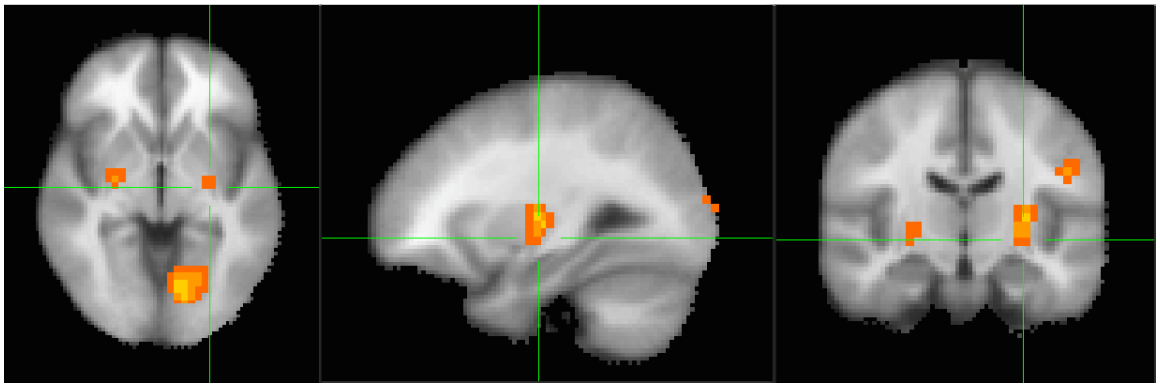

Figure 3b. Aim 1: Overall F-test for Emotional Task activation (-28L 14P -4I)

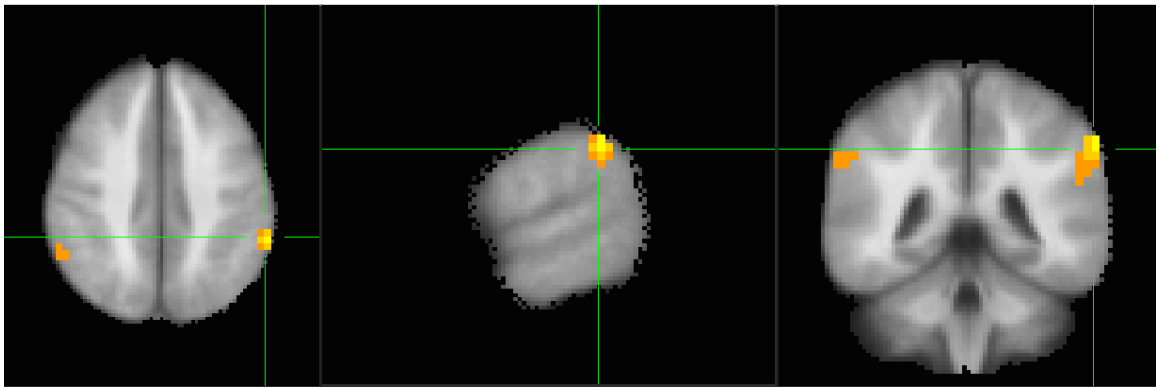

Figure 3c. Aim 1: *Group F-test (n.s.) (-60L -42P 40S)*

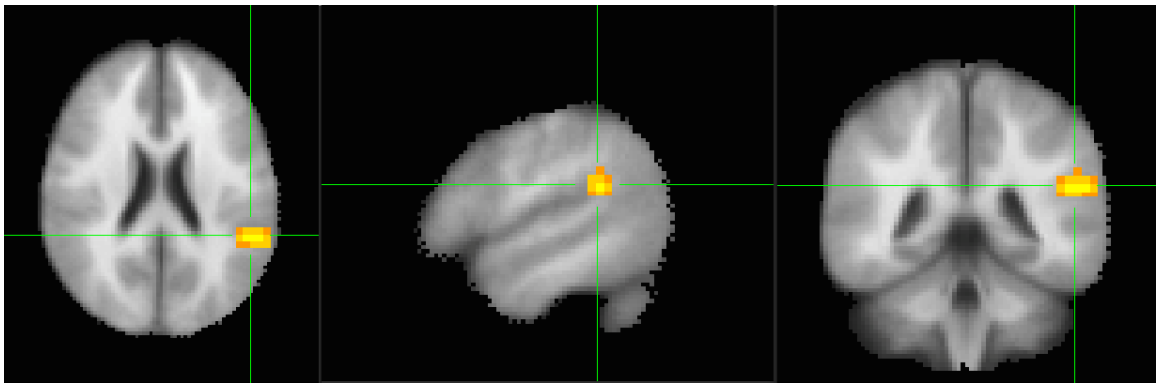

Figure 3d. Aim 1: N-back and emotion interaction F-test (-52L -42P 22S)

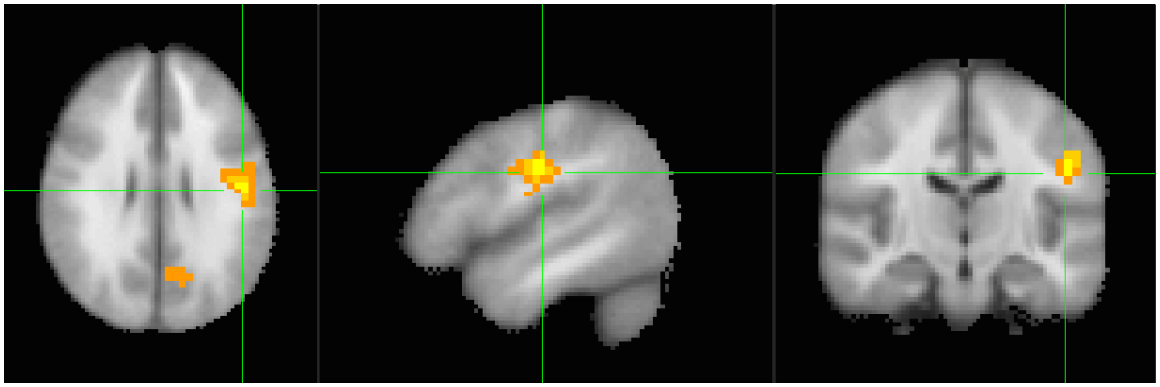

Figure 3e. Aim 1: Group and emotion interaction F-test (-48L -16P 28S)

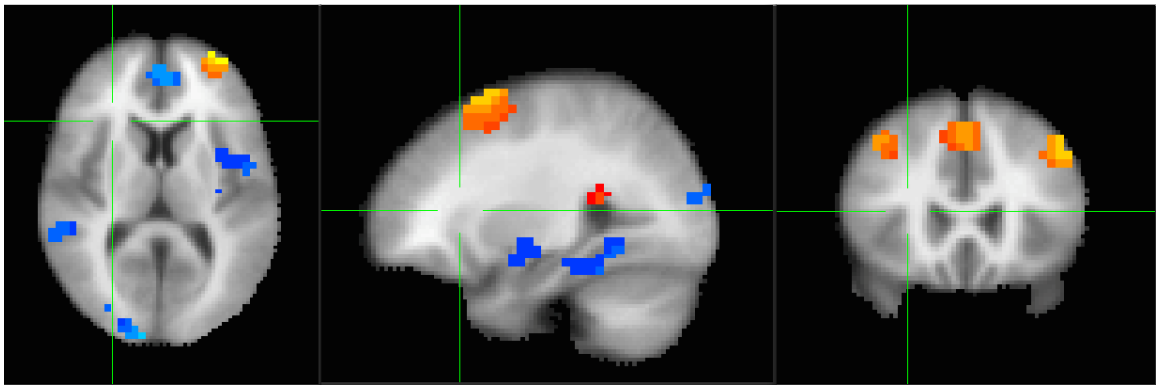

Figure 3f. Aim 1: (2-1)-back contrast Task activation t-test across all groups (28R 24A 10S)

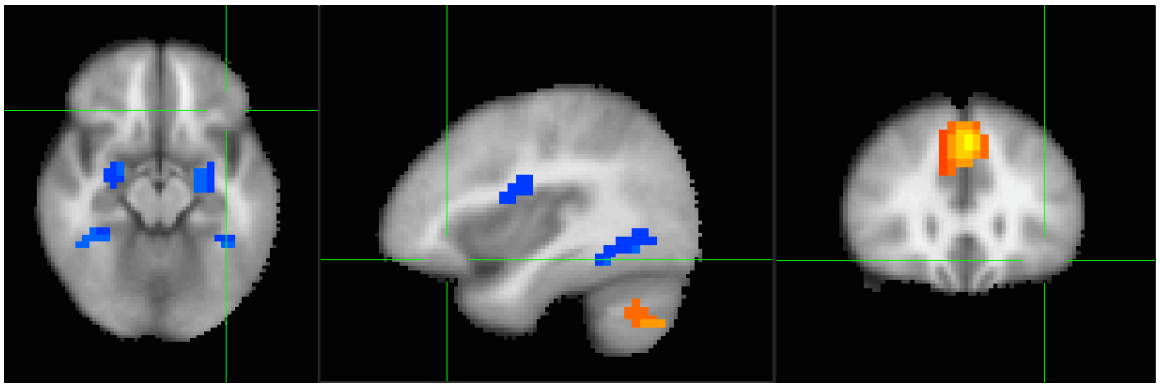

Figure 3g. Aim 1: (3-1)-back contrast Task activation t-test across groups (-38L 30A -14I)

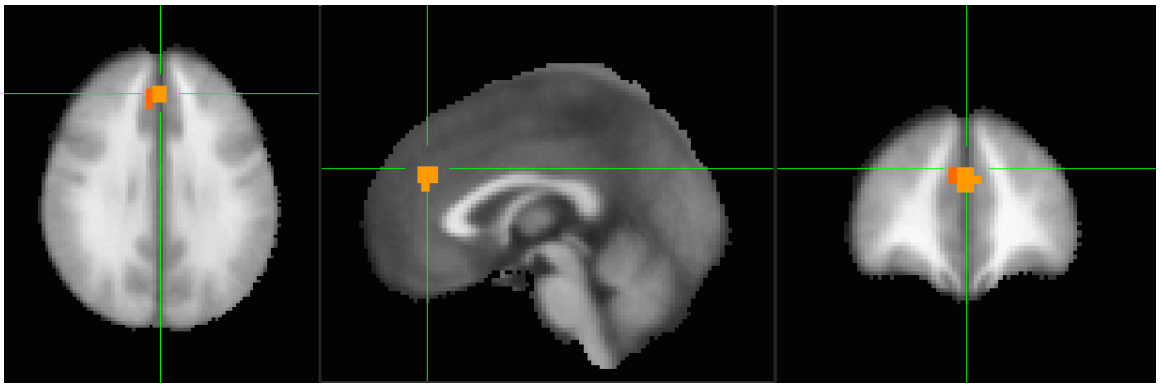

Figure 3h. Aim 1: (3-2)-back contrast Task activation t-test across groups (0L 40A 30S)

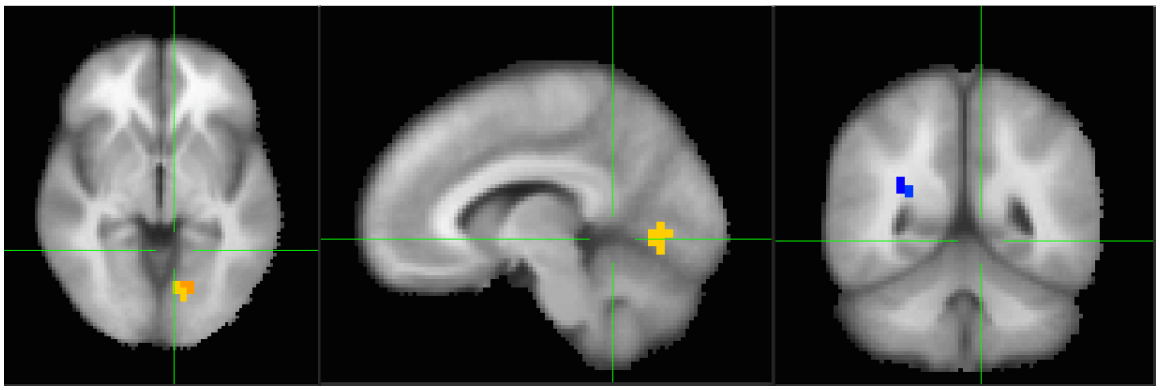

Figure 3i. Aim 1: Happy – Neutral contrast Task activation t-test across all groups (-8L -50P -4I)

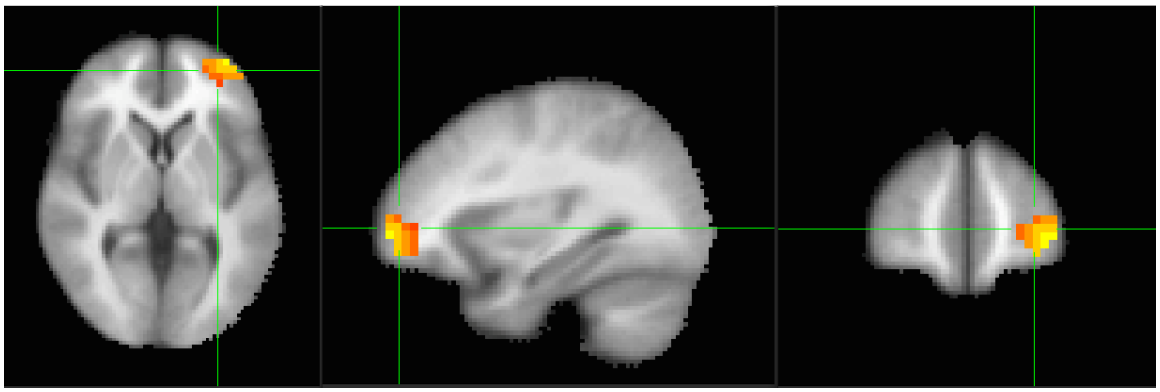

Figure 3j. Aim 1: Group and emotion interaction at (2-1)-back contrast t-test (-32L 54A 2S)

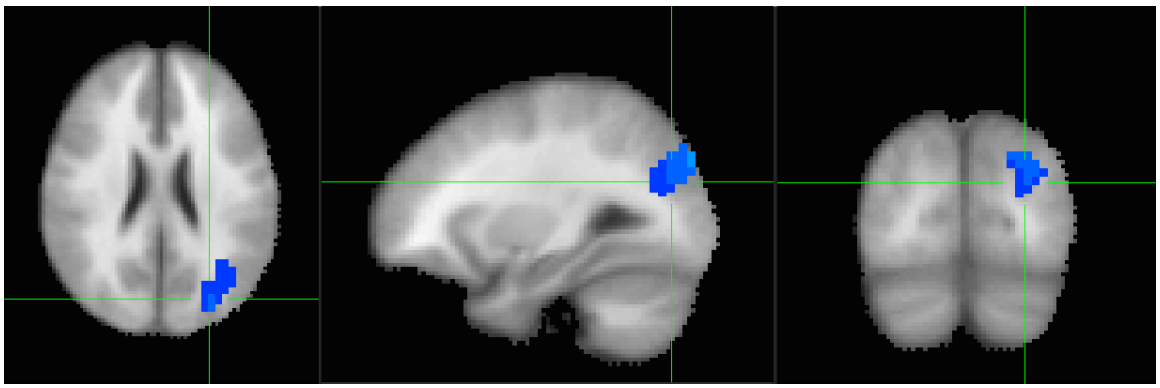

Figure 3k. Aim 1: Group and emotion interaction at (3-1)-back contrast t-test (-28L -78P 24S)

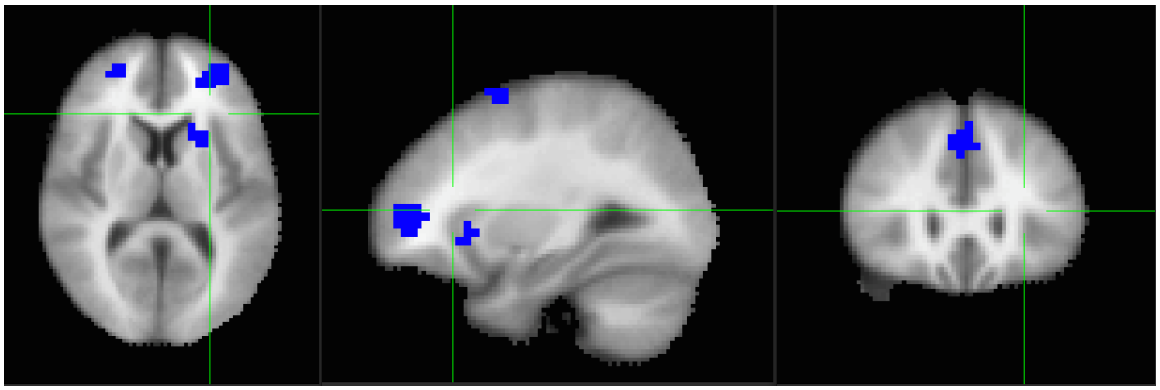

Figure 4a. Aim 2: RTSD at (2-1)-back contrast t-test (-28L 28A 10S)
All β values thresholded by t-statistic for significance

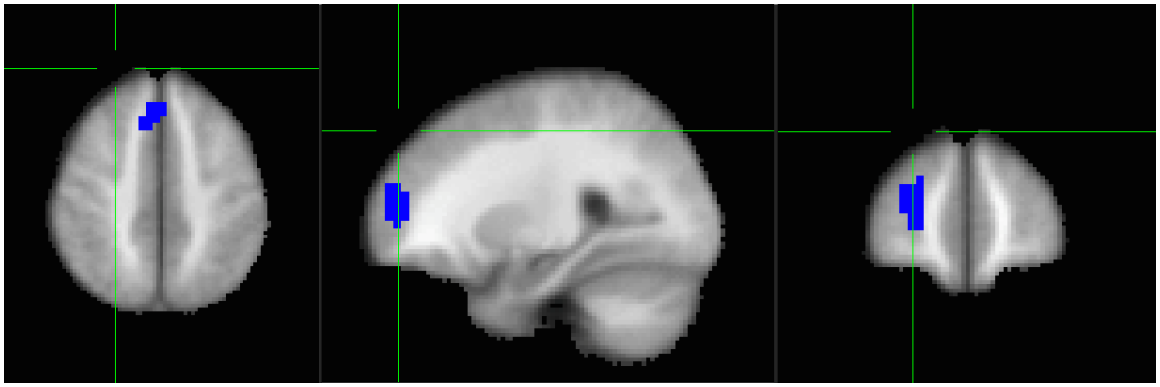

Figure 4b. Aim 2: RTSD at (3-1)-back contrast t-test (26R 54A 48S)
All β values thresholded by t-statistic for significance

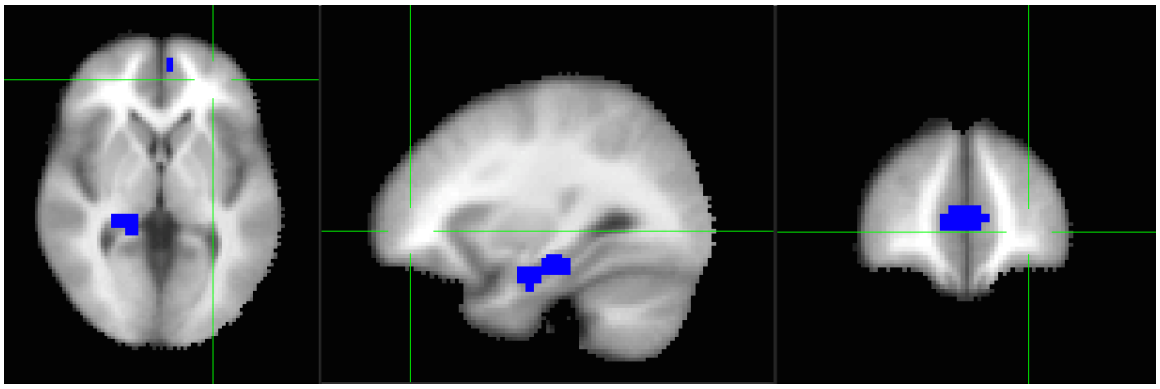

Figure 4c. Aim 2: LOC at happy – neutral contrast t-test (-30L 48A 0S)
All β values thresholded by t-statistic for significance

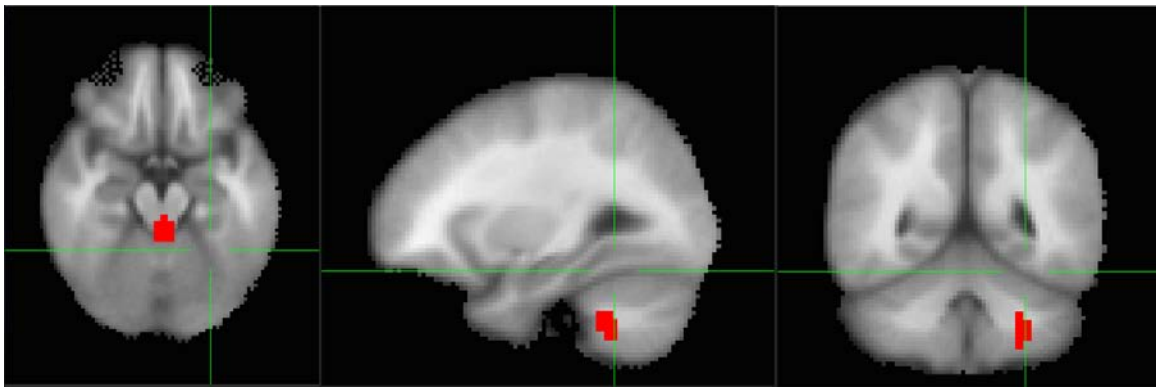

Figure 5a. Aim 3a: NSI symptoms at (2-1)-back contrast (-28L -50P -18I)
All β values thresholded by t-statistic for significance

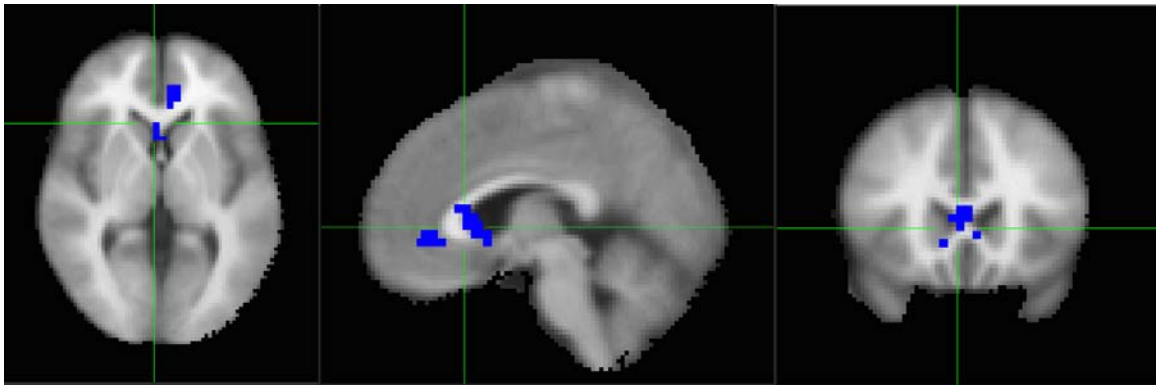

Figure 5b. Aim 3a: NSI at happy – neutral contrast (-10L 36A -4I)
All β values thresholded by t-statistic for significance for Aims 2 & 3

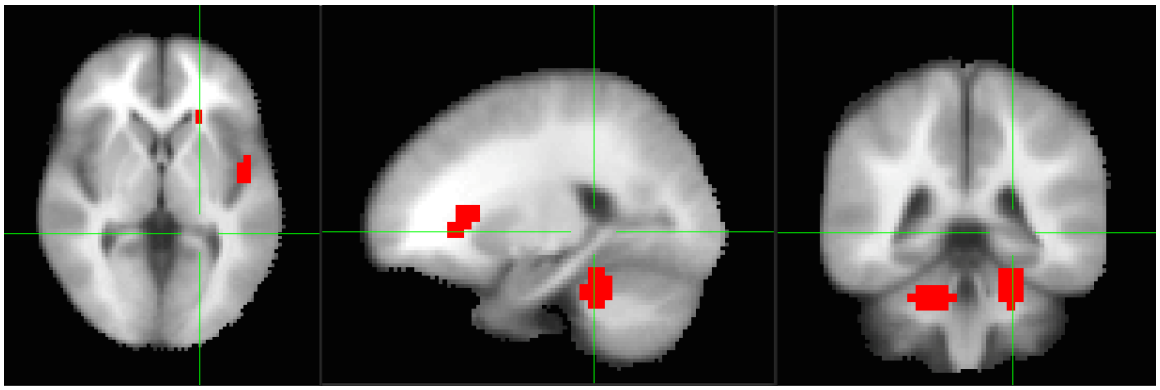

Figure 5c. Aim 3a: PTSD symptom score at happy – neutral contrast (-22L -40P 0S)
All β values thresholded by t-statistic for significance

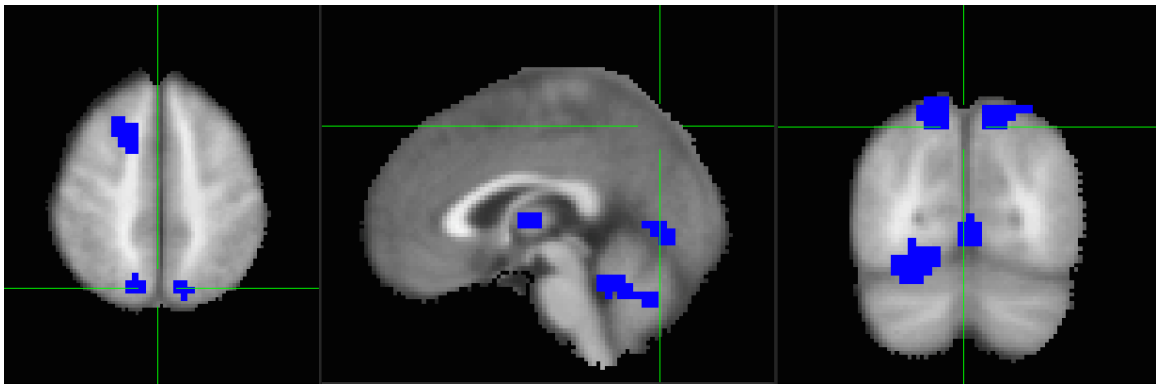

Figure 5d. Aim 3a: PTSD symptoms at (3-1)-back contrast (2R -72P 50S)
All β values thresholded by t-statistic for significance

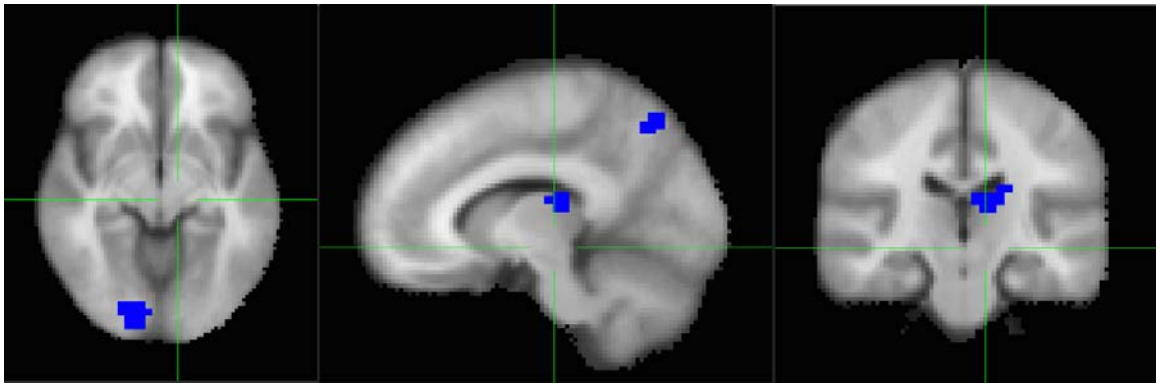

Figure 5e. Aim 3a: PTSD symptoms at (2-1)-back contrast (-10L -22P -8I)
All β values thresholded by t-statistic for significance

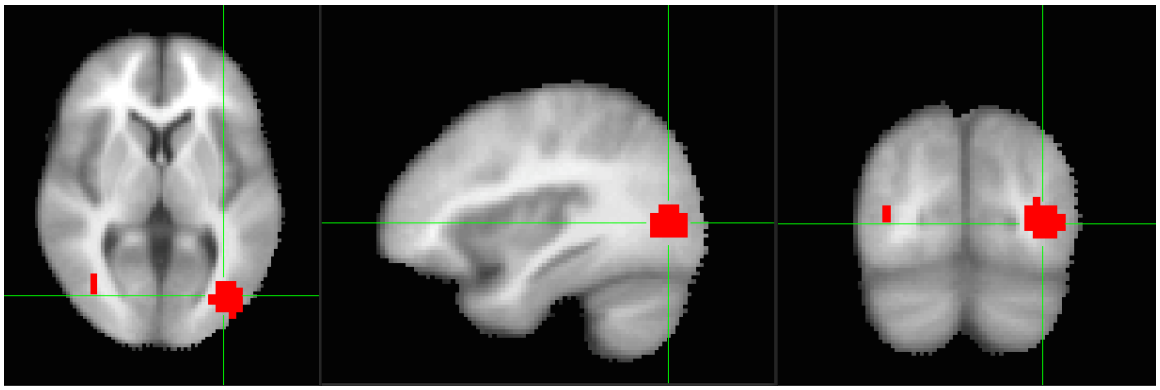

Figure 6a. Aim 3b: Somatic subdomain NSI at (2–1)-back contrast (-36L -76P 4S) *All β values thresholded by t-statistic for significance*

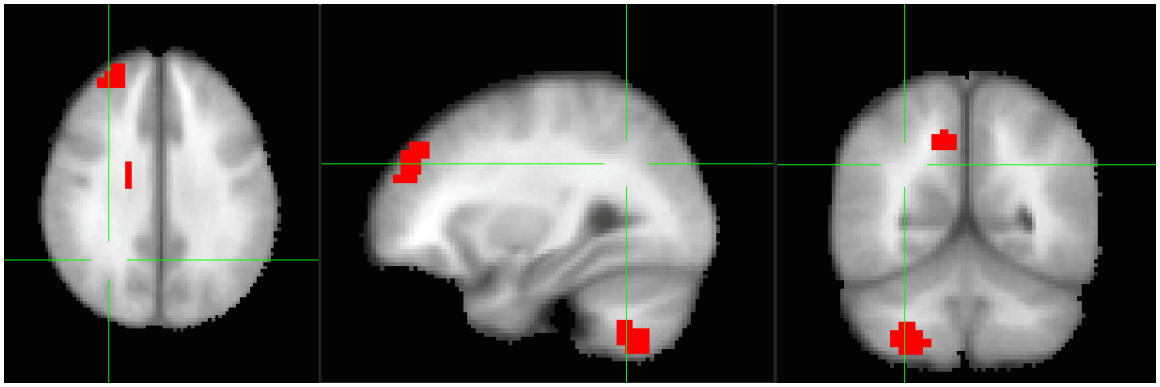

Figure 6b. Aim 3b: Somatic subdomain NSI at happy – neutral contrast (30R -56P 32S) *All β values thresholded by t-statistic for significance*

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