Using Resting-State Functional Connectivity to Detect Uncomplicated Mild Traumatic Brain Injury in U.S. Military Populations

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Abstract

Detection of uncomplicated mild traumatic brain injury (mTBI) is difficult due to nonspecific symptoms and a lack of biomarkers for current diagnostic methods. New biomarkers are needed to more sensitively screen for mTBI. Our study searched for patterns in resting-state functional connectivity among U.S. military members diagnosed with mTBI that differ from those in healthy controls. We analyzed data from 254 U.S. military personnel deployed to a combat theatre in the Middle East from 2010-2013. These military personnel underwent initial magnetic resonance imaging and screening for mTBI following medical evacuation to Landstuhl Regional Medical Center (LRMC), the primary triage center for all evacuated combat causalities. Using U.S. military personnel allowed us to account for mechanism of injury in a controlled manner because injuries can be documented and traced in combat settings. We compared four distinct groups for our analysis; Blast TBI (n=79), Non-Blast TBI (n=44), Non-Blast Control (n=96), and Blast Control (n=35) while covarying for age and gender. These groups allowed us to compare and control for different types of mechanisms to find any differences in resting-state connectivity related to TBI or blast exposure. We hypothesized that resting-state networks would be disrupted in mTBI populations when compared to controls. We used two different methodologies to test this hypothesis. The first method was a seed-based analysis examining group differences in the correlations from the posterior cingulate cortex (PCC, a key hub within the Default Mode Network) to the whole brain. The second analysis used a seven-network parcellation to compute correlations between all seven networks to the Default Mode Network (DMN). We were unable to distinguish any group from controls, suggesting differences in resting-state functional connectivity are not a robust biomarker of injury.

Keywords: TBI, Functional connectivity, Resting-state fMRI, Brain networks

Exploring Resting State Functional Connectivity in Blast TBI Populations

BACKGROUND

Traumatic brain injury (TBI) is damage to brain tissue resulting from rapid acceleration/deceleration or physical impact (Vos et al., 2012). There are an estimated 2.8 million civilian TBI-related emergency room visits, hospitalizations, and deaths annually in the U.S. alone (Taylor, Bell, Breiding, & Xu, 2017). In some cases TBI has been shown to be associated with short- and long-term clinical consequences (Taylor et al., 2017). The severity of these outcomes range from dizziness to long-term mental health issues and even death (Chapman & Diaz-Arrastia, 2014; Taylor et al., 2017). TBI is also associated with several long-term comorbidities: higher rates of depression, post-traumatic stress disorder (PTSD), neurobehavioral issues, and possibly increased risk of dementia (Reid & Velez, 2015; Singh, Mason, Lecky, & Dawson, 2018). With TBI prevalence so high, there is a critical need for methods to detect injury in order to begin treatment for possible short- and long-term negative outcomes (Taylor et al., 2017).

There are three clinical severity levels of TBI: mild, moderate, and severe (Reid & Velez, 2015). The severity level is based on the following factors: (1) loss of consciousness (LOC); (2) post-traumatic amnesia (PTA), where the patient doesn't remember events after the injury; (3) retrograde amnesia (RA), where the patient doesn't remember events before the injury; (4) alteration of consciousness (AOC), such as being dazed and confused; (5) Glasgow Coma Scale (GSC), where the patients response rate to various stimuli is measured; (6) and the presence of neuroimaging exam abnormalities (Jennett & Bond, 1975; O'Neil et al., 2013; Reid & Velez, 2015). Incidence rates for less severe injuries are possibly under-reported due to lack of medical attention and inaccurate screening along with being easily overlooked when compared to more

severe forms of TBI (Adrian, Mårten, Salla, & Lasse, 2016). Mild TBI (mTBI) is diagnosed if LOC is less than 30 minutes, AOC lasts less than 24 hours, and PTA lasts less than 24 hours, but all three are present in some duration (Reid & Velez, 2015). mTBI is by far the most common form of TBI diagnosed in the U.S. military, contributing to 84.9% of TBI cases (DVBIC, 2018).

In the civilian sector, mTBI has a wide range of causes. Most of these are physical blows to the brain, such as falls, accounting for 28% of cases, and automotive related incidents accounting for another 20% (Dempsey et al., 2009). In the military, mTBI is a common type of brain injury (Chapman & Diaz-Arrastia, 2014; McKee & Robinson, 2014). It is so common that TBI is known as the "signature injury" of Operation Iraqi Freedom (Chapman & Diaz-Arrastia, 2014).

Sources of military TBI can differ from civilian TBI in that some are combat-related, such as arising from blast exposure (Chapman & Diaz-Arrastia, 2014; Reid & Velez, 2015). Blast exposure is exposure to the high-pressure shockwave that results from the detonation of weapons such as improvised explosive devices (IED) (Reid & Velez, 2015). Not only do some of the injury mechanisms differ between civilian and military TBI, some other key aspects do as well. Military brain injuries may be left untreated until mission completion and/or occur concurrently with loss of sleep and high stress (Chapman & Diaz-Arrastia, 2014).

Detection of mTBI is inherently difficult. This is because diagnosis frequently relies on self-report or witness accounts. Self-report becomes an issue when the patient is suffering from PTA or LOC/AOC, as they are unable to accurately recount what happened (Chapman & Diaz-Arrastia, 2014). Some symptoms of mTBI such as confusion, headaches, and fatigue are relatively commonplace. This makes diagnosis of mTBI based on symptoms difficult because they can seem nonspecific (Chapman & Diaz-Arrastia, 2014).

It is estimated that 19% of deployed forces have sustained a brain injury in theatre, and 84.9% of clinician-diagnosed TBI in deployed and non-deployed personnel have been classified as mTBI (DVBIC, 2018). However, due to the complicated nature of detection and the frequency of blast exposure, prevalence of mTBI among deployed personnel in combat zones is estimated to be as high as 59% (Reid & Velez, 2015). Injuries that happen during missions may not receive proper and/or immediate treatment, or possibly even diagnosis, until the solider returns. In these instances, the brain injury can be left untreated and accompanied by intense physiological stress and sleep deprivation commonly found in combat scenarios (Chapman & Diaz-Arrastia, 2014). Prior work has proposed that as many as 320,000 troops (15-22%) returning from operations in Iraq and Afghanistan have sustained mTBI (McKee & Robinson, 2014).

Early screening and diagnosis of mTBI is important because more recent efforts suggest that mTBI can lead to longer term impact than previously appreciated. mTBI has been associated with poor health outcomes one year after injury, such as a possible increase in mental health symptoms, depression, and post-traumatic stress disorder (PTSD) (Mac Donald, Johnson, et al., 2017).

A commonly used neurological assessment for TBI is The Glasgow Coma Scale, which assesses motor response, verbal response, and eye opening reflex to determine the level of consciousness of the individual (Chapman & Diaz-Arrastia, 2014; Jennett & Bond, 1975). Radiological imaging (usually computed tomography, CT) is often used in conjunction with neurological assessments to come to a diagnosis (Chapman & Diaz-Arrastia, 2014). However, while CT is relatively accessible and inexpensive, it is not as sensitive as other technologies to brain changes specifically associated with milder forms of brain injury that are not associated with detectable lesions, such as mTBI (Adrian et al., 2016; Chapman & Diaz-Arrastia, 2014).

Magnetic resonance imaging (MRI) has multiple advanced neuroimaging techniques that might allow for far greater detection. However, MRI can be more expensive and less accessible, especially given their uncertain clinical utility.

Advanced MRI techniques such as diffusion tensor imaging (DTI) and functional MRI (fMRI) are just beginning to be used to quantify pathophysiological changes associated with mild brain injury (Chapman & Diaz-Arrastia, 2014). The damage to white matter tracts that is associated with TBI is detectable with DTI (Mac Donald, Barber, et al., 2017). TBI appears to cause microstructural alteration to the neurons that make up white matter tracts (McKee & Daneshvar, 2015). These alterations, such as axonal damage and reduced cell functioning, have been reported to negatively impact cognitive performance in memory networks (Clark et al., 2017; Palacios et al., 2012).

Resting-state fMRI might hold promise for understanding the physiological impact of brain injury by probing cognitive symptoms. Correlations between the blood oxygen-level dependent signal (BOLD) in different regions of the brain, measured using fMRI taken when subjects are resting while awake, map out large-scale networks that can be disrupted in many diseases (Mohan et al., 2016; Raichle, 2015). The integrity of these large-scale networks depends, in part, on the integrity of white matter connections between cortical regions. Damaged white matter then may cause disruptions in the correlated activity of brain networks, thus resting state fMRI may highlight system disruptions following brain injury. Given TBI-related disruption to white matter, it is plausible to suggest that there may be some measurable impact on resting-state functional connectivity in mTBI as well.

The DMN is the network associated with intrinsic thought and a resting, non-tasked, brain. This network can be mapped with resting-state functional connectivity, possibly allowing

us to detect patterns of network disruptions that may come from damaged brain tissue thus making it a probable biomarker for detecting injury. Thus resting-state functional connectivity may allow clinicians to detect early changes in connectivity indicative of brain injury that may also predict later outcome.

The key question of our research is whether resting-state connectivity patterns can be used to distinguish mTBI and healthy control groups. We hypothesized that resting-state functional connectivity will differ between the mTBI and non-head-injured controls. To examine this question, we compared the resting state fMRI scans of U.S. Military personnel deployed to a combat theatre during the time frame of 2010-2013, who were diagnosed with mTBI. Data for this project are from the EVOLVE study (Mac Donald, Johnson, et al., 2017).

METHODS

Subjects

Two hundred and fifty-four participants from the U.S. Army, U.S. Air Force, U.S. Marines, and U.S. Navy were screened for mTBI from October 2010 through May 2013 following medical evacuation to Landstuhl Regional Medical Center (LRMC), a U.S. Military hospital located in Landstuhl, Germany. A follow-up interview was conducted 12 months later at Washington University, St. Louis. The initial screening procedure consisted of a self-report survey consisting of (1) exposure to TBI mechanism (blast, fall, impact); (2) symptoms immediately following the event (loss of consciousness (LOC), confusion, dazed); and (3) symptoms since the event (such as amnesia or headaches) (Dempsey et al., 2009). Participants also had to (1) give verbal consent to the study in person; (2) have no previous history of TBI or mental health diagnosis; (3) be enrolled in the study within 30 days of the event; (4) be a U.S.

military service member; (5) have no pre-deployment history of a major psychological disorder; (7) have no contraindications to MRI such as embedded metallic fragments; and (8) have an agreement to monthly correspondence with a follow-up interview up to 12 months later. The in-person verbal consent excluded participants with more severe levels of TBI. Upon a positive or negative TBI screening, participants were designated to one of four groups.

a. Blast + impact TBI (**Blast TBI**, n=79): participants with blast-plus-impact TBI
b. **Non-blast TBI** (n=44): participants with TBI caused by mechanisms other than blast
c. **Non-blast control** (n=96): participants without TBI and without blast exposure
d. **Blast control** (n=35): participants with blast exposure but without TBI

Inclusion in the blast TBI and non-blast TBI groups required a positive mTBI screening from LRMC, meeting the previously mentioned study criteria, and either blast exposure or a non-blast mechanism resulting in a change in neurological status, LOC, or PTA. Medical histories for all blast TBI participants indicated a blast exposure coupled with an additional form of impact. No Blast TBI participants experienced isolated blast exposure. The Non-blast TBI group sustained TBI from mechanisms such as falls, vehicle collisions, being struck, etc. None of the mechanisms sustained by this group involved blast exposure. Non-blast controls were medically evacuated for non-combat orthopedic injuries, gastrointestinal, dermatological, and women's health reasons. Blast controls had blast exposure but did not experience LOC, AOC, or PTA and had a negative TBI screening. Blast control and Non-blast TBI groups allow us to examine any differences in sub-concussive exposures. By examining TBI without blast exposure, blast exposure without TBI, and Blast TBI, we are able to see if there is any difference between mechanisms of injury.

Table 1
Group Demographics (n=254)

Groups	*Age Median*	*Age Maximum*	*Age Minimum*	*Percent Male*
Blast TBI	25.00	46.00	19.00	94.59
Non-Blast Control	30.00	48.00	20.00	87.50
Blast Control	32.00	46.00	20.00	87.10
Non-Blast TBI	27.00	49.00	20.00	91.18

MRI Data Collection

Data were collected on a Siemens Magnetom Verio 3T MRI scanner located at LRMC. Each subject had a single T1-weighted 3D MPRAGE and three BOLD scans at each timepoint. The MPRAGE protocol consisted of a voxel size of 0.9x0.9x0.9 mm, 2000/3.03ms TR/TE, 8-degree flip angle, FOV of 225mm, and 4:06 minute acquisition time. Each of the three BOLD scans used a voxel size of 4.0x4.0x4.0 mm, 34 slices, 2120/27ms TR/TE, 90-degree flip angle, FOV 256mm, interleaved slice collection, and a 5:22 minute acquisition time. Participants were asked to hold still for the duration of the scan. No other specific instructions were given or enforced.

MRI Preprocessing

Data were processed using Analysis of Functional NeuroImages (AFNI), version 17.3.00, and FMRIB Software Library (FSL), version 5.0.9 (Cox, 1996; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2011). This workflow represents best practices for removal of sources of noise, including motion, in resting-state data (Jo et al., 2013). Each of the subject's 2-4 resting-state fMRI scans were concatenated and processed as one to enhance data quality after the removal of censored volumes. By using AFNI command "*afni_proc.py"* in version 17.300 found

in Appendix A we were able to ensure a high level of reproducibility and portability by generating the pipeline for the analysis in one step. This kept the bulk of preprocessing standardized for each subject.

Data were skull-stripped, co-registered to the subject T1 image, resampled from 4mm to 2mm, and registered to MNI152 space using the MNI152 2009c atlas (resampled from 1mm to 2mm) provided by AFNI. Head motion during scanning was a concern because it can cause systematic changes to functional connectivity (Power et al., 2014; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). ANATICOR, found in AFNI, was used to censor volumes affected by motion and remove BOLD signal noise from our resting-state scans (Jo, Saad, Simmons, Milbury, & Cox, 2010). We calculated mean absolute and mean relative motion using AFNI.

Rather than developing an *a priori* motion threshold we examined the impact of different thresholds on our individual groups. The reason for this is that we wanted to be sensitive to any motion differences between groups, as some groups may move more than others due to injuries. This allowed us to avoid differentially impacting any one group. This process, shown in appendix B, allowed us to determine the appropriate threshold.

We excluded subjects if all resting-state scans contained average motion above our threshold. Exclusion of participants from fMRI analysis was dependent upon criteria developed while being blinded to groups. The decision of whom to eliminate and what motion criteria to use was done before we conducted any analysis. Of the remaining subjects, censored volumes were removed to avoid erroneous regression calculations using AFNI's *3dTcat.*

Quality assurance was performed post-processing using pipelines generated by AFNI. We spot-checked skull-strips, registrations, and other preprocessing steps manually using the AFNI generated script *@ss_review_driver* while outliers and a more comprehensive check

looking for outliers was performed using a summary table generated with *gen_ss_review_table.py*.

fMRI Data Analysis

All analyses were done using a Make pipeline which allowed us to standardize the process for each subject (Askren et al., 2016). This ensured reproducibility by enforcing each subject to be processed using the exact same method regardless of when the analysis was performed.

Our first approach was a seed analysis to examine connectivity maps between the four groups. We created a 10 mm sphere standard-space mask in the PCC (1, -51, 29), which has been identified as a primary hub in the DMN (Raichle, 2015). For each subject's data we used FSL's *fslmeants* to extract the mean time course of the PCC seed. We then Fisher Z-transformed the time courses followed by AFNI's *3dTcorr1d* to make a map of computed correlations of the time course to all other voxels. Then, using an unpaired *T*-test on these transformed correlations we were able to identify any differences in network connectivity between our four groups. Finally, these masks were cluster-corrected using the AFNI cluster correction procedure. Gender and age were used as covariates in the analysis.

Our second analysis using a Yeo parcellation was motivated by the goal of being able to detect connectivity differences between our injured population and a standardized set of healthy controls which is more in-line with a clinical type diagnosis. The power in this type of comparison comes from the ability to contrast our military-sourced and -injured sample to a completely unrelated and different sample. This is unlike a seed based or independent component analysis where the connectivity differences comes from within the sample, which is more

appropriate for detecting differences between groups rather than for diagnosis. The seven networks as identified by Yeo were the DMN, Frontoparietal Network (FPN), Dorsal Attentional Network (DAN), Ventral Attentional Network (VAN), Visual Network (VN), Limbic Network (LN), and Somatomotor Network (SMN) (Yeo et al., 2011). Our primary interest was in the correlations of the DMN and executive functioning networks such as the FPN and DAN between our four groups. Any changes in correlations between these separate networks could signify a possible disruption related to mTBI.

Statistical Analysis

The Yeo parcellation analysis was carried out using a script developed by colleague Trevor Day. This script used the same preprocessed data as the seed-analysis and worked by computing the mean time course of each network and correlating it with the other networks. The results of this are tables of network pair's correlation strengths. These were imported to R, version 3.5.1, and analyzed using the *psych* library, version 1.8.10 (R Core Team, 2018; Revelle, 2018). In R the correlation data were Fisher Z-transformed and then a *T*-test was performed with Bonferroni correction of each network pair for each of our four groups.

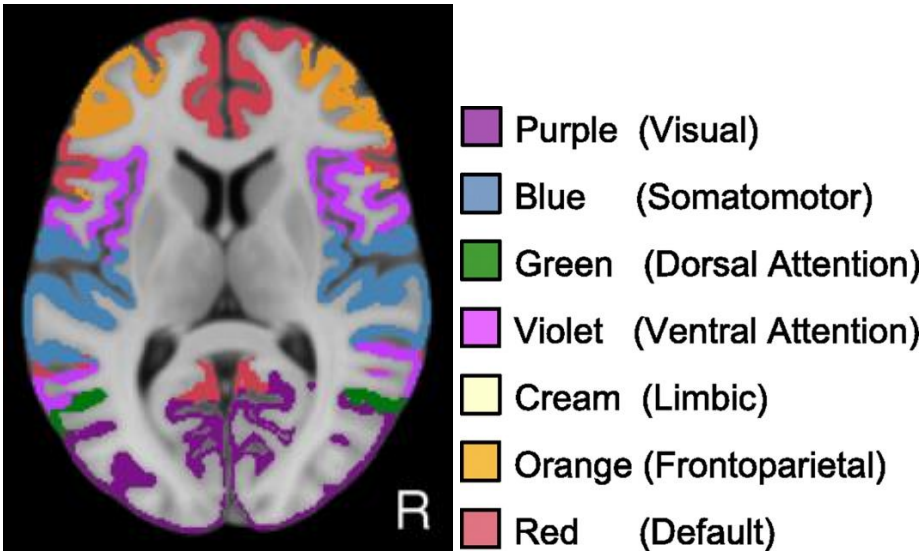

Figure 1. Map identifying the 7 networks and their locations on the cortex. Adapted from (Yeo et al., 2011).

We also performed several exploratory analyses using the Yeo correlation data. The first analysis broke our sample up into two groups, Blast and Non-Blast. This was motivated by the possibility of there being network disruptions that could be associated with diffuse white matter damage from the shockwave found in blast conditions. We examined the correlation strengths for each network pair and compared those strengths between the Blast and Non-Blast group.

The second exploratory analysis restricted our subjects to 15-day time-post-injury (TPI) criterion. This criterion retained only subjects that were scanned within 15 days of injury and reduced our sample to 189. The reasoning for this was to attempt to control for possible differences that may be associated with time and injury duration prior to scan. With the reduced sample size, we examined differences in correlation strengths of the seven network pairs, looking for differences related to the DMN.

The third exploratory analysis further limited the TPI sample into different age brackets based on an age threshold to rule out possible age cohort effects and address outliers. For the first comparison we split the sample into two distinct groups, 30 years old and younger, and 31 years

old and over. The second and third comparison were done using the ages 35 and 40. The seven network correlation pairs were compared between the age segregated group pairs to examine any possible cohort effects.

RESULTS

Table 2
Demographics (n=219)

Groups	*Age Median*	*Age Maximum*	*Age Minimum*	*Percent Male*
Blast TBI	25.00	43.00	20.00	94.59
Non-Blast Control	29.00	48.00	20.00	87.50
Blast Control	32.00	46.00	20.00	87.10
Non-Blast TBI	26.50	49.00	20.00	91.18

Note. 219 subjects remained after motion thresholding. All analyses were done with this sample.

Seed-analysis

Using the final sample found in Table 2**,** we were unable to detect mTBI with the DMN. No statistically significant different patterns of connectivity between the PCC and the whole brain survived cluster correction at the 0.05 alpha level for our main comparison, however we identified gender and age differences.

We identified a pattern of higher connectivity between the PCC and the temporal lobe in men compared to women in the Non-Blast Control group when compared to the Non-Blast TBI (Figure 2).

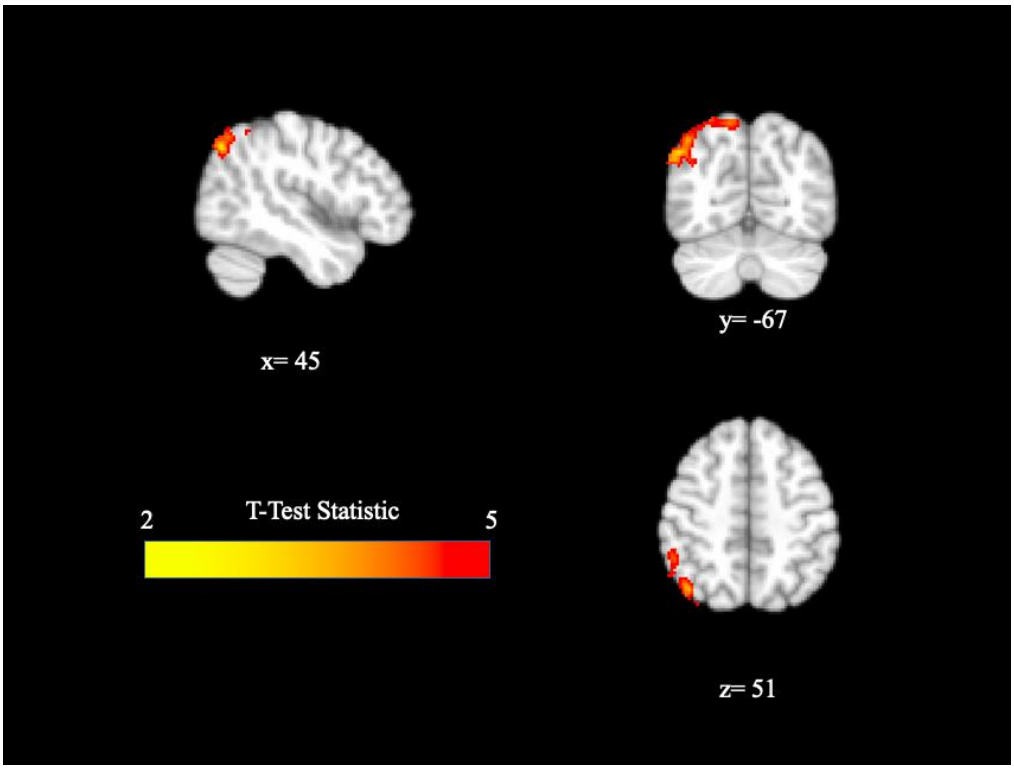

Figure 2. Non-Blast Control and Non-Blast TBI gender related connectivity differences. This figure illustrates gender related differences found in Non-Blast control and Non-Blast TBI groups

There was also a pattern of lower connectivity in between the PPC and left parietal lobe with greater age in the Non-Blast Control group when compared to the Blast Control group (Figure 3).

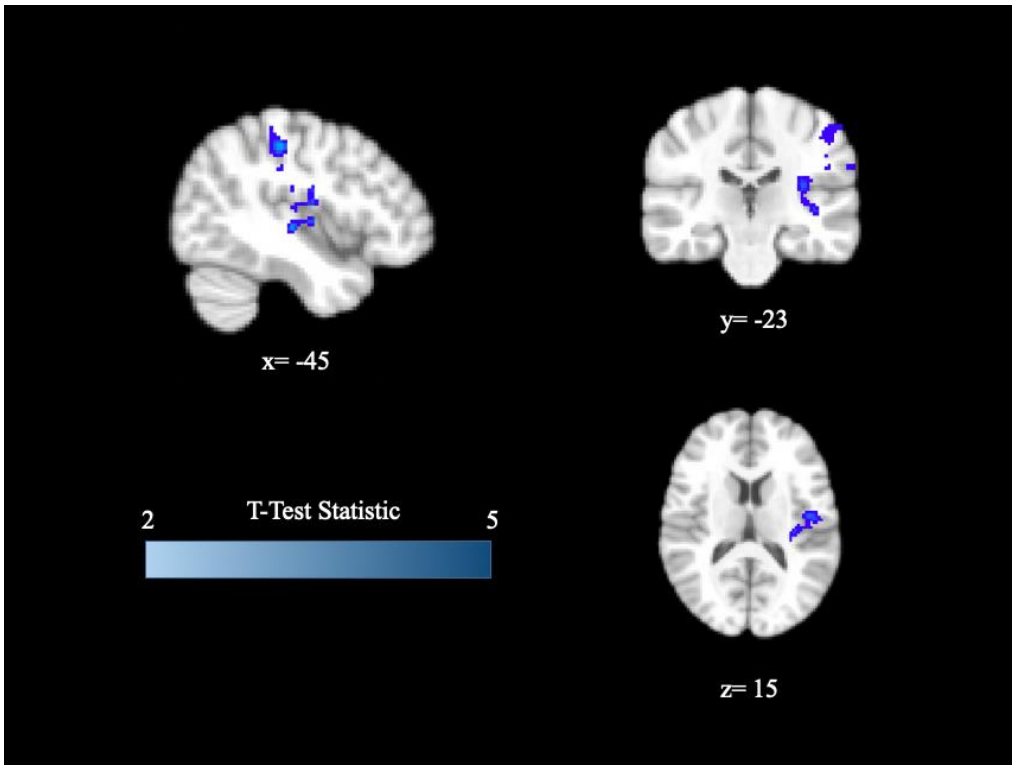

Figure 3. Non-Blast Control and Blast Control connectivity differences related to age.

Higher connectivity between the PCC and right parietal lobe was found with greater age in the Blast TBI group when compared to Non-Blast TBI (Figure 4). However, this cluster was so small that the negative cluster did not meet the threshold.

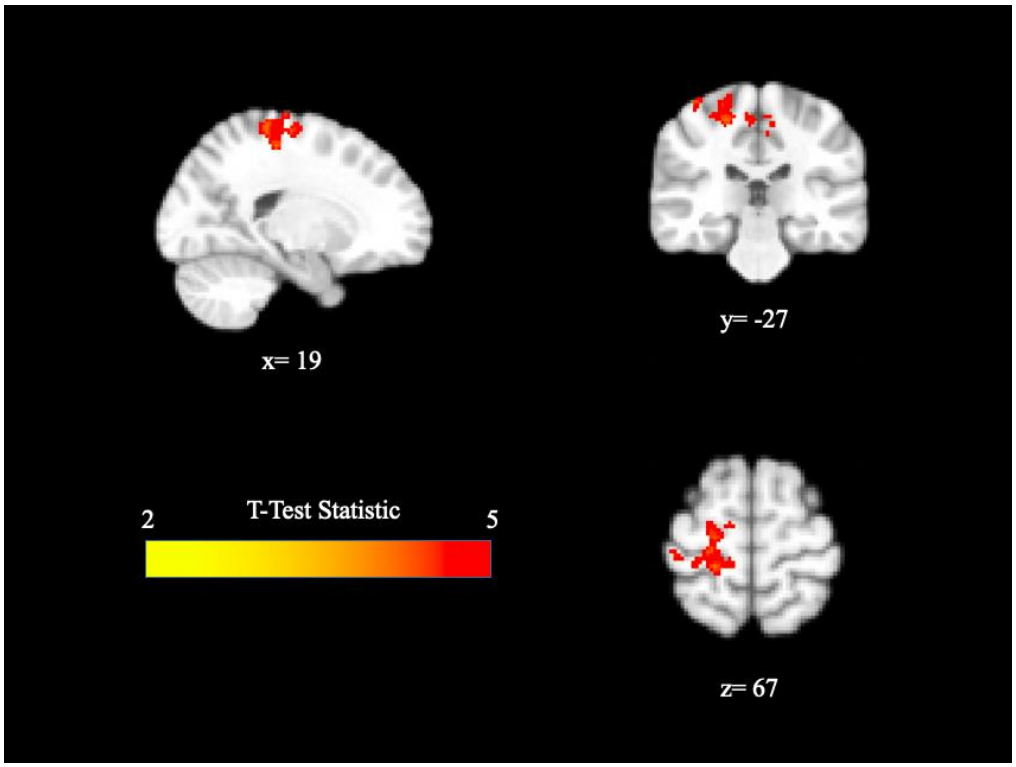

Figure 4. Blast TBI and Non-blast TBI connectivity differences related to age.

Among men, higher connectivity was found between the PCC and the right occipital lobe in the Blast TBI group compared to Non-Blast TBI (Figure 5).

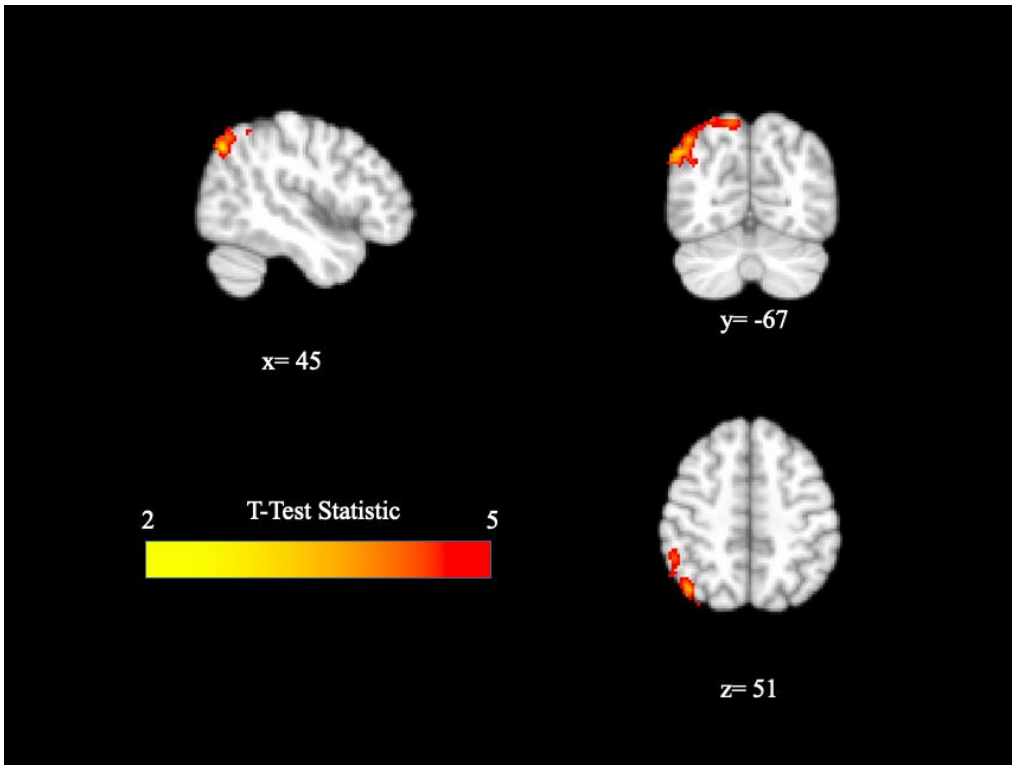

Figure 5. Blast TBI and Non-Blast TBI connectivity differences related to gender.

Finally, a pattern of lower connectivity between the PCC and the cingulate gyrus was found with higher age in the Blast TBI group compared to the Blast Control group (Figure 6).

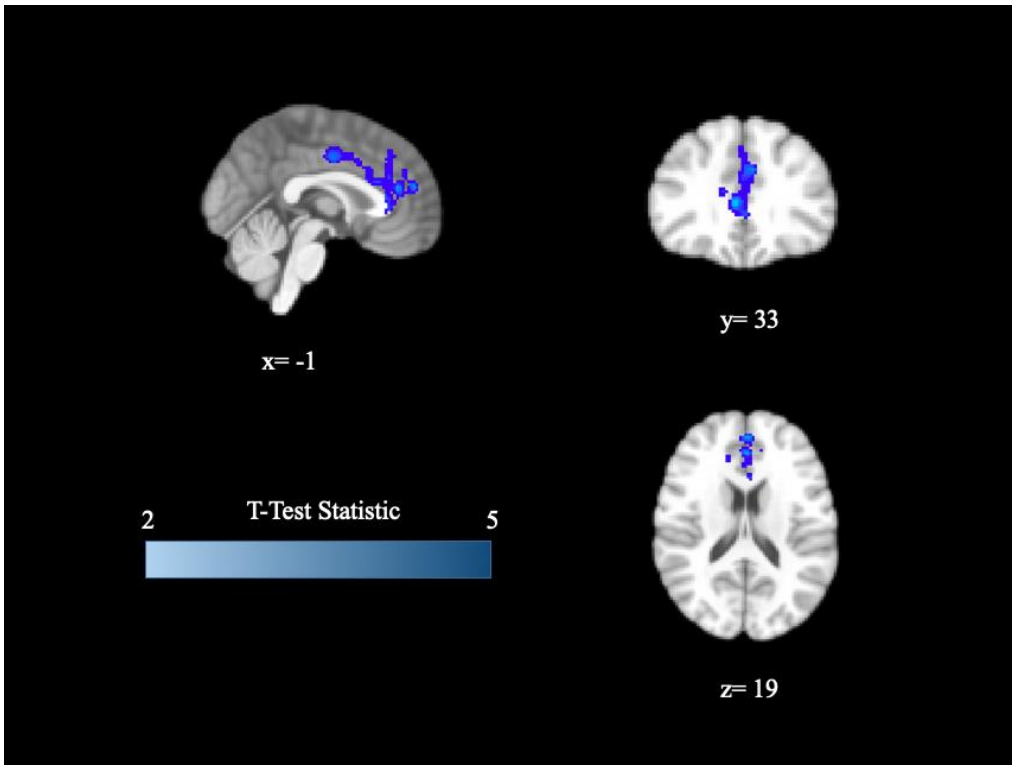

Figure 6. Blast TBI and Blast Control connectivity differences related to age.

Yeo Parcellation

We were unable to distinguish between TBI and healthy controls using the 7 network Yeo parcellation. There were no network correlation differences between any of the groups or covariates that were statistically significant at a Bonferroni corrected alpha level (p=0.05/21).

DISCUSSION

Prior published work suggested that we should expect differences in resting-state connectivity, specifically between the PCC and other brain regions (Caeyenberghs et al., 2014;

Han et al., 2014; Johnson et al., 2012). Using our groups (Blast TBI, Non-Blast TBI, and Blast Exposed Control), we were unable to distinguish any group from Non-Blast Control. In contrast to published studies, our results suggest that early differences in functional connectivity may not be a robust biomarker for uncomplicated mTBI. The absence of significant results may be a result of the heterogeneous nature of TBI.

Our seed-based analysis using the PCC, a key hub in the DMN, allowed us to examine the connectivity of the DMN to the rest of the brain (Dosenbach et al., 2007; Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008). Because the DMN is one of the most active in resting-state networks, we expected if any disruptions were to be found that they would be evident in this network. Other studies have shown DMN disruption using independent component analyses (ICA) (Iraji et al., 2015; Vakhtin et al., 2013). We found no disruption to the most active network while at rest which is in direct contrast to prior research where disruptions were found. This inconsistency may be the result of the differences in methodologies; where we used a seed-based approach instead of an ICA.

We used the 7 network parcellation as identified by Yeo to examine differences in the correlation strengths of primary cognitive networks (Yeo et al., 2011). The strength of this approach comes from comparing our groups to a different and completely unrelated standard sample. This approach is more akin to a clinical type diagnostic where the sample is compared to a set standard. Our results showed no difference in the correlation strengths of these large-scale networks in our blast and non-blast TBI samples. Prior research suggests that disruptions in the DMN associated with TBI should be evident in these network correlations, but we were unable to detect any if they do exist using this method. This demonstrates that using network

correlations to detect mTBI may not yet be sensitive enough. The fact that we don't see significant results could be an issue of how we chose to identify networks.

Another weakness of our methods could come from the difficulty of accounting for the heterogeneous nature of TBI. Where the injury is localized could influence which networks are affected and to what extent, leaving little for consistent group differences. This localization motivated us to look at blast exposure, which may have a more diffuse impact on the brain due to the associated shockwave. Other research has used different approaches such as an ICA which are more specific to the sample population and the differences between them. Future research could benefit from examining patterns of network correlations as a whole instead of as individual networks.

One of the main limitations of our study is the range of ages in our different groups, making it difficult to distinguish between what are group differences or age differences. Our sample had a large bimodal range of ages. Because of this, there were groups with statistically significant age differences, leading to possible cohort effects. We also had an unequal gender representation as well as unequal populations from different branches of the military.

Overall, we were unable to detect any differences in our TBI samples when compared to healthy controls. Our results suggest that it is unlikely that resting-state functional connectivity will be useful for detecting uncomplicated mTBI in this subacute phase via either the seed-based or Yeo parcellation method of analysis.

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Appendix A

This is the AFNI command that we ran to preprocess our data. This command was written into a script to ensure consistency and reproducibility while also keeping clear documentation.

```
afni_proc.py -subj_id $IDNUM                                    \
-dsets $RESTDIRS/rest.nii.gz                                    \
-copy_anat MPRAGE/T1.nii.gz                                     \
-blocks despike tshift align tlrc volreg blur mask regress      \
-align_opts_aea -cost lpc+ZZ                                    \
-tlrc_base MNI152_T1_2009c+tlrc                                 \
-tlrc_NL_warp                                                   \
-volreg_warp_dxyz 2                                             \
-volreg_align_e2a                                               \
-volreg_tlrc_warp                                               \
-volreg_align_to MIN_OUTLIER                                    \
-regress_anaticor                                               \
-regress_censor_motion 0.35                                     \
-regress_censor_outliers 0.1                                    \
-regress_bandpass 0.0 0.2                                       \
-regress_apply_mot_types demean deriv                           \
-regress_est_blur_epits                                         \
-regress_est_blur_errts
```

Appendix B

We explored the effects of motion censoring on the number of subjects lost and the distribution of subjects lost across the different groups in order to determine the appropriate threshold. We initially censored frames with motion more than 0.35mm. This resulted in the immediate exclusion of 6 subjects. The amount of censored volumes in these subjects resulted in a lack of degrees of freedom for our regression model. Thus, AFNI was unable to fully process the remaining data. We then assessed additional thresholds of .15, .20, and .25. Settling on an additional threshold of .25, we were left with 219 subjects. Despite the reduction in subjects, this threshold yielded no significant difference when using a Chi-Square test of independence ($p = 0.21$) between our groups.

Table B.1
Motion Threshold

Motion Threshold	Excluded Subjects	Percentage Excluded	Remaining Subjects	Percentage Remaining
35%	6	2%	248	98%
25%	29	11%	219	86%
20%	33	13%	215	85%
15%	40	16%	208	82%

Note. Initial sample contained 254 subjects. We started with a threshold of 35%. Further thresholding was examined to see how much of the sample would be lost when using more rigorous thresholds