

## Reduced lateral prefrontal cortical volume is associated with performance on the modified Iowa Gambling Task: A surface based morphometric analysis of previously deployed veterans



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### ABSTRACT

Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are two of the most common consequences of combat deployment. Estimates of comorbidity of PTSD and mTBI are as high as 42% in combat exposed Operation Enduring Freedom, Operation Iraqi Freedom and Operation New Dawn (OEF/OIF/OND) Veterans. Combat deployed Veterans with PTSD and/or mTBI exhibit deficits in classic executive function (EF) tasks. Similarly, the extant neuroimaging literature consistently indicates abnormalities of the ventromedial prefrontal cortex (vmPFC) and amygdala/hippocampal complex in these individuals. While studies examining deficits in classical EF constructs and aberrant neural circuitry have been widely replicated, it is surprising that little research examining reward processing and decision-making has been conducted in these individuals, specifically, because the vmPFC has long been implicated in underlying such processes. Therefore, the current study employed the modified Iowa Gambling Task (mIGT) and structural neuroimaging to assess whether behavioral measures related to reward processing and decision-making were compromised and related to cortical morphometric features of OEF/OIF/OND Veterans with PTSD, mTBI, or co-occurring PTSD/mTBI. Results indicated that gray matter morphometry in the lateral prefrontal cortex (LPFC) predicted performance on the mIGT among all three groups and was significantly reduced, as compared to the control group.

### 1. Introduction

Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are two of the most common consequences of combat deployment (Dolan et al., 2012). PTSD, a disorder mainly characterized by exposure to actual or threatened death or serious injury (American Psychiatric Association, 2013), affects estimates of 10–30% of previously deployed combat Veterans from Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND; Dolan et al., 2012; Hoge et al., 2007). Similarly, a significant percent (e.g., 15–25%) of OEF/OIF/OND Veterans are also affected by mTBI (Hoge et al., 2008). Mild TBI is characterized as a traumatically induced

physiological disruption of brain function which contains at least one of the following: (i) any period of loss of consciousness, (ii) any loss of memory for events immediately before or after the accident, (iii) any alteration in mental state at the time of the accident, and (iv) focal neurological deficits that may or may not be transient (Head, 1993). Mild TBI is unique from moderate and severe traumatic brain injury in length of loss of consciousness and posttraumatic amnesia (Head, 1993). Because of the high prevalence of trauma-related events during combat exposure, estimates of comorbidity of PTSD and TBI are as high as 42% in combat exposed OEF/OIF/OND Veterans (Hoge et al., 2008; Nelson et al., 2009). Literature suggests that combat exposure, rather than deployment itself, increases the likelihood of self-reported post-

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traumatic symptoms or a PTSD diagnosis following deployment (Smith et al., 2008), calling for the need of specific control groups (i.e., combat deployed Veterans with no PTSD/mTBI diagnosis). Recent work suggests that an occurrence of TBI may render individuals more susceptible to PTSD (Elder and Christian, 2009; Mayou et al., 2000; Stein and McAllister, 2009; Vasterling et al., 2009). Therefore, it is paramount to investigate not only individuals with singular diagnostic PTSD or mTBI, but also individuals with co-occurring PTSD/mTBI, to associate different deficit profiles in an attempt to specialize treatment.

Behaviorally, the most consistent finding in the extant literature indicates that individuals with either PTSD or TBI show similar patterns of executive function deficits, such as attention and working memory, when compared to control individuals using standard neuropsychological assessments (Leskin and White, 2007; Uddo et al., 1993; Vasterling et al., 1998, 2002). Although neuropsychological research is less abundant among individuals with mTBI, as opposed to moderate or severe TBI, these individuals have also been shown to display deficits in executive functioning (Lipton et al., 2009). Even scarcer are studies examining individuals with co-occurring PTSD/mTBI, however individuals with these conditions have demonstrated deficits in attention and processing speed as compared to control individuals (Nelson et al., 2009). Similarly, previously deployed OEF/OIF/OND combat Veterans with co-occurring PTSD/mTBI exhibit increased behavioral impulsivity and reduced inhibitory control, as compared to combat deployed non-diagnostic Veterans (Depue et al., 2014; Swick et al., 2012).

Possibly underlying these behavioral deficits, consistent neuroimaging research indicates that individuals with either PTSD or TBI show abnormal structure and function of the prefrontal cortices (Karl et al., 2006; Lipton et al., 2009; Shin et al., 2006; Sponheim et al., 2011; Thomaes et al., 2010). Specifically, individuals diagnosed with PTSD exhibit reduced gray matter in the ventromedial prefrontal cortex (vmPFC; Karl et al., 2006; Shin et al., 2006; Sponheim et al., 2011), dorsolateral prefrontal cortex (dlPFC; Thomaes et al., 2010) and in the amygdalar/hippocampal complex, when compared to control individuals (Karl et al., 2006; Kasai et al., 2008; Kitayama et al., 2005; Rauch et al., 2003; Woodward et al., 2006). Similarly, individuals with moderate and severe TBI also exhibit volumetric reductions in the vmPFC, as compared to controls (Ariza et al., 2006; Himanen et al., 2005; Mollica et al., 2009), suggesting that mTBI may also demonstrate similar morphometric differences as PTSD, and moderate and severe TBI in the vmPFC. However, this is relatively unknown in regard to mTBI. Therefore, among these individuals it appears as though the most consistent neuroimaging findings indicate abnormalities of the vmPFC (Karl et al., 2006; Mollica et al., 2009).

Taken together, deficits in classically defined executive function (e.g., attention, memory, processing speed, response inhibition), putatively associated with IPFC function (Corbetta and Schulman, 2002; Depue et al., 2010; Depue et al., 2015), and abnormalities of the vmPFC in combat deployed Veterans with PTSD, mTBI, or both seems clear, however, less research examining reward processing and decision-making has been conducted. This is surprising as the most associated behavioral relationships with the vmPFC are reward processing and decision-making. One of the hallmark neuropsychological tests measuring reward processing and decision-making is the Iowa Gambling Task (IGT; Bechara et al., 1994). Studies indicate the direct relationship of impaired performance on the IGT and damage to the vmPFC (Bechara et al., 1994, 1996, 1999, 2000; Fellows and Farah, 2005). The IGT simulates real-life decision-making by assessing whether participants can learn to sacrifice immediate rewards in favor of long-term gain (Lawrence et al., 2009). The IGT requires a participant to select a card from one of four card decks. Two of the decks are considered 'advantageous' as choosing cards from these decks ultimately leads to gains; conversely, the other two decks are considered 'disadvantageous' as choosing cards from these decks leads to losses. Performance on the IGT is dependent upon a participant's ability to learn to identify the two 'advantageous' decks from the two 'disadvantageous' decks to inform

future decisions about whether to "play" or "pass" a card from each deck.

A compendium of neuroimaging research (Bechara et al., 2000) suggests that individuals who have vmPFC lesions perform more poorly on the IGT, as they are insensitive to positive or negative future consequences, which subsequently affects learning. Impaired performance is not limited to lesions in the vmPFC, as studies have also demonstrated that lesions to the dlPFC, a region implicated in working memory and attention (Barbey et al., 2013; Corbetta and Schulman, 2002) and decision-making, are associated with poor performance on the IGT (Clark et al., 2003; Fellows and Farah, 2005; Manes et al., 2002). Given that the vmPFC and dlPFC each appear to be uniquely involved in decision-making and reward processing, Manes et al. (2002) suggested that the ventral and dorsal regions of prefrontal cortex must interact to make rational decisions.

Although scarce, behavioral research indicates that individuals with PTSD also demonstrate difficulties with decision-making and reward processing (Killgore et al., 2008; Levine et al., 2005; Sailer et al., 2008) and suggest these individuals may have difficulty identifying positive rewards over time due to decreased task-related motivation and/or cognitive fatigue (Sailer et al., 2008). Still, there are only a few studies to date, which have used the IGT to investigate decision-making and reward processing within these populations (Levine et al., 2005; Levin et al., 2010; Pustilnik et al., 2016). Research from Levin et al. (2010) comparing previously deployed combat Veterans from OEF/OIF/OND with a history of mTBI and a comparison group without head blast exposure, indicates comparable performance on the IGT. However, it is important to note that results from Levine et al. (2005) suggest that individuals with mTBI learn at a slower rate and demonstrate lower overall performance relative to a control group.

Given the strong neuroanatomical evidence of alterations in the vmPFC and dlPFC in individuals with PTSD and mTBI and initial behavioral indications of deficits in decision-making and reward processing, the current study sought to be the first to investigate brain morphometry associated with decision-making and reward processing in previously deployed OEF/OIF/OND Veterans with co-occurring PTSD/mTBI using the modified version of the IGT (mIGT; Cauffman et al., 2010; Tanabe et al., 2013). According to Cauffman et al. (2010), the mIGT prevents participants from differentially ignoring certain decks while attending to others, and thus may be better at assessing learning rates given an equal amount of experience with all decks. As reward and punishment cannot be untangled from perseveration on the standard version of the IGT (Bechara et al., 1994), the mIGT ensures that cards are drawn equally from each of the four decks, so that any deficit that can be attributed to learning about rewards and punishment and informing future decisions will be more easily identifiable. Hence, the mIGT enables one to examine decisions and learning rates, specifically on decks that are associated with reward, punishment or a combination of both (i.e., total plays overall).

Therefore, the current study is the first, to our knowledge, to examine decision-making and reward processing, as it relates to surface-based brain morphometry. Furthermore, we examined these processes in previously deployed Veterans with either PTSD or mTBI, or both compared to deployed Veterans with no PTSD or mTBI diagnosis. The following hypotheses were posited: (i) previously deployed OEF/OIF/OND Veterans with PTSD, mTBI, or co-occurring PTSD/mTBI will demonstrate poorer performance on the mIGT when compared to unaffected previously deployed OEF/OIF/OND Veterans, (ii) previously deployed OEF/OIF/OND Veterans with PTSD, mTBI, or co-occurring PTSD/mTBI will demonstrate reduced gray matter (GM) in vmPFC and dlPFC regions involved in decision-making and reward processing when compared to unaffected OEF/OIF/OND deployed Veterans, (iii) reduced GM of prefrontal cortical regions of the vmPFC and dlPFC will also be associated with performance on the mIGT in PTSD, mTBI, PTSD/mTBI, as compared to, unaffected previously deployed OEF/OIF/OND Veterans, and (iv) previously deployed OEF/OIF/OND Veterans with

**Table 1**  
Demographic results from the current study.

Characteristic	Control (n = 23)	PTSD (n = 21)	mTBI (n = 18)	PTSD/mTBI (n = 26)	p value
Age	30.61 (23–45)	29.95 (23–40)	29.22 (22–42)	30.23 (5.26)	0.88
Gender					0.05
Male	82.6% (19)	76.1% (16)	100% (18)	96.2% (25)	
Female	17.3% (4)	23.8% (5)*†	0% (0)*	3.8% (1)†	
Race					0.94
Caucasian	65.2% (15)	71.4% (15)	66.7% (12)	80.8% (21)	
African American	13.0% (3)	4.8% (1)	5.6% (1)	3.8% (1)	
American Indian	0.0% (0)	4.8% (1)	0.0% (0)	0.0% (0)	
Asian	0.0% (0)	0.0% (0)	11.1% (2)	3.8% (1)	
Hispanic	17.4% (4)	14.3% (3)	11.1% (2)	11.5% (3)	
Multiracial	4.3% (1)	4.8% (1)	5.6% (1)	3.8% (1)	
Years of Education	14.78 (12–18)	13.80 (11–16)	13.77 (11–17)	13.81 (11–17)	0.17
Handedness					0.97
Right	82.6% (19)	71.4% (15)	77.7% (14)	80.8% (21)	
Left	8.6% (2)	23.8% (5)	11.1% (2)	11.5% (3)	
Bimanual	8.6% (2)	4.7% (1)	11.1% (2)	7.7% (2)	

Note: Total subject numbers for each demographic variable are presented in parentheses. \* and † indicate post-hoc comparisons which are statistically significant between groups, with each group signified by a symbol ( $p \leq 0.05$ ).

co-occurring PTSD/mTBI will demonstrate the lowest behavioral performance on the mIGT and greatest reduction of GM in the vmPFC and dlPFC, given that co-occurring PTSD/mTBI encompasses symptoms of both conditions.

## 2. Methods

### 2.1. Participants

A total of 88 previously deployed OEF/OIF/OND Veterans participated in the present study. The sample was comprised of twenty-one Veterans diagnosed with PTSD (16 males;  $M$  age = 29.95,  $SD$  age = 4.97), 18 Veterans diagnosed with mTBI (18 males;  $M$  age = 29.22,  $SD$  age = 5.08), 26 Veterans diagnosed with co-occurring PTSD/mTBI (23 males;  $M$  age = 30.23,  $SD$  age = 5.26), and 23 Veteran controls without PTSD or mTBI diagnoses (19 males;  $M$  age = 30.61,  $SD$  age = 6.72) (Table 1). Recruitment was primarily accomplished through fliers circulated in the Denver area. All individuals were required to provide consent, which was approved through the Colorado Multiple Institutional Review Board, as well as other required review boards. Individuals were compensated monetarily for their participation. Demographic characteristics of our sample, including age, sex, race, and years of education, are shown in Table 1.

### 2.2. Recruitment

**Inclusion Criteria.** Inclusion criteria for participants included (1) age between 18 and 45, (2) at least one OEF/IND/OND deployment, and (3) currently receiving or eligible to receive physical and/or mental health care through the VA Eastern Colorado Health Care System.

**Exclusion Criteria.** Exclusion Criteria included (1) history of other significant neurological diseases (other than mild TBI for appropriate group) as assessed by interview and chart review; (2) history or diagnosis of lifetime moderate or severe TBI for the mTBI group, or any history of TBI for the PTSD and control group, as assessed by interview and chart review; (3) history or diagnosis of non-active duty related

mild TBI or PTSD disorder as assessed by interview and/or chart review; (4) diagnosis of schizophrenia or bipolar I disorder as assessed by administration of the Structured Clinical Interview for the DSM IV (SCID); (5) problematic drinking behavior that consistently exceeds recommended drinking limits per day, for examples, diagnosis of current alcohol abuse disorder or alcoholic dependence disorder per the SCID, or five or more alcoholic drinks per day, four out of seven days per week for the previous two weeks; (6) use of illicit substance(s) more than five times in the two weeks before study enrollment; (7) inability to read the informed consent document or adequately respond to questions regarding the informed consent procedure; (8) contraindication to having an MRI; and (9) having been previously enrolled in other VA studies which administered identical or similar instruments to those used in this study.

### 2.3. Diagnostic criteria/measures

PTSD was assessed using the SCID and PTSD symptom severity was assessed by the Trauma Symptom Inventory (TSI). Higher scores on the TSI indicate greater severity of trauma history. TBI was assessed by the Ohio State University of Traumatic Brain Injury-Identification Method (OSU TBI-ID) structured clinical interview, which includes assessment of TBI symptoms. Those with moderate to severe TBI were excluded. Though severity of TBI by the OSU TBI-ID is mostly determined according to loss or alteration of consciousness, the following criteria was used to determine TBI severity: (1) mild TBI: A TBI with normal structural imaging, 0–30 min of loss of consciousness (LOC), a moment and up to 24 h of alteration of consciousness/mental state (AOC), 0–1 day of posttraumatic amnesia (PTA), or a best available Glasgow Coma Scale Scores (GCS) of 13–15 recorded within the 24 h of the injury event, (2) moderate TBI: A TBI with normal or abnormal structural imaging, > 30 min and < 24 h of LOC, > 1 and < 7 days of PTA, or a GCS score of 9–12, and (3) severe TBI: A TBI with normal or abnormal structural imaging, > 24 h of LOC, > 7 days of PTA, or a GCS score < 9. To assess impulsivity we used the Barratt Impulsivity Scale (Patton et al., 1995). Higher scores on Barratt Impulsivity Scale indicate more impulsive behavior. Handedness was assessed by self-report, using the variables 0 = right, 1 = left, and 3 = bimanual.

### 2.4. Modified Iowa Gambling Task

We used a modified version (Cauffman et al., 2010; Tanabe et al., 2013) of the standard Iowa Gambling Task (Bechara et al., 1994) where participants made a play/pass decision with regard to each of the four decks preselected on each trial, rather than choosing to draw from any of the four decks on any trial as was the process in the original IGT. This type of modification has been shown to be more sensitive to individual differences in performance because of the ability to determine the independent effects of gains and losses on subsequent card selection (Peters and Slovic, 2000). Forcing participants to make decisions about each deck in a pseudorandom order eliminates the possibility that individuals will employ different search strategies across the decks, as is possible with the original version of the task. In addition to modifying the response option (i.e., play/pass), we also modified the outcome feedback, such that participants received information on the net gain or loss associated with a card, rather than information on both a gain and the loss separately (Bechara et al., 1994). This modification was made to equate working memory loads across groups during feedback and also to ensure that participants did not unequally weight the rewards and punishments within a given trial.

For each trial, one of the four decks was highlighted with an arrow, and participants were given four seconds to decide to play or pass that card. A running total of the participant's "earnings" appeared on each screen. If participants passed on a given card, the image of the card on the screen displayed the message "Pass" and the total amount of money earned did not change. If participants chose to "Play," a monetary

**Table 2**  
Behavioral results from the current study.

Measure	Control (n = 23)	PTSD (n = 21)	mTBI (n = 18)	PTSD/mTBI (n = 26)	p value
<b>Modified Iowa Gambling Task</b>					
Advantageous	0.85 (0.56–1)	0.63 (0.31–0.088)	0.88 (0.71–1)	0.85 (0.52–1)	0.41
Disadvantageous	1.29 (0–2.5)	0.82 (0.55–1)	1.44 (0.95–2.42)	0.70 (0.43–0.97)	0.37
Total Prop Play	0.76 (0.56–0.99)	0.72 (0.55–0.91)	0.76 (0.6–0.89)	0.77 (0.48–0.98)	0.37
Advantageous Frequency	0.86 (0.46–1)*	0.76 (0.43–1)*	0.84 (0.56–1)	0.83 (0.57–1)	0.15
Advantageous Magnitude	0.83 (0.53–1)†	0.87 (0.63–1)	0.92 (0.7–1)†	0.87 (0.47–1)	0.15
Disadvantageous Frequency	0.64 (0.33–1)	0.57 (0.23–0.86)	0.57 (0.36–0.8)	0.64 (0.20–0.97)	0.32
Disadvantageous Magnitude	0.72 (0.46–1)	0.68 (0.4–0.9)	0.72 (0.3–1)	0.75 (0.47–1)	0.58
<b>Barratt Impulsivity Scale</b>					
Attention	14.43 (8–25)*†‡	19.14 (11–28)*	17.94 (11–27)†	20.38 (12–31)‡	< 0.0001
Motor	21.52 (15–31)*‡	24.76 (16–32)*	23.94 (14–20)	24.81 (14–37)‡	0.11
Nonplanning	19.95 (12–33)*†‡	24.52 (11–32)*	24.55 (13–35)†	25.88 (12–38)‡	0.003
<b>Trauma Symptom Inventory</b>					
Intrusive Experiences (IE)	2.65 (0–10)*‡	14.66 (3–24)*^	4.11 (0–16)§	16.35 (1–23)‡§	< 0.0001
Defensive Avoidance (DA)	3.52 (0–15)*‡	14.90 (4–22)*^	6.55 (0–16)§	15.12 (4–24)§	< 0.0001
Dissociation (DIS)	3.13 (0–8)*‡	14.28 (2–27)*^	5.50 (1–17)§	12.31 (2–27)‡§	< 0.0001

Note: Group performance ranges for each behavioral measure are presented in parentheses. \*, †, ‡, ^, and § indicate post-hoc comparisons which are statistically significant between groups, with each group signified by a symbol ( $p \leq 0.05$ ).

outcome was displayed on the current card and the total amount of money earned was updated. The payoff schedules for each deck reflected the net outcomes of the original IGT. As in the original task, two of the decks are advantageous and result in a monetary gain over repeated play. The other two decks are disadvantageous and produce a net loss over repeated play. In addition, within each type of deck (advantageous vs. disadvantageous), there was one deck in which the losses experienced are infrequent but relatively large (magnitude deck), and one in which they are consistent and relatively small (frequency deck). The task was administered in six blocks of 20 trials each with an equal number of trials drawn from each of the four decks within a block. Participant performance was calculated based on the number of plays and passes for each deck.

### 2.5. Structural neuroimaging acquisition

All structural MRI images were acquired using a Philips 1.5 T Achieva 16-channel MS scanner located at the Denver Veterans Affairs Medical Center. An eight-channel head coil was used for radiofrequency transmission and reception. Foam padding was placed around the head, within the head coil, to limit head motion during the scan. Structural images were obtained via a T1-weighted 3D TFE in 160 sagittal slices. Imaging parameters were as follows: echo time ( $T_E$ ) = 3.2 ms, repetition time ( $T_R$ ) = 7100 ms, flip angle = 8.0°, field of view (FoV) = 240 mm, and voxel size = 1.0 \* 1.03 \* 1.0 mm. Scan parameters were consistent for all imaging sessions.

### 2.6. Structural neuroimaging analysis

Surface-Based Morphometry (SBM). Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (free-surfer-Linux-centos4\_x86\_64-stable-pub-v5.3.0), which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications. Briefly, this processing includes motion correction and averaging (Reuter et al., 2010) of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models are complete, a number of deformable procedures were performed for further data processing and analysis

including surface inflation, registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units based on gyral and sulcal structure, and creation of a variety of surface-based data including maps of cortical volume, surface area, thickness, curvature, sulcal depth, and local gyrification index. Group level analyses were performed using FreeSurfer's Query, Design, Estimate, and Contrast (QDEC), which uses the general linear model. Regressors for mIGT performance (advantageous deck frequency, magnitude and overall proportion, disadvantageous deck frequency, magnitude and overall proportion, advantageous and disadvantageous deck frequency, magnitude and proportion) as well as intracranial volume (ICV) and age, both of which were used as nuisance regressors in all analyses. Vertex-wise thresholding was applied at the  $p < 0.001$  level and cluster-wise thresholding was applied at the  $p < 0.05$  level using permutation testing via Monte Carlo simulation for all analyses. All neuroimaging analyses report *negative log(p)* scores and *p* values corrected for multiple comparisons.

## 3. Results

### 3.1. Demographic and behavioral results

Group comparisons were made using Analyses of Variance (ANOVAs) and Fisher's exact tests, as appropriate. When comparing demographic information (see Table 1) for PTSD, mTBI, co-occurring PTSD/mTBI and controls, there were no overall significant differences between the groups in terms of age ( $p = 0.71$ ), race ( $p = 0.90$ ), years of education ( $p = 0.17$ ) and handedness ( $p = 0.97$ ). There were significant differences in sex ( $p = 0.05$ ) with a higher proportion of females in the PTSD group relative to the mTBI and PTSD/mTBI groups. Behavioral performance results (Table 2) indicate there were no significant differences between groups for plays of advantageous decks ( $p = 0.41$ ), plays of disadvantageous decks ( $p = 0.37$ ), total proportion of decks played ( $p = 0.37$ ), advantageous frequency ( $p = 0.15$ ), advantageous magnitude ( $p = 0.15$ ), disadvantageous frequency ( $p = 0.32$ ), and disadvantageous magnitude ( $p = 0.58$ ). Post-hoc analyses indicate statistically significant differences between the control and PTSD group for advantageous frequency and between control and mTBI group for advantageous magnitude such that the control group played more than the PTSD group, but conversely, the mTBI group played more than the control group.

There were significant differences for the Barratt Impulsivity Scale (BIS) for Attention ( $p < 0.001$ ) and Nonplanning ( $p = 0.003$ ) with higher levels in the PTSD, mTBI and the combined PTSD/mTBI groups

relative to the control group. While not statistically significant across groups for Motor ( $p = 0.12$ ), post-hoc analyses indicated higher levels of impairment in the PTSD and PTSD/mTBI groups relative to the control group. For the Trauma Symptom Inventory, there were significant differences for Intrusive Experiences ( $p < 0.001$ ), Defensive Avoidance ( $p < 0.001$ ), and Dissociation ( $p < 0.001$ ) with higher scores for the PTSD and PTSD/mTBI groups relative to the mTBI and controls groups.

### 3.2. Structural neuroimaging results

Whole brain surface based morphometry (SBM) analyses using FreeSurfer were conducted initially to examine between group differences. Results indicated no significant differences in cortical GM thickness, volume or surface area between any of the patient groups, as compared to controls. Next we examined each group's relationship between mIGT performance and morphometric measures (GM thickness, volume and surface area) within the four groups individually (PTSD, mTBI, co-occurring PTSD/mTBI, and controls). Third, we examined whether the single diagnostic group regressed with mIGT performance findings were also significantly different from the control group using whole brain between-group analyses. Below we discuss which brain regions' morphometric measures regressed with mIGT performance were significant (non-significant results are not discussed) at both the within and between group levels. Importantly, analyses were also controlled for sex and handedness, however these variables had no significant effect on the presented results.

Results from within the PTSD group (Fig. 1A) revealed that increased plays of the advantageous magnitude deck was associated significantly with decreased GM volume [ $t(13) = -5.11$ ;  $p < 0.0001$ ; Tal = -31, 9, 54; peak vertex = #14; cluster size = 3144] of the left dlPFC. A between group comparison of the regression slopes indicated they were significantly different for the PTSD than control group (Fig. 1B) [ $t(36) = 3.36$ ;  $p = 0.0004$ ; Tal = -31, 9, 54; peak vertex = #14; cluster size = 2890].

Results from within the mTBI group (Fig. 1C) revealed that increased playing of cards across all decks was associated significantly with decreased GM volume [ $t(15) = -2.78$ ;  $p < 0.007$ ; Tal = 38, 16, 38; peak vertex = #109; cluster size = 2020] of the right dlPFC. A between group comparison of the regression slopes indicated they were different for the mTBI than control group (Fig. 1D) [ $t(38) = 2.26$ ;  $p = 0.015$ ; Tal = 38, 23, 41; peak vertex = #103562; cluster size = 513], however, although the difference was significant at the vertex-wise threshold, it did not pass clusterwise threshold.

Results from within the PTSD/mTBI group (Fig. 1E) revealed that increased plays across all decks was significantly associated with decreased GM surface area [ $t(23) = -3.58$ ;  $p < .0008$ ; Tal = 39, 41, 24; peak vertex = #3; cluster size = 9146] of the right ventral lateral PFC (vlPFC). A between group comparison of the regression slopes indicated they were significantly different for the PTSD/mTBI than control group (Fig. 1F) [ $t(46) = 4.04$ ;  $p < .0001$ ; Tal = 33,47, 8; peak vertex = #3; cluster size = 2198].

Of note, there were no significant results related to whole brain morphometry regressed with mIGT performance within the control

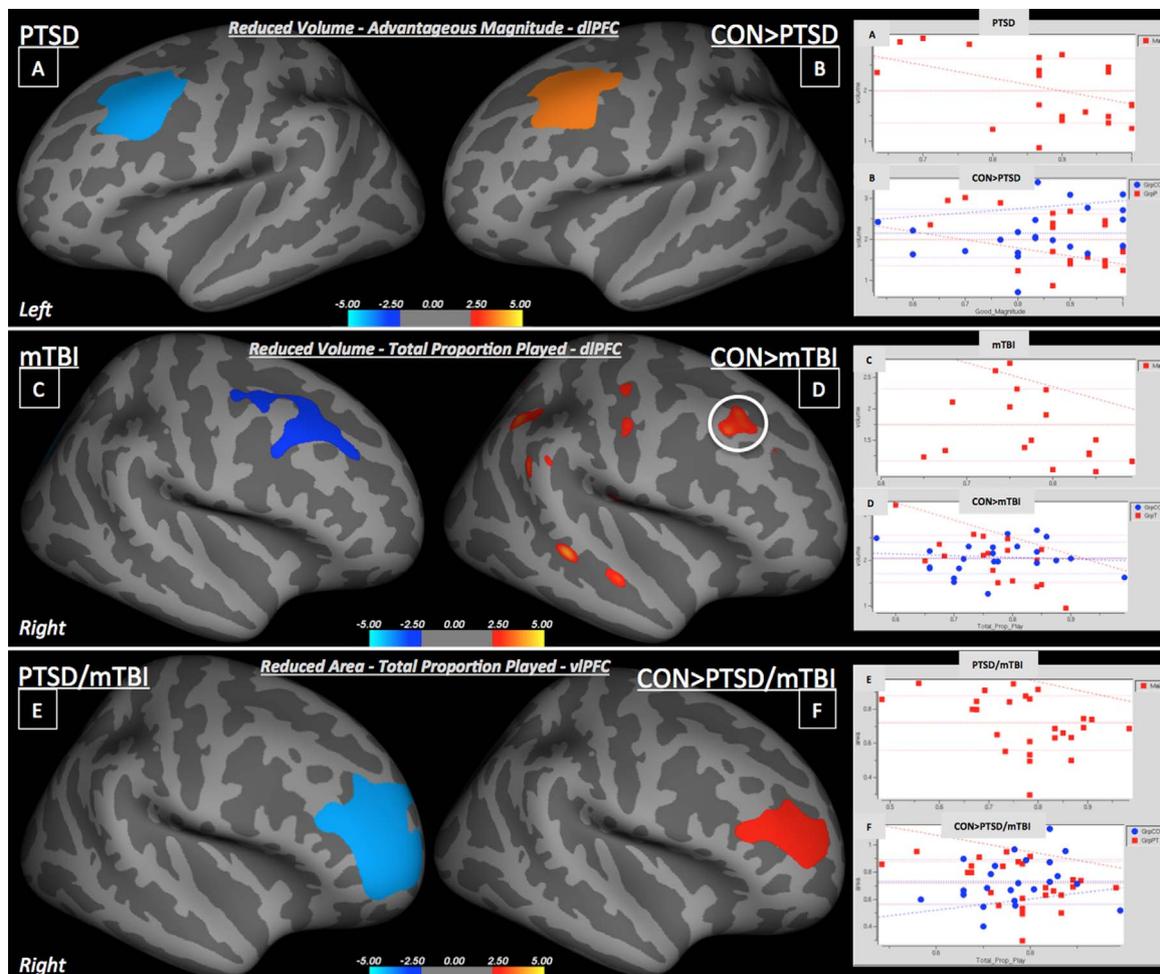


Fig. 1. Whole brain regression of mIGT performance and morphometry with scatter plots. A. Within group PTSD, B. Control compared to PTSD group, C. Within group mTBI, D. Control compared to mTBI group, E. Within group PTSD/mTBI, F. Control compared to PTSD/mTBI. Color bar indicates scale of  $-\log_{10}(p)$ . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

group, importantly, suggesting the findings discussed above are statistically driven by the individual patient groups.

#### 4. Discussion

The current findings are the first to show a relationship between decision-making, reward processing and brain morphology in previously deployed Veterans from OEF/OIF/OND affected by PTSD, mTBI and co-occurring PTSD/mTBI. Consistent with our hypotheses, individuals with PTSD, mTBI or co-occurring PTSD/mTBI demonstrated morphological differences in IPFC regions within group, as well as when compared to a control group of unaffected previously deployed Veterans in connection to performance on the mIGT. More specifically, when examining the groups individually, as well as comparing to a control group of unaffected deployed Veterans, reduced left dlPFC morphometry was associated with increased plays of ‘advantageous’ magnitude decks in Veterans with PTSD, and reduced right dlPFC and vlPFC morphometry were associated with increased plays averaged across all decks (i.e., ‘advantageous’ and ‘disadvantageous’) in Veterans with mTBI or co-occurring PTSD/mTBI, respectively. With exception of performance between the control group and PTSD group for ‘advantageous’ frequency and between the control and mTBI group for ‘advantageous’ magnitude, generally, our behavioral results did not support the hypothesis that OEF/OIF/OND deployed Veterans with PTSD, mTBI, and co-occurring PTSD/mTBI would demonstrate poorer performance on the mIGT when compared to unaffected previously deployed Veterans. These results suggest that all deployed Veterans, regardless of diagnoses post-deployment, were able to distinguish between ‘advantageous’ and ‘disadvantageous’ decks.

While no wide spread behavioral differences were observed (except for a significant reduction in advantageous frequency in the PTSD, as compared to control group), we feel that it is meaningful to report the relationship between reduced morphometry and behavioral performance in the context of reward and decision-making. It is possible the task did not provide sufficient load for individual groups to exhibit behavioral differences, but did provide enough sensitivity to detect morphometric changes. These morphometric changes may indicate strategic differences between groups (control vs. patient Veterans) in approaching reward and decision-making situations, which may be related to impulsivity (as indicated by group differences in the BIS). While tentative, this study suggests that future investigation concerning reward and decision-making processes in Veterans is warranted.

At first glance, the findings of decreased GM morphometry of left dlPFC in relation to increased plays of the ‘advantageous’ magnitude deck in the PTSD group appear to be counterintuitive (e.g., more plays of an advantageous deck with less GM); however, considering the results from the other two groups (i.e., mTBI, and PTSD/mTBI) may facilitate interpretation. Specifically, the mTBI and PTSD/mTBI groups exhibited an association between reduced GM morphometry in both ventral and dorsal PFC in connection to increased plays overall, while the PTSD group exhibited such a relationship for only the ‘advantageous’ magnitude deck. This pattern could suggest that reductions in IPFC GM morphometry are associated with an overall tendency to play any deck, but only the advantageous deck was sensitive in the PTSD group. Interestingly, this same relationship (i.e., more plays – reduction in IPFC GM morphometry) does not hold in unaffected previously deployed Veteran controls, perhaps suggesting a strategic difference in the impetus to actually “play” the decks. While mIGT behavioral performance results were not significantly different between groups, morphometric differences (i.e., reductions of IPFC GM morphometry) were consistent across the patient groups, suggesting that GM morphometry may affect motivation and learning strategic information. Evidence to support this idea can be taken from the group differences in reported impulsivity using the BIS. The affected groups exhibited higher impulsivity on two of the three subscales, namely the Attention and Non-Planning subscales, than the control group lending support to the idea

that perhaps more impulsive decision-making is guiding these individuals’ strategy. Specifically, GM in regions of both the dorsal and ventral attentional networks appear reduced across group, therefore suggesting possible reductions in attentional control when performing decision-making tasks (Corbetta and Shulman, 2002).

The results of the current study suggest that previously deployed Veterans affected by PTSD, mTBI, or co-occurring PTSD/mTBI demonstrate morphological differences within group in the dlPFC and vlPFC, respectively, as well as compared to unaffected Veteran controls in relation to performance on the mIGT. Although our findings are novel to morphological differences present within these populations when performing a reward processing and decision-making task, other studies have demonstrated that exposure to combat experiences in OEF/OIF/OND Veterans increases the tendency to engage in risky decision-making following their return from deployment (Killgore et al., 2008). Increased risky behaviors following deployment may affect all previously deployed Veterans similarly, regardless of PTSD, mTBI or co-occurring PTSD/mTBI diagnoses, and may provide evidence for why only small behavioral differences were observed between affected and unaffected groups.

The current findings suggest that deployed Veterans affected by PTSD, mTBI and co-occurring PTSD/mTBI may engage in more risky decision-making than Veterans without PTSD and/or mTBI diagnoses, due to morphological differences in the IPFC. Although there were no differences in behavioral performance on the mIGT, reduced IPFC morphology was associated with increased plays of ‘advantageous’ and ‘disadvantageous’ decks. The IPFC, a region associated with higher order executive function and decision-making processes (Talati and Hirsch, 2005), appears to affect the ways in which previously deployed Veterans affected by PTSD, mTBI and co-occurring PTSD/mTBI process information. Given previous research suggesting that individuals affected by PTSD, mTBI or co-occurring PTSD/mTBI demonstrate impaired decision-making abilities (Sailer et al., 2008; Killgore et al., 2008; Levine et al., 2005), reductions in IPFC GM morphometry may be linked to impulsivity, as indicated by increased BIS scores.

While the current study revealed interesting relationships between decision-making and reward processing in previously deployed OEF/OIF/OND Veterans and brain morphology, several limitations must be acknowledged. This study represented only an initial examination of decision-making, reward processing and inhibitory control in previously deployed OEF/OIF/OND Veterans. One possibility is that these strategies existed prior to deployment. Future studies investigating decision-making, reward processing and inhibitory control difficulties in deployed Veterans might fruitfully conduct similar evaluations prior to deployment and immediately following deployment to provide a further understanding regarding how PTSD, mTBI, and co-occurring PTSD/mTBI affect the relation between morphology and performance on decision-making, reward processing and inhibitory control tasks post-deployment.

Additionally, previous research findings suggest sex-differences are associated with brain activity and performance (Bolla et al., 2004), and the use of a predominantly previously deployed male sample may prevent the generalization of these findings to previously deployed females. More specifically, Bolla et al. (2004) found that during performance of the IGT, males activated extensive regions of the right and left lateral orbitofrontal cortex (OFC) and the right dlPFC, whereas females activated the left medial OFC, suggesting distinct brain mechanisms may be employed by males as compared to females. Furthermore, although post-deployment adjustment between males and females is similar and both populations report similar symptoms consistent with PTSD (Street et al., 2013), due to the use of the IGT, which at least in its standard version may show sex differences, our results may not be equally generalizable to male and female previously deployed Veterans.

Although there are several limitations observed in the current study, this is the first study, to the authors’ knowledge, to examine the relation between morphological differences and performance on a decision-

making and reward processing experimental paradigm in a sample of previously deployed Veterans diagnosed with PTSD, mTBI or co-occurring PTSD/mTBI. Moreover, it serves to add to current literature by providing evidence that structural differences in the IPFC are associated with performance on a reward processing and decision-making experimental paradigm in OEF/OIF/OND previously deployed Veterans.

#### 4.1. Conclusions

The current study demonstrates that reduced IPFC GM morphometry is associated with increased plays of advantageous magnitude decks in deployed Veterans diagnosed with PTSD and increased plays of all cards in general in deployed Veterans diagnosed with mTBI and co-occurring PTSD/mTBI, when compared to unaffected previously deployed Veteran controls. Although behavioral performance on the mIGT was similar for all groups, the current study identified differences in impulsivity between unaffected previously deployed Veterans and previously deployed Veterans diagnosed with PTSD, mTBI or co-occurring PTSD/mTBI, as compared to unaffected previously deployed Veterans. These results suggest that previously deployed Veterans with PTSD, mTBI, or co-occurring PTSD/mTBI may exhibit increased impulsivity and reduced inhibitory control during activities that involve decision-making and reward processing.

#### Contributors

NDF, FN, LKK, TS, SCP, BED analyzed neuroimaging data and wrote the manuscript. JHO-M, MCB, TAH, JF collected and analyzed clinical data. LAB, MTB, BED conceptualized the study.

#### Conflicts of interest

The author's have no conflicts of interest.

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