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### **The Relationship Between Depressive Symptomology, Motivational Deficits and Striatal Activity in Traumatic Brain Injury (TBI)**

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~~THE~~ RELATIONSHIP BETWEEN DEPRESSIVE SYMPTOMOLOGY,  
MOTIVATIONAL DEFICITS AND STRIATAL ACTIVITY IN  
TRAUMATIC BRAIN INJURY (TBI) ~~/~~

by

Angela Spirou

A Master's Thesis Submitted to the Faculty of

Montclair State University

In Partial Fulfillment of the Requirements

For the Degree of

Master of General Psychology

May 2017

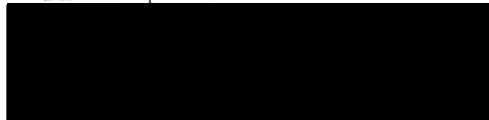
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## Abstract

Individuals with traumatic brain injury (TBI) have been shown to have high prevalence rates of depression. Reward processing and motivational deficits have been shown to be associated with depression, since both constructs rely on the fronto-striatal network. In this study, we examined depressive symptomology, motivational tendencies and striatal activation during wins and losses in individuals with TBI. Participants (TBI and healthy controls [HC]) completed a gambling task composed of wins and losses in an MRI scanner. Depressive symptomology was assessed with the Chicago Multiscale Depression Inventory (CMDI), while motivational tendencies were assessed with the Behavioral Inhibition/Behavioral Activation (BIS/BAS) scale. Significant between-group differences were observed in BAS ( $p=.01$ ), BAS-Drive ( $p = 0.003$ ), BAS-Reward Responsiveness ( $p = 0.04$ ) and in all CMDI subscales (Mood:  $p = .01$ ; Evaluative:  $p = 0.02$ ; Vegetative:  $p = .001$ ), with significant correlations seen between both questionnaires. Using VBM analysis and the segmentation of subcortical structures, a significant GM decrease in both the right ACC and bilateral NAcc was seen in the TBI group. A positive correlation was found in the TBI group between the CMDI-Mood subscale and activation of the left NAcc during loss trials ( $r = -.858, p < 0.05$ ), while a strong negative correlation in the TBI group was found between BIS and activation of the right NAcc during win trials ( $r = -.852, p < 0.05$ ). When split between high and low BIS scores, the TBI group scoring higher on BIS showed significantly lower levels of NAcc activation during win trials ( $p < 0.05$ ). No demographic between-group differences were detected. The current study replicates previous evidence in non-TBI individuals with depression, as well as provides pioneering evidence on the existence of the association between striatal engagement in depressive symptomology and motivation in individuals with TBI.

THE RELATIONSHIP BETWEEN DEPRESSIVE SYMPTOMOLOGY, MOTIVATIONAL  
DEFICITS AND STRIATAL ACTIVITY IN  
TRAUMATIC BRAIN INJURY (TBI)

A THESIS

Submitted in partial fulfillment of the requirements  
For the degree of Masters of General Psychology

by

ANGELA SPIROU

Montclair State University

Montclair, NJ

2017

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## LIST OF ABBREVIATIONS

TBI	Traumatic Brain Injury
HC	Healthy Controls
BG	Basal Ganglia
VS	Ventral Striatum
NAcc	Nucleus Accumbens
MDD	Major Depressive Disorder
BOLD	Blood Oxygen Level Dependent
CMDI	Chicago Multiscale Depression Inventory
BIS	Behavioral Inhibition Scale
BAS	Behavioral Activation Scale
GM	Gray Matter
ACC	Anterior Cingulate Cortex

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The Relationship between Depressive Symptomology, Motivational Deficits and Striatal Activity  
in Traumatic Brain Injury (TBI)

An estimated 57 million people worldwide have been hospitalized due to a traumatic brain injury (TBI; Murray & Lopez, 1996), with at least 2% of the U.S. population alone living with TBI associated disabilities (Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999). Even with such a high prevalence, treatment of TBIs has proven to be difficult since no two traumatic events are identical. For example, a TBI can be classified as being either mild, moderate, or severe depending on the extent of acquired damage. Furthermore, the severity of secondary or lasting injuries depend upon the type of TBI acquired, whether it be impact or non-impact (Prins, Greco, Alexander, & Giza, 2013), the location of the trauma on the brain, and also the individual's age and gender.

But even with the uniqueness of each TBI's initial primary injury, research has shown high rates of similar consequential outcomes or secondary complications. Specifically, TBI has not only been seen to result in long-term physical, cognitive and behavioral complications, but also emotional ones as well (Consensus, Conference, Institutes, & National Institute of Health, 1998), including a 1.5 times increased risk of depression (Holsinger et al., 2002). In fact, several studies have cited depression as being the most reported psychiatric complication in this population (Holsinger et al., 2002), with prevalence estimates between 6-77% (Kreutzer, Seel, & Gourley, 2001), which are substantially higher than the general population (6.7%; Hudak et al., 2011; Kessler, Chiu, Demler, & Walters, 2005). Furthermore, despite the uniqueness of the initial injury itself, the risk of developing depression as a secondary consequence is similar

amongst individuals with TBI (Rosenthal, Christensen, & Ross, 1998), showing that depression may be a unifying secondary sequela within this population. This unification amongst a clinical population with individualized ranges of disability can prove to be a key component in furthering future rehabilitative practices that could positively influence a wide range of individuals.

Unfortunately, the understanding of the link between TBI and depression is poorly understood compared to the knowledge of how depression affects the brain and behavior of non-TBI individuals with depression. In order to gain more insight into the relationship between TBI and depression, one must first take into account the research findings that correspond to depression in the general population, and then see if these trends are also present in TBI. Specifically, one must not only look at depression from both behavioral and neural standpoints, but also at how the two are interconnected.

### **Questionnaires on Depression & Motivation**

Many of the features of depression in TBI are not well established within the DSM, such as guilt and self-criticism (Seel, Macciocchi, & Kreutzer, 2010). The Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1998) is a questionnaire that takes into consideration an individual's dysphoric tendencies, self-criticism and vegetative states, and most importantly, was developed in order to measure depression in populations with non-psychiatric medical illnesses. This measure is valuable to use in the TBI population for two key reasons. First, as stated earlier, the questionnaire has a subscale in which measures self-criticism, which is a marker for depression in TBI (Seel, Macciocchi, & Kreutzer, 2010). Second, the CMDI

separates feelings of dysphoria from feelings of fatigue. Since populations with neurological disorders experience fatigue due to the disorder itself, vegetative tendencies need to be separated from mood in order to gain a more accurate reading of depressive symptomology (Dobryakova, DeLuca, Genova, & Wylie, 2013). That is, with the CMDI's subscales, an individual with TBI's fatigue scores will not impact their mood scores, which can lead to a more accurate reading of depressive symptomology in a population with a neurological disorder.

One of the most well established hallmarks of depression is the symptom of anhedonia, which is a reduction of pleasure or interest in stimuli that were once deemed rewarding or pleasurable (Eshel & Roiser, 2010). However, this commonly used definition fails to form a distinction between two critical aspects of anhedonia; the initial reduction of a response to a reward and the motivational deficit to pursue rewards in general (Treadway & Zald, 2011). In order to measure these two aspects of anhedonia, researchers use the Behavioral Inhibition Scale / Behavioral Activation Scale (BIS/BAS; Carver & White, 1994). The BIS/BAS measures both aversive and appetitive motivation, which leads to scores that reflect how likely an individual is to either inhibit movement towards goals, or to pursue goals, respond positively to rewards and seek new experiences (Carver & White, 1994).

### **Neurobiological Differences of Depression and Motivational Deficits**

Since the capacity to feel pleasure is an important step during reward processing (Der-Avakian & Markou, 2012), many studies have focused on the functional and structural abnormalities of the reward circuit in individuals suffering from depression (Pujara & Koenigs,

2014). For example, grey matter volume differences in the ventromedial parts of the basal ganglia (BG) have been seen in depressed individuals, with less volume being associated with more bouts of depression (Drevets, Price, & Furey, 2008). Furthermore, the striatum, a key input nucleus of the BG and a brain region that has been shown to play an integral part of the reward circuit, has been seen to function abnormally in non-TBI depressed individuals (Eshel & Roiser, 2010).

The ventral striatum (VS), composed of the nucleus accumbens (NAcc), has been studied in connection with Major Depressive Disorder (MDD) research due to its role of assigning values to rewards (Der-Avakian & Markou, 2012) and mediating motivational behaviors (Berridge & Kringelbach, 2008). It has been seen on numerous occasions that in response to rewarding stimuli, for example during a gambling task (Steel, Kumar, & Ebmeier, 2007), the VS activation (measured with blood oxygen level dependent activity [BOLD]) is attenuated in individuals with MDD when compared to healthy controls (HCs; Diener et al., 2012; Greening, Osuch, Williamson, & Mitchell, 2013; Harvey, Pruessner, Czechowska, & Lepage, 2007; Heller, Johnstone, Shackman, Light, & Peterson, 2009; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; McCabe, Cowen, & Harmer, 2009; Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012; Schaefer, Putnam, Benca, & Davidson, 2006; Stoy, Schlagenhaut, Sterzer, Bermpohl, & Hagele, 2012). Furthermore, a study using a monetary task consisting of wins and losses, showed that individuals with a longer duration of depression and/or more frequent bouts of depression showed greater hypoactivation in the VS during the processing of monetary wins when compared to newly depressed individuals. (Hall, Milne, & MacQueen, 2014). Indeed,



individuals suffering from depression have been seen time and again to be hyposensitive to the presentation of positive feedback, while responding in a more robust way to negative feedback (Der-Avakian & Markou, 2012). Due to these differences seen in reaction to wins and losses, it is important to use a behavioral paradigm that tests how individuals respond to rewarding stimuli, such as a card-guessing task. The card-guessing task has been shown to stimulate goal-oriented behavior (participants have a goal to win money), allowing researchers to examine participants' reactions to not only gaining money, but to losing money as well (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000).

### **Current Thesis**

With the knowledge gained from previous work done on the behavioral and neural components of non-TBI depressed individuals, hypotheses can be made about populations that show high prevalence rates of depression. Specifically, the aim of this thesis is to not only look at depressive symptomology and motivational deficits in TBI, but to also examine how these two constructs are associated with striatal activation. We hypothesize that, compared to healthy controls, individuals with TBI will show higher rates of both depressive symptomology, and motivational deficits, and also show blunted striatal activation in response to positive feedback or rewarding outcomes and less grey matter when compared to healthy individuals.

## **Research Design and Method**

### **Participants**

Eighteen participants (9 TBI and 9 Healthy Controls [HC]) between the ages of 18 and 65 were recruited to participate through the Subject Information Management System (SIMS), a database at Kessler Foundation, which maintains contact information for both TBI and HC populations. TBI participants were first recruited in order to adequately match HCs to the TBI group in age, gender and education. Exclusionary criteria included any current diagnosis of a neurological disorder (except for a TBI for the TBI group), history of alcohol/drug abuse, significant history of psychiatric illness, claustrophobic tendencies and presence of ferrous metal within body. For the TBI group specifically, participants needed to have a TBI severity of moderate or severe based upon time spent unconscious and be at least one year post TBI in order to control for spontaneous recovery (i.e., recovery from consequences of TBI before consequences become irreversible and classified as sequelae [Leon-Carrion & Machuca-Murga, 2001]).

Participants showed no significant differences between groups in either gender, age or education. The TBI group was composed of 4 males and 5 females, with a mean age of 40.22 years and a mean education of 15.56 years. The HC group was composed of 2 males and 7 females, with a mean age of 39.33 years and a mean education of 16.00 years. TBI specific variables include duration of TBI, severity, and also the cause of the trauma. The mean duration of the TBI was 9.33 years with 4 participants having a moderate TBI and 5 having a severe TBI. A majority of the TBI sample (78%) gained the TBIs through a vehicular accident, while others gained them through either being struck by a vehicle as a pedestrian or through assault from another. All demographic information for both groups is listed in Table 1. The research was

approved by the Institutional Review Boards of both Kessler Foundation and Montclair State University.

## **Materials**

**Chicago Multiscale Depression Inventory.** The Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1998) is based off of Beck's (1967) three primary categories of a depressive experience; dysphoric mood, vegetative symptoms, and negative evaluation. The CMDI is composed of the following three subscales; (1) Mood, which measures dysphoria, (2) Evaluative, which measures self-criticism, and (3) Vegetative, which measures physical malfunctioning (Nyenhuus et al., 1998). The Vegetative subscale is further broken down into Fatigue/Lethargy, Sleep Disturbance and Cognitive Inefficiency. The CMDI is presented as a Likert rating scale (1 [not at all] – 5 [extremely]) with 50 words. Participants have to circle the number of the phrase that best describes their emotional state during the past week. Examples of words listed for each subscale are (1) sad, glum, and woeful for Mood, (2) punished, despised, and hated for Evaluative, and (3) tired, easily awakened, and unable to concentrate for Vegetative.

**Behavioral Inhibition / Behavioral Activation Scale.** The Behavioral Inhibition / Behavioral Activation Scales (BIS/BAS) are based off of Gray's (1987) biopsychological theory of emotion, which claims that behavior and emotion are managed by two motivational systems; a behavioral inhibition system (BIS), and a behavioral activation system (BAS). The BIS, or aversion motivational system, is a unidimensional system which is hypothesized to control anxiety in the presence of threatening or anxiety-provoking cues, and inhibit behavior that may

lead to painful or negative consequences (Cambell-Sills, Liverant & Brown, 2004). Overall, this system is highly sensitive to signals of non-reward and punishment, and due to its inhibitory actions, leads to a decrease in the movement towards goals (Carver & White, 1994). The BAS, or appetitive motivational system, is a multidimensional system hypothesized to produce positive affect in response to reward and promote movement towards desired goals (Campbell-Sills, Liverant & Brown, 2004). The BAS scale is composed of three distinct subscales; (1) Drive, which measures the persistent pursuit of goals, (2) Fun Seeking, which measures the desire for new rewards and the willingness to approach a potentially rewarding event, and (3) Reward Responsiveness, which measures positive responses to rewarding outcomes (Carver & White, 1994). Overall, this system is highly sensitive to signals of reward and non-punishment. The BIS/BAS is presented as a Likert rating scale (1 [strongly agree] – 4 [strongly disagree]) with 24 phrases asking participants to rate a level of agreement pertaining to each phrase. Examples of phrases listed for each subscale are (1) “I feel pretty worried or upset when I think or know somebody is angry at me” for BIS, (2) “If I see a chance to get something I want, I move on it right away” for BAS Drive, (3) “I crave excitement and new sensations” for BAS Fun Seeking, and (4) “When I get something I want, I feel excited and energized” for BAS Reward Responsiveness.

### **Procedure**

**MRI data acquisition.** Participants underwent an MRI scan of the head, conducted on the Siemens Skyra 3.0T scanner at the Kessler Foundation Rocco Ortenzio NeuroImaging Center. Images were acquired with a standard 20-channel radio-frequency head coil. 32

contiguous slices were obtained in an oblique orientation of 30° to the anterior commissure-posterior commissure line in order to reduce signal dropout in the ventral portions of the ventral-medial prefrontal cortex (Deichmann, Gottfried, Hutton, & Turner, 2003). Structural images (1 x 1 x 1 mm) were acquired using a standard T1-weighted pulse sequence, and were used to localize functional activation. Functional data was acquired with a standard T2\*-weighted echo planar sequence (3 x 3 x 3 mm voxels, TR = 2 sec, TE = 30 ms, flip angle = 90, FoV = 256mm, slice gap = 1mm) with BOLD contrast.

**fMRI data acquisition.** Prior to beginning the neuroimaging procedure, participants were informed of details concerning the modified card-guessing task they would be performing in the fMRI (Delgado et al., 2000). In order to gain familiarity with the task, all participants practiced the task before entering the scanner to ensure accuracy in following the directions. Each participant was exposed to the same practice, which consisted of 3 trials per condition. The card-guessing task consisted of two conditions: reward and no reward. Being a within-subjects design, each participant experienced both conditions. Participants were informed that there would be an opportunity to win a monetary bonus of \$1.00 during each reward trial. Unbeknownst to the participants, the probability of winning or losing was set to 50%. The no reward condition served as the control condition.

Once the practice was finished, participants were then stripped of any metal before entering the Siemens Skyra 3.0T scanner. Within the MRI, participants were asked to lay flat on their backs and had an option to have a pillow placed under their knees for comfort. Participants were then fitted with hearing protection, and if needed, were fitted with MRI safe glasses. A

head coil was placed over the participants' heads with a mirror attached to it. The participants were notified that they would not need to move their heads due to the mirror reflecting the card-guessing task off of a projector located at the back of the MRI. A Lumina LS-PAIR button response unit was used, which is a dual response box with two buttons per hand, and placed under the participants' hands within the MRI. Finally, participants were once again informed of the necessity to stay still during all scanning procedures.

During the reward condition (see Figure 1), participants viewed an image of the back of a card for 3 seconds, portrayed as a black rectangle with a question mark in the center. During that time, participants guessed whether or not the value behind the card was higher or lower than 5. The values on the cards ranged from 1-4 and 6-9, excluding 5. Participants pressed either the left button on the response box if they guessed the number to be lower than 5, or the right button on the response box if they guessed the number to be higher than 5. This was then followed by an interstimulus duration depicted by a fixation point of varied duration lasting 1-5 seconds. This varied duration, or jitter, allows for the hemodynamic response to be deconvolved during analysis for accurate data representation. After the fixation point, participants were given feedback in order to see if they guessed correctly. A green check mark ( $\checkmark$ ) indicated a win of \$1.00 while a red X mark (X) indicated a loss of \$0.50. Trials were separated from each other with a fixation point.

During the no reward (control) condition (see Figure 1), participants viewed the face of the card on every trial, thus seeing its number. Participants then indicated whether or not the number shown was higher or lower than 5 by pressing either the left button on the response box

if the number was lower than 5 or the right button on the response box if the number was higher than 5. This was then followed by a fixation point of varied duration lasting 1-5 seconds. After the fixation point, participants were shown a pound sign (#) in order to indicate that their response was recorded. Therefore, no monetary gains or losses was presented during this condition.

Overall, each participant experienced 3 blocks of the no reward condition and 3 blocks of the reward condition. Each block consisted of 60 trials, with the order of conditions and trials within each condition being randomized. The overall time of neuroimaging procedures lasted 60 minutes.

Once completed, all participants were debriefed and informed as to the purpose of the study and that all participants were to receive a fixed monetary bonus of \$5 in addition to the base payment of \$50 for participation. The deception used in telling the participant before the task that they have the opportunity to win \$1.00 during each reward trial was done in order to have participants work towards a goal; winning more money if guessing correctly.

**Questionnaires.** After all neuroimaging procedures, participants were then asked to complete questionnaires in order to measure depressive symptomology (Chicago Multiscale Depression Inventory) and to measure motivational tendencies (Behavioral Inhibition / Behavioral Activation Scales). Questionnaires were given last so that fatigue did not interfere with the MRI section due to populations with neurological disorders experiencing high fatigue (Dobryakova, DeLuca, Genova, & Wylie, 2013; Dobryakova, Genova, DeLuca, & Wylie, 2015). Additionally, any fatigue that may have been gained from the scanner sessions should not affect

questionnaire data due to the questionnaires asking about either feelings in general or feelings dealing with the past week, and not asking about feelings felt within the moment. Questionnaires are not counterbalanced due to each of them studying different constructs and being independent on one another.

### **Data Analysis**

**Functional MRI data.** Preprocessing of the functional data (T-2 weighted images) for each scanning session was performed using Analysis of Functional Neuroimaging (AFNI) suite (Cox, 1996), which entailed motion correction using six parameters, spatial smoothing (6mm, FWHM), voxel-wise linear detrending and high-pass temporal filtering. The resulting data were warped into Talairach stereotaxic space (Talairach & Tournoux, 1998).

Single-subject fixed-effect analysis on regressors corresponding to the 1 sec time period of outcome presentation was convolved with a canonical hemodynamic response function. Motion parameters were included as regressors of no interest. The beta weights associated with the conditions of interest (reward vs. no reward) were then entered into the random-effect, group-level analysis. Specifically, an ANOVA with valence as a between-subjects factor (positive vs. negative) and group as a within subjects factor was conducted on parameter estimates associated with the time period of positive and negative feedback presentation. The parameter estimates were then used to conduct Pearson's correlations with data gained from the CMDI and BIS/BAS questionnaires, including all subscales, for both groups.

**Secondary analysis of individual differences in TBI.** Median splits were performed on the TBI group's CMDI, BIS and BAS scores in order to create two TBI groups of high and low



scores from each questionnaire. Once groups were made based on the median splits, t-tests were conducted on the rate of activation of the NAcc during both wins and losses. This was done in order to see if differences in high/low TBI scoring subjects on CMDI and BIS/BAS data has a neurobiological basis.

**Questionnaire data.** Independent samples t-tests were conducted on both the CMDI and BIS/BAS questionnaire data to see if there were differences in depressive symptomology and motivational tendencies between HC and TBI groups. Pearson's correlations between groups and with collapsed groups, were then conducted in order to look for relationships between the questionnaire data.

**Structural MRI data.**

*Volumetric analysis of GM difference between groups.* With T1 weighted structural images, overall gray matter (GM) differences between groups was analyzed using FSL-VBM (Douaud et al., 2007, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized voxel-based morphometry (VBM) protocol (Good et al., 2001) carried out using FSL tools (Smith et al., 2004). Once both brain extraction and GM-segmentation was completed, a left-right symmetric, study-specific GM template was created by registering all images to the MNI 152 standard space using non-linear registration (Andersson, Jenkinson, & Smith, 2007) and then averaging and flipping the images along the x-axis. All native images were then non-linearly registered to the study-specific GM template and modulated in order to compensate for any contraction/enlargement. Smoothing was then performed using an isotropic Gaussian kernel with a sigma of 3mm. Finally, permutation-based non-parametric inference through FSL's randomise

(Winkler, Ridgway, Webster, Smith, & Nichols, 2014) was run, and threshold-free cluster enhancement (TFCE)-based thresholding results were displayed.

***Volumetric analysis of the striatum.*** Segmentation of the NAcc, caudate and putamen was accomplished using FIRST (FSL v3.2.0), which is based on a Bayesian framework. FIRST allows for the relationships between the subcortical structures' sizes and shapes to be investigated. Linear registration on T1 images using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady & Smith, 2002; Greve & Fischl, 2009) was first performed in a two-stage manner (Patenaude, Smith, Kennedy, & Jenkinson, 2011). The first stage aligned the T1-weighted images on the MNI152 template with a 1mm resolution using 12 degrees of freedom. The second stage created a subcortical mask defined by the first stage that excluded any unwanted regions outside of the subcortical structures being segmented. All segmentation outputs were quality checked for segmentation error. Once segmentation was proven to be successful, a volumetric analysis was performed on the structure bilaterally by using the appropriate intensity with `fslstats` in order to gain the volume of the NAcc, caudate and putamen in  $\text{mm}^3$ . A volumetric scaling factor was obtained through SIENAX (Smith, De Stefano, Jenkinson, & Matthews, 2001; Smith, Zhang, Jenkinson, Chen, & Matthews, 2002), which is part of FSL (Smith et al., 2004), in order to normalize all brain tissue volume for differences in subject head size. Independent samples t-tests were then conducted between the region volumes of both groups. The subcortical volumes were then used to conduct Pearson's correlations with data gained from the CMDI and BIS/BAS questionnaires, including all subscales, for both groups.

## Results

### Functional MRI Data

After using a 2x2 ANOVA with valence as a between-subjects factor (positive vs. negative) and group as a within subjects factor, no significant differences were observed in activation of the striatum during either positive or negative feedback presentation between groups. However, significant relationships were found between activation of the NAcc and questionnaire data for the TBI group after conducting Pearson's correlations. Specifically, the TBI group showed a significant positive relationship between activation of the left NAcc during loss trials and CMDI's Mood subscale ( $r = .858, p < 0.05$ ; see Figure 2), suggesting individuals with more dysphoric tendencies are less sensitive to loss. Also, a significant negative relationship between activation of the right NAcc during win trials and BIS ( $r = -.852, p < 0.05$ ; see Figure 3) in the TBI group was observed, suggesting that individuals who exhibit higher levels of aversive motivation are less sensitive to rewards. All correlations were corrected for multiple comparisons using a Bonferroni corrected p-value of 0.004.

**Secondary analysis of individual differences in TBI.** Significant differences in activation of the right NAcc during win trials was found between high and low BIS scoring TBI groups ( $p < 0.05$ ; see Figure 4). Specifically, an independent samples t-test showed that the TBI group scoring high on the BIS subscale had significantly less activation of the right NAcc during win trials compared to the TBI group scoring lower on the BIS subscale. There were no differences in activation found when the TBI group was split between high and low scores of both the CMDI and BAS.

### Questionnaire Data

An independent samples t-test showed that the TBI group scored significantly higher on all subscales of the CMDI (Mood: Mean<sub>TBI</sub> = 29.78, Mean<sub>HC</sub> = 15.13,  $p = 0.01$ ; Evaluative: Mean<sub>TBI</sub> = 16.89, Mean<sub>HC</sub> = 8.50,  $p = 0.02$ ; Vegetative: Mean<sub>TBI</sub> = 29.89, Mean<sub>HC</sub> = 28.25,  $p = 0.01$ ) compared to the HC group, with highest differences seen in the Vegetative Fatigue/Lethargy subscale (Mean<sub>TBI</sub> = 15.33, Mean<sub>HC</sub> = 12.75,  $p = 0.0007$ ). No differences were seen in the Vegetative subscales of Sleep Disturbance and Cognitive Inefficiency between groups. As for the BIS/BAS questionnaire, the TBI group scored significantly lower on the BAS scale overall (Mean<sub>TBI</sub> = 37.11, Mean<sub>HC</sub> = 18.67,  $p = 0.01$ ), with differences in the BAS subscales of Drive (Mean<sub>TBI</sub> = 9.33, Mean<sub>HC</sub> = 12.89,  $p = 0.003$ ) and Reward Responsiveness (Mean<sub>TBI</sub> = 16.22, Mean<sub>HC</sub> = 18.22,  $p = 0.04$ ), but not in the Fun Seeking subscale, as compared to the HC group. No group differences were observed on the BIS scale (see Table 2).

After correcting for multiple comparisons using a new  $p$ -value of 0.004 through a Bonferroni correction, no significant correlations between questionnaires remained for the TBI and HC groups separately. Groups were then collapsed in order to see significant relationships between questionnaires. Specifically, the BAS scale was seen to be negatively correlated with CMDI's Vegetative subscales of Fatigue/Lethargy ( $r = -.705$ ,  $p < 0.05$ ) and Cognitive Inefficiency ( $r = -.673$ ,  $p < 0.05$ ) and also CMDI overall ( $r = -.608$ ,  $p < 0.05$ ). Furthermore, significant negative correlations was seen between BAS Drive and CMDI's Vegetative Fatigue/Lethargy ( $r = -.654$ ,  $p < 0.05$ ), and BAS Fun Seeking and CMDI's Vegetative Cognitive

Inefficiency ( $r = -.682$ ,  $p < 0.05$ ). The correlation matrix between questionnaires is shown in Table 3.

### **Structural MRI**

**Volumetric analysis of GM difference between groups.** Group comparisons between the brain injured and healthy groups showed a significant decrease in GM after using the VBM analysis. Specifically, the TBI group showed to have a significantly smaller right anterior cingulate cortex (ACC) compared to HCs ( $p < 0.05$ ; see Figure 5).

**Volumetric analysis of the striatum.** After gaining the volumes of the NAcc, putamen and caudate through the FIRST analysis, independent samples t-tests between the TBI and HC groups revealed significant volumetric differences in the NAcc bilaterally (right:  $p = 0.01$ ; left:  $p = 0.02$ ), with the TBI group showing less volume in the NAcc on average (see Figure 6). No significant volumetric differences were found in the bilateral caudate and putamen between groups (see Table 4). Furthermore, no significant correlations between questionnaire data and striatal volume remained for both TBI and HC groups separately, and TBI and HC groups collapsed, after correcting for multiple comparisons through a Bonferroni corrected p-value of 0.004 was used.

## **Discussion**

### **Depression and Motivational Tendencies in TBI as Reflected By Questionnaires**

**Depression and Appetitive Motivation.** As predicted, the TBI group showed higher depressive symptomology compared to HCs in all three of Beck's (1967) main characteristics of

depression; dysphoric tendencies, self-critical behaviors and fatigue levels. Furthermore, the highest difference between groups was seen with fatigue levels, which replicates previous findings showing fatigue to be a common sequela in populations with neurological disorders (Chaudhuri & Behan, 2004). With fatigue being a common symptom of both depression and neurological disorders, many have assigned fatigue levels as the reason behind reports of the high occurrence of depression in these clinical populations (Nyenhuis et al., 1998). But as we see here, even with the absence of vegetative symptoms, the TBI group still shows a higher rate of negative mood presentation, supporting the presence of depressive symptomology within this group.

Since Beck's (1967) cognitive theory of depression, the theory the CMDI is based off of, another diagnostic criterion has been added to depression. This criterion specifies that a depressed individual needs to also exhibit a loss of interest in activities that were once deemed pleasurable (Feighner et al., 1972). Now termed as anhedonia, a large number of works have not only studied this construct and its relationship with depression, but also the multidimensional characteristics within itself. Treadway and Zald (2011) have stated that in order to fully understand anhedonic tendencies, one must take into account both the individual's response to rewards and the reduced motivation in order to pursue them. These features are present within the TBI group of this current study, as they have shown to be both less likely to respond positively to rewarding stimuli and also less motivated in the pursuance of goals when compared to HCs. Furthermore, negative relationships between depression and motivation were observed as per the correlations between the CMDI and BIS/BAS questionnaires, suggesting that the more depressed an individual is, the less appetitive motivation the individual has. Specifically, the

higher the fatigue levels, the less likely one would show enough motivational drive to pursue goals. Indeed, with the concept of anhedonia, the relationship between depressive symptomology and positive motivational constructs is more easily understood.

**Fun Seeking in TBI.** Many investigators have speculated on the connection between risky behaviors and the occurrence of TBIs, implying that an individual's premorbid characteristics included some form of impulsivity (Goldstein & Levin, 1990). With this in mind, one would hypothesize that the TBI group would score higher on the BAS-Fun Seeking subscale compared to HCs, since this subscale rates the craving for new experiences and also the likelihood of making extemporaneous decisions. It might be surprising that the data gained shows no differences between TBI and HC groups in fun seeking behavior. But once participant self-reports on the questions asked are taken into consideration, an explanation can be made. Many participants acknowledge the possible risk involved in looking for new experiences, stating that most of their adventurous behaviors stopped once they obtained a TBI. And so, due to previously acquired consequences gained by risky decision-making (such as gaining a head trauma), participants report being more aversive to fun seeking post-TBI. With this speculation, an assumption can be made that the TBI group doesn't necessarily lack motivation to seek new sensations, but is actively inhibiting these behaviors in order to suspend any future occurrence of negative outcomes.

**Aversive Motivation.** Many studies have associated abnormalities in the behavioral inhibition system with depression (Kasch, Rottenberg, Arnow, & Gotlib, 2002), due to depressed individuals exhibiting hypersensitivity towards punishment (Whitmer, Frank & Gotlib, 2012).

According to Gray (1987), the BIS is not only associated with negative affect, but also inhibits behavior that may lead to a negative outcome due to its sensitivity towards punishment and novelty. With a more depressed sample, such as the TBI group, one would expect heightened scores on the BIS, but instead, there were no significant differences found on the BIS scale between groups. Interestingly, this finding replicates a recent study from Wong, Rappoport, Meachen, Hanks, and Lumley (2016), in which TBIs did not score higher on the BIS scale. Instead, the authors reported findings that are inconsistent with previous work. The authors found that even though the TBI group endorsed the BAS scale, which measures appetitive motivation and positive affect, the TBI group still reported negative affect as well. Not only does this shed light on the way a TBI affects emotional and motivational constructs and the differences on how they're expressed between healthy individuals and those with head traumas, but also shows the necessity for more specialized questionnaires. Specifically, new questionnaires need to take these differences in expression of depression and motivation into account in order to more accurately measure differences in the TBI group.

### **Neurobiological Bases of Depression and Motivation in TBI**

The main input structure of the BG is the striatum, with the NAcc being closely associated with reward and reward/error prediction (Knutson et al., 2001). On the other hand, the ACC is involved in reward, motivation and emotion (Haber, 2011), and has also been implicated in the modulation of emotional behavior (Drevets, Savitz, & Trimble, 2009). Since the ACC projects information to the NAcc, one can say that both structures play a key role in the development of reward-based behaviors (Haber, 2011). Thus, a disruption in these pathways can



lead to dysfunctional reward expectations, which may inevitably contribute to the presentation of anhedonia (Furman, Hamilton, & Gotlib, 2011). But even though significant group differences in activation were not seen between groups, correlations between NAcc activity and both mood states and motivation were found. Specifically, the TBI group showed a positive relationship between dysphoric tendencies and activation in the left NAcc during loss trials. Interestingly, this finding does not mimic findings in MDD where depressed individuals are more sensitive to negative outcomes. Instead, the current study shows a relationship which implies an opposite trend, where the depressed sample of individuals with TBI are less sensitive to negative outcomes. Additionally, a negative relationship was seen between aversive motivation and activation in the right NAcc during win trials in the TBI group, which implies a decreased reaction to rewarding outcomes when one is motivationally inhibited to pursue goals. This implication became stronger once a significant difference in activation in the right NAcc during win trials was seen when the TBI group was split between high and low BIS scores. Interestingly, even though there were no group differences in BIS via behavioral measures, the TBI group presented a neural sensitivity to rewards when split by high and low BIS scores, whereas the HC group did not.

Furthermore, previous literature shows that within MDD populations, there is both attenuated functional connectivity between the NAcc and ACC (Furman, Hamilton & Gotlib, 2011) and GM abnormalities in the ACC (Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013), which has been associated with negative mood states (Damasio et al., 2000). This same decrease in GM was seen in the right ACC and bilateral NAcc of the TBI group. This smaller amount of volume within key brain structures implicated in behaviors of motivation and reward

only further supports the need to continue investigating the neurobiological underpinnings of depression and motivation in TBI.

### **Limitations and Future Directions**

The main limitation which must be considered before interpreting these findings is the small sample size used. With the heterogeneity found within TBI amongst its symptoms and comorbid conditions, a larger sample is needed in order to make any findings generalizable. In addition, a larger sample size may give way to more robust findings in differences in activation, which can help lead to a greater understanding of the neuro underpinnings connected to depression and motivation in TBI.

Future studies should include questionnaires in which measure anhedonia directly in order to gain a more accurate understanding of the motivational constructs associated with anhedonic tendencies in TBI. In addition, a sensation seeking questionnaire should be added to further analyze risk seeking behaviors and the effect they may have on accurate decision making in the TBI population. Finally, as for future participants, studies should look at differences between clinically depressed individuals with TBI compared to non-TBI individuals diagnosed with MDD.

### **Conclusions**

Difficulties found in the treatment of TBI can be said to be due largely to the individualized aspects of TBIs, such as differences in severity, type of trauma, areas in which the brain is affected, and also age and gender. Even so, a large percentage of individuals with TBI battle with comorbid depression, which comes hand in hand with motivational deficits. Since

depression is a popular presenting symptom, it can also be a target for rehabilitative practices. Specifically, TBI treatments should include teaching of coping skills and ways to increase one's motivation. Less depressive symptomology can lead to less isolation and a higher integration into the community, while increases in motivation can lead to a possible return to the work force post-TBI. These changes could thus lead to a higher quality of life in which future endeavors are less defined by the trauma sustained.

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Table 1

*Group Demographic Information (N=18)*

Variable	Groups		sig
	TBI	HC	
Gender (M/F)	4M/5F	2M/7F	n.s.
Age	40.22 (9.74)	39.33 (10.42)	n.s.
Education	15.56 (1.67)	16.00 (2.65)	n.s.
TBI Duration (yrs)	9.33 (5.22)	-	
TBI Severity <sup>a</sup>	4M/5S	-	
TBI Cause			
Vehicular Accident	78%	-	
Struck by Vehicle	11%	-	
Other	11%	-	

*Note:* Data shown as Mean (Standard Deviation). <sup>a</sup>M = moderate; S = severe.

Table 2

*Group Questionnaire Data*

Questionnaire	Groups		sig
	TBI	HC	
<b>CMDI</b>			
Mood	29.78 (4.79)	15.13 (4.09)	p < 0.05
Eval	16.89 (4.88)	8.50 (3.29)	p < 0.05
Veg - Tot	29.89 (5.49)	28.25 (6.41)	p < 0.05
Veg - FL	15.33 (3.04)	12.75 (3.65)	p < 0.05
Veg - SD	8.22 (3.46)	9.13 (2.90)	n.s.
Veg - CI	6.33 (2.40)	6.38 (2.07)	n.s.
CMDI - Tot	76.56 (9.53)	51.88 (8.48)	p < 0.05
<b>BIS/BAS</b>			
BIS	21.44 (4.85)	18.67 (3.24)	n.s.
BAS - Tot	37.11 (4.54)	43.78 (5.31)	p < 0.05
BAS - D	9.33 (2.45)	12.89 (1.90)	p < 0.05
BAS - FS	11.56 (2.45)	12.67 (2.45)	n.s.
BAS - RR	16.22 (1.98)	18.22 (1.86)	p < 0.05

*Note.* Data shown as M(SD). Eval = Evaluative; Veg-Tot = Vegetative Total score; Veg-FL = Vegetative Fatigue/Lethargy; Veg-SD = Vegetative Sleep Disturbance; Veg-CI = Vegetative Cognitive Inefficiency; CMDI-Tot = total score for all CMDI subscales; BAS-Tot = total for all BAS subscales; BAS-D = BAS Drive; BAS-FS = BAS Fun Seeking; BAS-RR = BAS Reward Responsiveness

Table 3

*Correlation Matrix Between Questionnaires for Both Groups Combined*

Questionnaire	1	2	3	4	5	6	7	8	9	10	11
<b>CMDI</b>											
1. Mood	-										
2. Eval	.694*	-									
3. Veg - Tot	.696*	.467	-								
4. Veg - FL	.657*	.463	.848*	-							
5. Veg - SD	.097	.066	.433	-.026	-						
6. Veg - CI	.686*	.425	.861*	.652*	.233	-					
7. CMDI - Tot	.938*	.815*	.835*	.761*	.223	.766*	-				
<b>BIS/BAS</b>											
8. BIS	.377	.154	.393	.526	-.333	.505	.366	-			
9. BAS - Tot	-.569	-.365	-.626	-.705*	.165	-.673*	-.608*	-.417	-		
10. BAS - D	-.589	-.370	-.487	-.654*	.375	-.588	-.568	-.474	.901*	-	
11. BAS - FS	-.432	-.244	-.613	-.616	.061	-.682*	-.501	-.513	.812*	.659*	-
12. BAS - RR	-.323	-.255	-.414	-.410	-.103	-.335	-.382	.038	.685*	.449	.277

*Note.* Data corrected for multiple comparisons. Eval = Evaluative; Veg-Tot = Vegetative Total score; Veg-FL = Vegetative Fatigue/Lethargy; Veg-SD = Vegetative Sleep Disturbance; Veg-CI = Vegetative Cognitive Inefficiency; CMDI-Tot = total score for all CMDI subscales; BAS-Tot = total for all BAS subscales; BAS-D = BAS Drive; BAS-FS = BAS Fun Seeking; BAS-RR = BAS Reward Responsiveness.

\*  $p < .05$

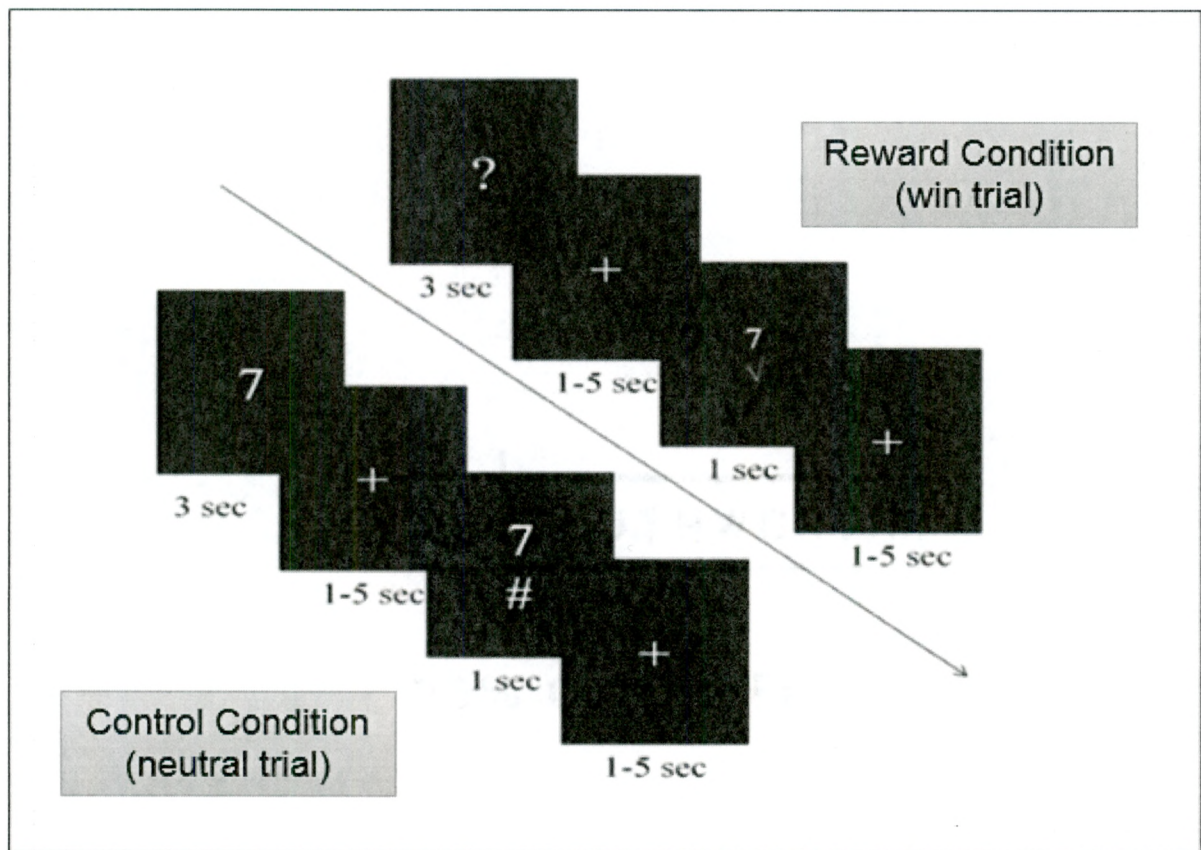


Table 4

*Group Volume Differences of the Striatum*

Region	Groups		sig
	TBI	HC	
R-NAcc	670.29 (125.35)	463.17 (171.14)	p = 0.01
L-NAcc	754.11 (158.35)	532.42 (194.47)	p = 0.02
R-Caudate	4795.50 (502.53)	4408.80 (743.46)	n.s.
L-Caudate	4681.83 (487.21)	4426.37 (778.62)	n.s.
R-Putamen	6796.31 (292.41)	6325.16 (1219.67)	n.s.
L-Putamen	6591.79 (431.43)	6139.04 (1066.49)	n.s.

*Note.* Data shown as M(SD) of mm<sup>3</sup>. NAcc = nucleus accumbens. R = right; L = left.



*Figure 1.* Card-Guessing Task paradigm shown to participants within MRI. During the Reward condition, participants are asked to guess if a card's value is more or less than five when prompted with a question mark. If guessed correctly, participants receive a green check mark, indicating the win of \$1.00 (shown above). If guessed incorrectly, participants receive a red X mark, indicating a loss of \$0.50. During the control condition, participants are shown numbers and indicate whether or not the number is higher or lower than five (shown above).

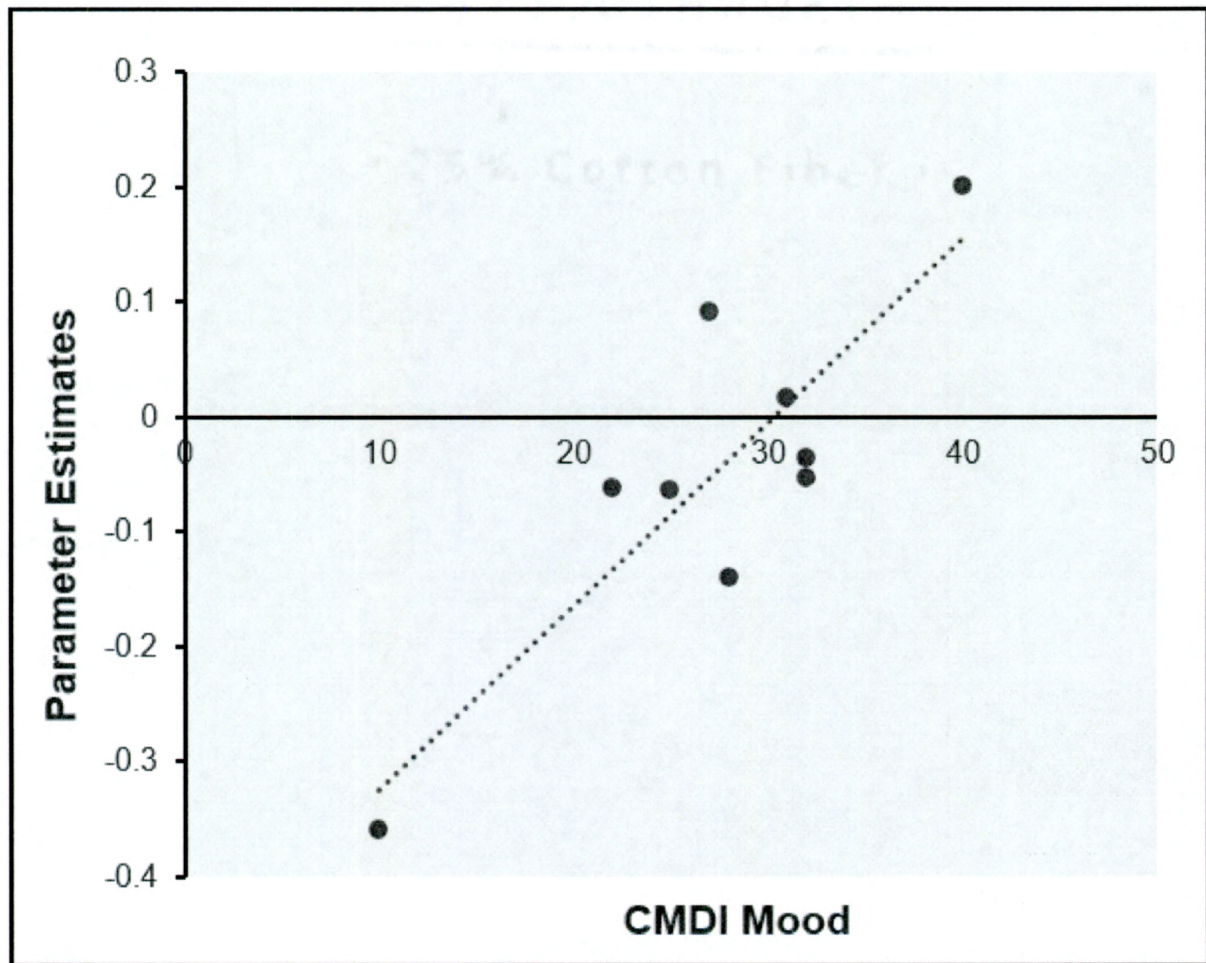
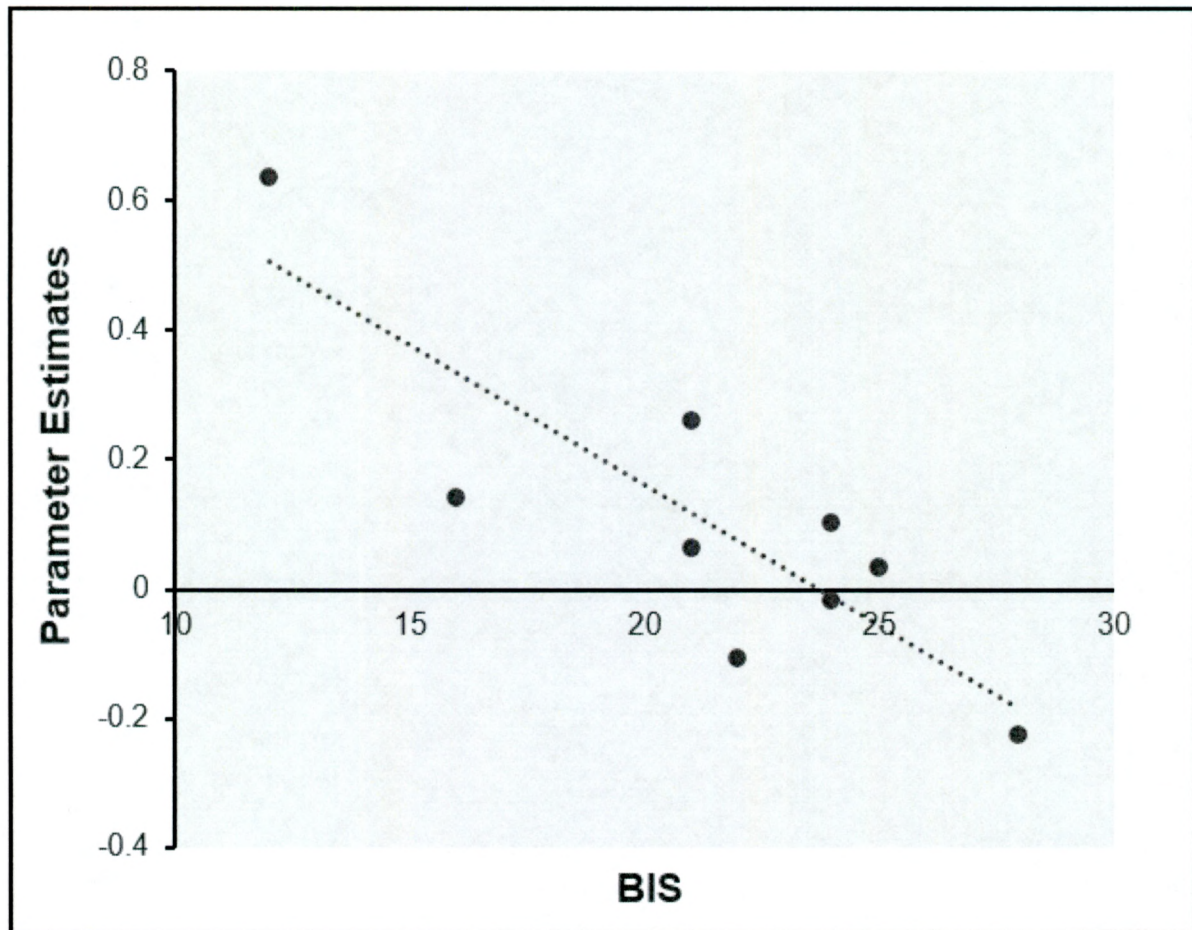
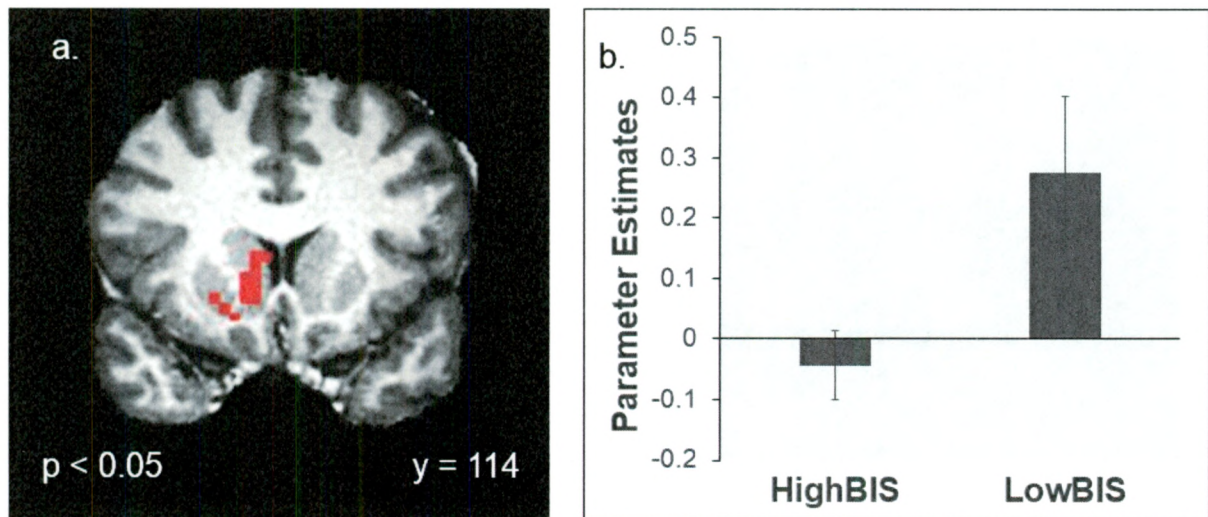


Figure 2. Correlation between NAcc activation of loss trials and CMDI-Mood in TBI.

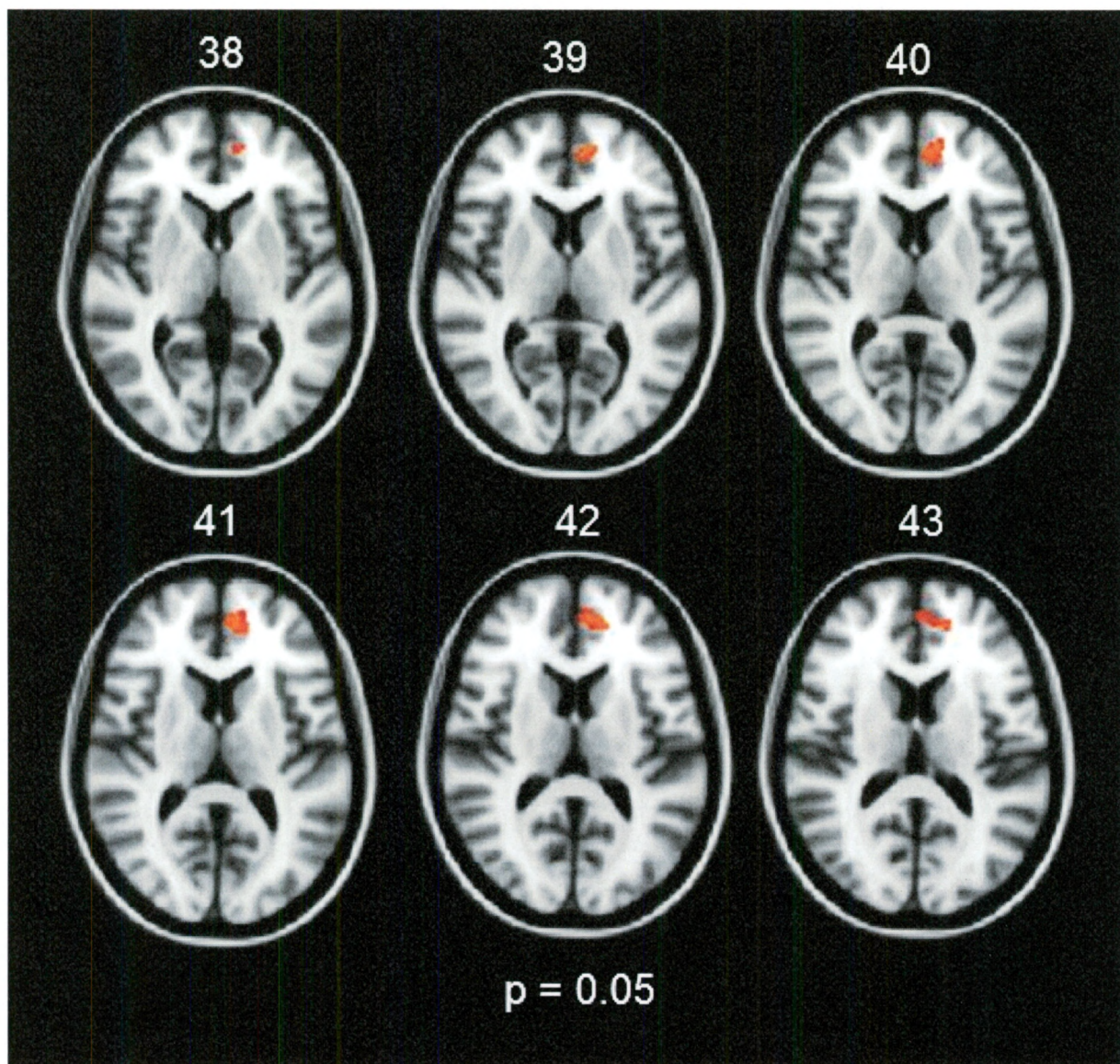
A strong positive correlation is seen between the activation of the NAcc during negative feedback (loss trials) and the CMDI-Mood subscale ( $r = .858$ ,  $p < 0.05$ ) in the TBI group. Activation is shown as parameter estimates associated with the time period during negative feedback.



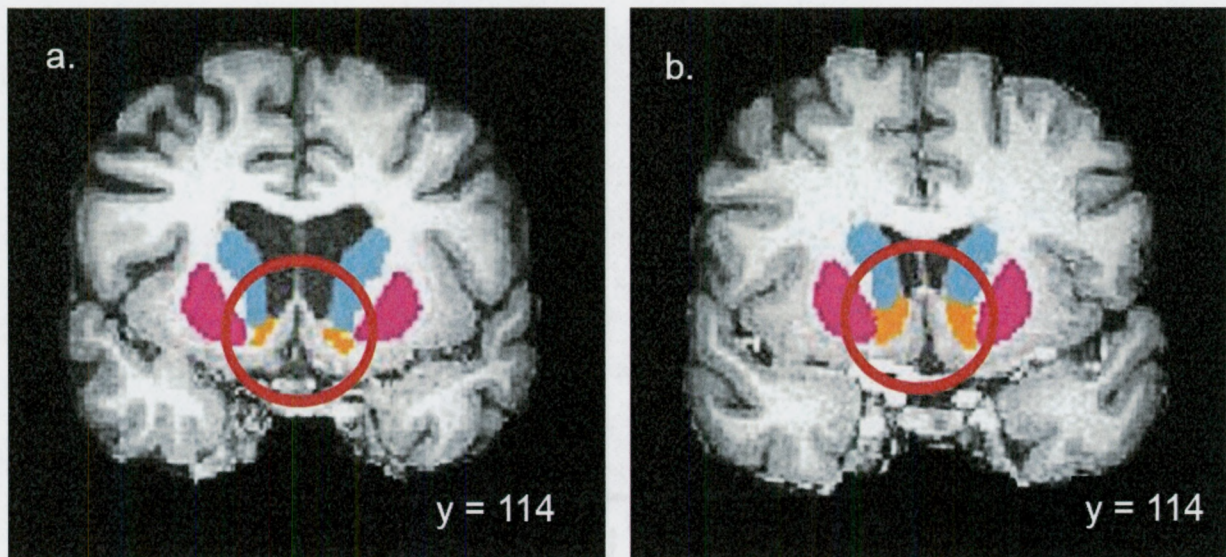
*Figure 3.* Correlation between NAcc activation of win trials and BIS in TBI. A strong negative correlation is seen between the activation of the NAcc during positive feedback (win trials) and the BIS scale ( $r = -.852$ ,  $p < 0.05$ ) in the TBI group. Activation is shown as parameter estimates associated with the time period during positive feedback.



*Figure 4.* Activation of NAcc between high and low BIS TBI groups. A significant difference in activation in the right NAcc is seen between TBI participants who scored either high or low on the BIS scale based on a median split (a.). The TBI participants who scored higher on the BIS scale are seen to show less activation in the right NAcc during win trials (b.). Activation is shown as parameter estimates associated with the time period during positive feedback.



*Figure 5.* GM differences between TBI and HC groups. The TBI group has a significant decrease in GM volume in the right ACC compared to HCs, as seen by the area shown in orange. Regions of activation are plotted onto axial slices, with numbers above each slice indicating Z coordinates in Talairach space.



*Figure 6.* Representative sample of TBI and HC participants' volumetric differences of the NAcc. Significant differences in NAcc volume is seen between the TBI and HC groups. Randomly selected representative samples of each group is depicted, with the NAcc colored orange and circled. The TBI participant (a.) shows a clear decrease in NAcc volume compared to the HC participant (b.). The segmentations of subcortical structures are plotted onto coronal slices of the given participant's own individualized brain structure.