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EXAMINING BRAIN NETWORK MODULARITY IN U.S. MILITARY PERSONNEL WITH BLAST VS. NON-BLAST RELATED MILD TRAUMATIC BRAIN INJURY

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ABSTRACT

EXAMINING BRAIN NETWORK MODULARITY IN U.S. MILITARY PERSONNEL WITH BLAST VS. NON-BLAST RELATED MILD TRAUMATIC BRAIN INJURY

By

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Problem: Traumatic brain injury (TBI) is a major health concern to the public, accounting for alarming numbers of hospitalizations and emergency department visits per year. mTBI is of particular concern because of the injury's 'invisible' nature. There are a lack of clinical findings on current evidence-based diagnostic protocols, and sufferers of this "silent" injury persistently complain of changes in functioning compared to their baseline abilities.

Methods: 103 active duty service members from the SCORE study comprised 3 groups: mTBI resulting from blast (bmTBI; n=32), mTBI not resulting from blast (e.g. falls, motor vehicle accidents) (mTBI; n=29), and orthopedic controls (OC; n=42). Participants completed an fMRI task assessing effort and a standardized neuropsychological battery. Whole-brain network modularity analysis was completed to determine the pathophysiology secondary to TBI, whether the pathophysiology differs based on the nature of injury, and whether altered modularity relates to cognition.

Results: Analysis of variance tests (ANOVA) revealed greater modularity in bmTBI than mTBI and OC at increased effort levels. Repeated measures ANOVAs revealed that increasing modularity values (Q) in bmTBI corresponded with increased effort level demands, while the Q in mTBI and OC was consistent across effort levels. Pearson correlations revealed minimal associations between Q and measures of processing speed. No significant correlations between Q and neuropsychological measures were observed in the OC group.

Conclusions: This study suggests that the pathophysiology of blast injury alters the modular structure of the brain in TBI to a greater extent than in TBI from other etiologies.

INTRODUCTION

Traumatic brain injury (TBI) is a major health concern to the public accounting for approximately 2.8 million hospitalizations and emergency department visits per year (Taylor, 2017), and deficits resulting from TBI have been shown to last months or years post-onset (Kenzie et al., 2017). Mild traumatic brain injury (mTBI) is of particular concern because of the injury's 'silent' or 'invisible' nature (Losoi et al., 2015). Mild TBI is invisible because of three reasons. First, there is no evidence of mTBI on routine clinical brain scans, and disruption of white matter integrity is often tough to see on an individual basis (Kenzie et al., 2017). Second, traditional cognitive testing (e.g., IQ testing) is often not precise enough to accurately identify the subtle cognitive and emotional control deficits (e.g. attention, memory, executive functions) that are frequent complaints of individuals with mTBI. Commonly, performance on these measures appears "within normal limits" in persons with mTBI (Kenzie et al., 2017). Additionally, with mild injuries there are often comorbid emotional deficits (e.g. mood/behavioral factors) making it challenging to tease apart the underlying nature of the disorder (Kenzie et al., 2017). Finally, people with mTBI persistently complain of changes in daily life that affect their quality of life, happiness, and ability to continue as productive in terms of education or vocational skills as they were premorbidly (Kenzie et al., 2017). Given these complexities, gaining further insight into the neurobiological underpinnings of mTBI is a needed first step to understanding the primary and secondary behaviors associated with brain injury. Ultimately, this information will also aid in developing and implementing suitable diagnostic protocols and treatments.

The neurobiology of mTBI is currently best understood via magnetic resonance imaging (MRI) techniques allowing visualization of brain structure and function in research application (e.g. visualization of white matter changes). In most cases, the structural MRI used in clinical application is unremarkable in mTBI (Kenzie et al., 2017). However, group studies using fluid attenuated inversion recovery (FLAIR) and diffusion tensor imaging (DTI) techniques have shown diffuse white matter abnormalities or changes at both the acute and chronic stages of recovery (Hayes, Bigler, & Verfaellie, 2016). These axonal injuries disrupt communication between neurons, which lead to diffuse and widespread inefficiency in the communication amongst neural networks.

Additional group research investigates brain activity in individuals with mTBI via functional MRI (fMRI) methods. fMRI can be conducted either when the brain is at "rest" or during a task in the scanner. Task-based fMRI allows for the study of regional activation or functional connectivity, and resting-state fMRI allows for the collection of functional connectivity data. These studies often use a "seed-based" approach, for which regions of interest are determined *a priori* by the researcher. Although informative, these methods are limited because they cannot offer a holistic or dynamic view of brain function.

Recently modularity analysis, a graph theory approach, has been applied to functional neuroimaging data. Graph theory looks at the brain in terms of a collection of nodes (e.g. brain regions) and edges (e.g. connectivity) as represented "graphically." Modularity examines whole-brain networks in a way that describes and quantifies the extent of network integration and segregation of the brain at rest or during task performance (Rubinov & Sporns, 2010). Modularity configures brain networks in terms of modules and edges. Modules are densely connected regions of the brain (nodes), also known as network communities, that are functionally close and often share neuronal communication. Edges are the connections between nodes. Modules that are composed of nodes that are connected to a variety of cognitive systems indicate integrated communication among brain networks. In contrast, modules composed primarily of nodes from a single cognitive system, indicate network segregation (Ray et al., 2019). Thus, "more modular" network structure indicates sparsely connected nodes and greater network segregation, whereas a "less modular" network structure indicates densely connected nodes and greater network integration. In other words, modularity analysis allows us to gain insight about how neuronal signals are distributed and processed throughout the whole brain as opposed to in individual regions or the connections between them (Rubinov & Sporns, 2010). Thus, long distance diffuse neuronal signal processing (integrated) is preferred and more efficient than processing in focal, islands (segregated).

Currently, there are limited investigations of brain network modularity, which is a problem because we do not have much insight as to how information is processed throughout the whole-brain and its networks. Modularity in healthy adults using task-based fMRI has shown that performance on behavioral task-based measures, particularly those requiring effort and cognitive control, call for more network integration (less modular structure) (Cohen & D'Esposito, 2016; Hearne et al., 2017; Ray et al., 2019; Westphal et al., 2017). That is, modularity demonstrates variance in healthy brains, and those with less modular networks (more integrated; less segregated) tend to perform better than those with more modular networks (more segregated, less integrated) during a cognitive task.

A few other studies explored brain modularity at rest as a potential biomarker or predictor of treatment response. At least three research studies (Arnemann et al., 2015; Baniqued et al., 2018; Gallen et al., 2016) have shown that more modular brain resting-state networks (more segregated; less integrated) are predictive of greater response to cognitive interventions in healthy adults with typical cognition (Baniqued et al., 2018; Gallen et al., 2016) and in individuals with TBI (Arnemann et al., 2015). For example, Arnemann and colleagues (2015) assessed resting-state modularity prior to a cognitive intervention and found that more modular network structure is predictive of better treatment outcomes as measured by performance on neuropsychological assessments pre/post intervention in mTBI participants. Healthy individuals "at rest" are more modular (less integrated) because they are not engaged in a task but become less modular (more integrated) during tasks requiring cognitive control. It has been suggested that being more modular (less integrated) at rest may be a biomarker of readiness to learn (Baniqued et al., 2018). That is, individuals with more modular brain network structure may have a greater capacity to learn and reconfigure their brain network organization, as well as a greater potential to benefit from cognitive interventions (Arnemann et al., 2015; Gallen et al., 2016).

Modularity work, specifically in mTBI, is also limited. Work by Ruiz & Vargas (2016) suggests that the axonal injuries resulting from simulated mTBI significantly disrupt the overall modular structure of whole-brain networks, resulting in more modular (more segregated; less integrated) whole-brain structure (Ruiz & Vargas, 2016). Additionally, Rowland and colleagues (2018) examined modularity at rest in Veterans with mTBI with or without Post-Traumatic Stress Disorder (PTSD) and found no group differences of modularity. This may suggest that the nature of mTBI itself disrupts modularity and the organization of whole-brain networks as the presence of psychopathology/mood disorders do not appear to make a difference. Other studies have focused their modularity analyses in individuals with TBI on specified networks and regions of the brain (e.g., within the lateral posterior parietal cortex), but results were disparate (Ravishankar et al., 2016; Sours et al., 2018; Venkatesen & Hillary, 2019).

U.S. military servicemen have high rates of mTBI resulting from engagement in OEF/OIF/OND, a series of conflicts in which blast exposure has been a common occurrence and led to a significant number of injuries (mTBI and more). To our knowledge, only one research study to date has directly examined the effect of blast, as the mechanism of injury. Han (2014) examined resting-state modularity in military personnel with mTBI resulting from blast exposure relative to blast-exposed controls without mTBI. Resting-state modularity was assessed 30-90 days post-blast, and again 6-12 months later. The most notable between-group difference was higher modularity in blast mTBI participants relative to controls at baseline, suggesting more modular network structure in blast mTBI. Authors of this study suggest that blast exposure is more disruptive to white matter integrity as a possible explanation for the more segregated network structure in blast-exposed mTBI. Interestingly, group differences in modularity did not persist at follow-up, suggesting that modularity may be flexible over time and potentially plastic as a response to experience or intervention. Results of the preliminary work in modularity are promising because they suggest that modularity may act as a biomarker of injury, as well as a marker of treatment outcomes. This makes it crucial to understand how modularity may be altered secondary to brain injury and whether these alterations differ based on the nature of injury.

In the current study, we investigate brain network modularity in a cohort of active duty US service members. This study has two purposes. First, the study will add to the literature by investigating modularity during task performance in mTBI relative to orthopedic control participants (OC), taking into consideration the role of blast injury versus other etiologies (e.g. motor vehicle accidents, falls). Secondly, this study investigates the association between modularity and behavioral measures of cognitive function (e.g. neuropsychological tests, fMRI task performance). We first hypothesize that modularity in individuals with mTBI is more modular (less integrated/more segregated) than orthopedic controls during a fMRI task assessing effort, in which effort level is manipulated. Additionally, we hypothesize that brain network structure in those with blast exposure (bmTBI) is more modular (less integrated/more segregated) than those with TBI resulting from other etiologies, given the proposal of Ruiz & Vargas (2016) that there is likely more diffuse axonal injury associated with blast. Lastly, we hypothesize that modularity will correlate with the effort fluctuations required by the effort fMRI task (state changes) as well as with neuropsychological measures assessed outside of the scanner (trait behaviors).

METHODS

Participants

Participants were recruited from The Study of Cognitive Rehabilitation Effectiveness (SCORE) in San Antonio, Texas. SCORE is a randomized control treatment trial assessing the effectiveness of cognitive rehabilitation in military service members who sustained a mild TBI or concussion after deployment to a warzone. Details of the cohort, including specifics about subject recruitment and inclusion/exclusion criteria have been comprehensively described elsewhere (Ramage, Tate, New, Lewis, & Robin, 2019). All procedures and protocol were approved by the Institutional Review Board and Human Studies Committee of the San Antonio Military Medical Center.

103 participants in the imaging component of the study (iSCORE) were aged 20-59 and comprised three groups: OC (n=42), mTBI (n=29), and bmTBI (n=32). The orthopedic control inclusion/exclusion criteria were: no history of mTBI within the last 3 years and no history of mTBI symptoms lasting longer than 48 hours. The mTBI inclusion/exclusion criteria were: mTBI occurring during military service, within the past 3-24 months, and injury etiology was not blast (e.g. motor vehicle accident, falls). The bmTBI inclusion/exclusion criteria was: blast injury

(e.g., from improvised explosive device, rocket-propelled grenade) occurring during military service, within the past 3-24 months. Additional exclusion criteria were: history of moderate or severe TBI, scheduled narcotic pain medications, participation in any intensive treatments (>5 appointments/week), spinal cord injury resulting in diminished use of upper extremities, blindness/low vision, or history neurological disorder (e.g. seizures, psychosis).

Measures

Constant Effort (CE) Functional Magnetic Resonance Imaging (fMRI) Task: Participants completed a task in the MRI scanner to examine continuous sense of effort and central fatigue over time (Solomon, Robin, & Van Daele, 1996). Prior to completing the task, participants were familiarized with the CE task protocol. The task required participants to squeeze a pneumatic bulb (IOPI, www.IOPImedical.com) with their right hand as hard as they could to determine their maximum sense of effort. Participants were then asked to squeeze the pneumatic bulb at prescribed levels of effort, either 25%, 50%, or 75% of their maximum effort. Outside of the scanner, participants were provided with biofeedback via LED display on the IOPI to assist in achieving desired effort levels for familiarization with the task. In the scanner, desired effort levels were displayed to participants via a brief text image (5 seconds) and squeezed at prescribed that effort level for 30 seconds, followed by 30 seconds of rest. Effort levels progressed from easiest to hardest level (25%-75%) with two trials at each effort level.

fMRI: Image Acquisition. Participants underwent multimodal MRI in a 3 Tesla Diemens Verio Syngo scanner (Siemens Medical Solutions USA, Malvern, Pennsylvania) at the San Antonio Military Medical Center. High-quality T1-weighted volumetric images were acquired to inspect anatomical integrity and for use in spatial normalization of the functional images and anatomical localization of functional findings. 176 sagittal 3D MPRAGE slices were obtained with the following parameters: slice thickness=1.0/0.5, TE/TR=2.6/2530, FOV=256mm, voxel size=1x1x1mm, 512x512 matrix, flip angle=7º, SENSE factor 2. 40 axial blood-oxygen-level-dependent (BOLD) echo-planar slices were obtained during the CE task with the following parameters: slice thickness=3.0/0.3 interleaved, FOV=240mm, voxel size=3.43x3.43x3.0mm, TE/TR=30/2500, flip angle=90 º, foldover direction=AP, fat shift direction=P, SENSE factor 2.0 resulting in 230 total images obtained over a 9.6-min continuous scan.

fMRI: Image Preprocessing. EPI images were corrected for head movement by affine registration using a two-pass procedure (SPM12, www.fil.ion.ucl.ac.uk/spm) after the first four dummy scans were removed. Next, the mean EPI image for each subject was spatially normalized to the MNI single subject template via the "unified segmentation" approach (Ashburner & Friston, 2005). The subsequent deformation field then was applied to the individual EPI volumes and a 5-mm full-width half mass (FWHM) Gaussian kernel smoothed the output images. Lastly, the images were spatially smoothed (8mm, FWHM).

Modularity analysis: 264 cortical nodes (i.e., regions of interests) representing the whole brain were extracted based on the functional parcellation of the Power atlas (Power, 2011), mapping each node to its corresponding brain network and anatomical region. Pearson correlations amongst all of the nodes were computed to create functional connectivity matrices for each subject by each CE task effort level (25%, 50%, 75%). Functional connectivity matrices were unidirectional and not weighted.

Modularity analyses were then calculated for each participant, using correlation matrices for each effort level, to acquire a whole-brain measure of network integration/segregation (Q) using the "community Louvain" Matlab script from the Brain Connectivity Toolbox (BCT) (Rubinov & Sporns, 2010). Modularity (Q) values ranged from 0-1, representing the goodness of fit of modular partitions by signifying the ratio of within-module connections (node-to-node edges within a module) to between module connections (node-to-node edges that are across multiple [at least 2] modules). A Q value closer to 0 represents integration across network communities with a higher ratio of connections to other modules, whereas a Q value closer to 1 represents segregated network communities with a lower ratio of node connections to other modules. This analysis provided Q values for each participant at each effort level as well as the partitions for the community structure. The same analysis was re-run using the average matrix for each group by effort level to derive group-level partition data for interpretation.

Clinical & behavioral assessment

mTBI Assessment: All participants with mTBI were assessed by the VA/DoD Clinical Practice Guidelines for the Management of Concussion or mild TBI (Barth et al., 2009). Specific assessment information is provided below.

Mood/behavioral Assessment: Participants completed self-report measures to assess various domains of psychological status and functioning. Post-traumatic stress disorder (PTSD) severity was measured using the PTSD Checklist for the DSM-4 (PCL-4) (Bliese et al., 2008). Anxiety and depression symptoms and severity were measured using the Symptom Checklist-90-R (SCL-90-R) (Derogatis & Savitz, 1999).

Neuropsychological Test Battery: Standardized neuropsychological assessments were completed pre-fMRI to assess the areas of attention, memory, and executive function. See Table 1 for names and descriptions of assessments.

Design and Statistical analyses

The current study is an experimental, between and within groups design. Descriptive statistics were calculated for demographic and clinical characteristics of the sample. Student's t-tests (for continuous variables) or χ^2 tests (for categorical variables) were performed to determine group differences between OC, mTBI, and bmTBI.

Analysis of variance tests (ANOVA) were used to determine the difference and direction of the effect of modularity between mTBI, bmTBI, and orthopedic controls. Repeated measures ANOVAs were used to determine within-group differences between task-based effort level (25%, 50%, and 75%). Pearson correlations were conducted to determine the association between modularity and performance on neuropsychological measures.

RESULTS

The groups were well matched for race, ethnicity, marital status and number of deployments. However, the OC group was significantly older, had a higher proportion of females, obtained higher levels of education, had a higher proportion of members in the Air Force, and served more years than either of the mTBI groups. While the mTBI and bmTBI groups did not differ for PTSD severity, both groups endorsed having more symptoms than the OC group (Table 2). The mTBI and bmTBI groups also endorsed more symptoms of depression and anxiety than the OC group (Table 2).

The groups did not differ for modularity at the 25% effort level, however the bmTBI group was more modular than the mTBI group at the 50% effort level, but not the OC group (Figure 1). The bmTBI group was more modular than the OC group at the 75% effort level, but not the mTBI group (Figure 1). Further, the bmTBI group had increasing modularity (Q) as the effort level increased (p =.013), while the mTBI and OC groups modularity value stayed consistent across effort levels (Figure 2).

Few weak but significant correlations were found between modularity (Q) and trail making age (r =.372, p = .047), trail making time (r = -.42, p = .023), and WAIS-IV processing speed (*r* = .368, *p* = .05) in the mTBI group at the 50% effort level (Table 5). Few minimal correlations were found between Q and WAIS-IV processing speed (*r* = .408, *p* = .023), WAIS-IV symbol search scaled score (*r* = .368, *p* = .032), and TOMM: Trial 2 (*r* = .432, *p* = .017) in the bmTBI group at the 50% effort level (Table 5). One minimal but significant correlation was found between Q and TOMM: Trial 2 (*r* = .414, *p* = .026) in the mTBI group at the 75% effort level (Table 5). No significant correlations between modularity (Q) and neuropsychological measures were observed in the OC group (Table 5).

DISCUSSION

The results of the present study suggest that the nature of *blast* injury alters the modular structure of the brain in TBI. U.S. military personnel with bmTBI had significantly more modular brain network structure (less integrated; more segregated) relative to those with non-blast mTBI or healthy orthopedic controls. This was particularly evident when the bmTBI group shifted to more modular network structure as effort level increased in the CE task, demonstrating a difference in the temporal unfolding of modular structure with increasing task demand. In contrast, the mTBI and OC groups' module structure remained relatively constant as effort level increased.

These findings highlight the importance in considering task performance versus resting-state fMRI acquisition for modularity and characterizing the nature of the injury in TBI. For example, Rowland and colleagues (2018) examined brain network modularity in Veterans with mTBI and posttraumatic stress disorder (PTSD), and found that the presence of PTSD and mTBI did not differ from mTBI without PTSD in terms of modularity, but they did not discern bmTBI from mTBI, or note the etiology of the injuries sustained in their participants. Thus, the lack of group differences in modularity in their study may indicate that the presence of PTSD does not alter modularity, and that heterogeneity of injury type across study groups may have affected the ability to detect differences. A possible explanation for the unique impact of blast on modularity may be that it results in more diffuse white matter injury, impeding the efficiency of neural signals to communicate and synthetize information across wide-spread brain networks (Hayes et al., 2016). It is necessary for future work to characterize the type of brain injury, as there is evidence from the current study that the presence of blast injury may uniquely affect the modular structure in mTBI.

Another factor unique to blast injury is that modularity increased with effort level in the bmTBI group. This may suggest that the more modular nature of those with bmTBI results in inefficient communication amongst networks, which impacts performance on tasks that require more cognitive control and rely on efficient network integration. This is similar to findings seen in studies examining performance on cognitive tasks in the scanner, relating poorer performance to more modular brain structure (Cohen et al., 2016; Hearne et al., 2017; Ray et al., 2019; Westphal et al., 2017). Of interest for future study is whether modularity in individuals with bmTBI relates to measures of fatigue, given that participants were required to expend cognitive control to maintain and increase effort levels.

Our study also hypothesized that modularity would be associated with performance on neuropsychological measures. The main association indicated that more modular community structure correlated with faster processing speed as assessed with the Trail Making Test and the WAIS Processing speed index. The same was true for the WAIS Symbol Search, another time pressured test. These correlations were seen only in the mTBI groups, and thus appeared to be an effect of TBI, not specific to blast injury. In both cases, it appears that the efficiency of processing when there is a time demand may be associated with the shift to more modular structure when the task becomes more effortful (i.e. the correlations were for Q at 25% in the mTBI group, 50% in the bmTBI group). Similarly, Q at 50% in the bmTBI and 75% in the mTBI group correlated with TOMM-2, suggesting that something about the responses on this test of memory malingering is associated with modularity at the higher effort levels.

Limitations

This was cross-sectional study and therefore does not allow for understanding changes in modularity as a function of recovery from brain injury. This could provide us with valuable information regarding the neuroplasticity of bmTBI and mTBI in the stages post-injury, as well as the adaptability of modular brain network structure over time. This is of particular importance given the population, US service members who often have polymorbid conditions (e.g., chronic pain, PTSD). The study groups differed for age, gender, education level, military branch, years served, as well as comorbid symptoms of PTSD, anxiety, and depression. We have reason to believe, however, that the impact of PTSD, anxiety, and depression may not impact brain network modularity due to previous work by Rowland and colleagues (2018) who found no differences in modularity based on presence of PTSD in individuals with mTBI. Nevertheless, this is another factor that future research should be aware of and account for.

Future directions

Our study could have been strengthened by collecting resting state data in combination with the task data in the fMRI. We would be curious to see if this finding would match those of Han (2014) where it was found that those with bmTBI have a more modular structure at rest. This piece could have provided valuable information regarding whether individuals with bmTBI have a significant propensity for the “ready to learn” state as proposed by colleagues (Arnemann et al., 2015; Baniqued et al., 2018; Gallen et al., 2016). Suggesting that those with more modular network structure may have a greater capacity to learn and reconfigure their brain network organization, essentially having a greater possibility to benefit from cognitive interventions. Future work may benefit from examining resting state modularity in bmTBI, mTBI, and OC to answer these questions.

Conclusion

Despite these limitations, our study provides important information regarding the nature of blast and its impact on brain network modularity in U.S. military personnel with mTBI. We can infer from our findings that the nature of blast in mTBI may result in greater brain network modularity, presumably as a result of more diffuse and disrupted white matter impeding the transmission of neural signaling throughout the whole brain. This in turn can impact an individual's ability to maintain effort and cognitive control overtime, as compared to individuals with or without mTBI not resulting from blast. This finding is especially relevant considering the large population of service members returning home with this "signature wound" of mTBI resulting from exposure to frequent blasts. Examining brain network modularity in this population in future clinical work may have the tremendous potential to identify soldiers via primary (biological) presentations, whom are likely to experience secondary behaviors such as fatigue and difficulty in tasks requiring cognitive control and sustained effort. This will allow for early identification and enrollment in interventions targeting such behaviors.

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Table 1. Neuropsychological measures and brief descriptions.

Test Name	**Description**
The Key Behaviors Change Inventory and Executive Functioning (KBCI**)**	Self-report assessment that measures emotional, behavioral, and executive functioning after brain injury. Consists of subsections: inattention, impulsivity, unawareness of problems, apathy, interpersonal difficulties, communication problems, somatic difficulties, emotional adjustment. (Kolitz, Vanderploeg, & Curtiss, 2003).
Delis-Kaplan Executive Function System (DKEFS)	Measures higher-level executive functions. (Delis, Kramer, Kaplan, & Holdnack, 2004).
Trail-Making Tests	A sub-section of the DKEFS that measures visual attention and task switching. (Delis et al., 2004).
Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV)	Measures global intelligence which include the following subsections: working memory, processing speed, verbal comprehension, perceptual reasoning. (Dumont, Veizel, & Zibulsky, 2014).
California Verbal Learning Test Second Edition (CVLT II)	Measures verbal learning and memory (immediate, delayed, recognition). (Dumont & Willis, 2008).
Wide Range Achievement Test: (WRAT)	Measures reading, spelling, and mathematical skills. (Robertson, 2010).
Test of Memory Malingering (TOMM)	Distinguishes between true or malingered memory (Tombaugh, 1997).

Table 2. Demographic and clinical characteristics of sample by group.

VARIABLE	OC	mTBI	bmTBI	Group Difference
n	42	29	32	
Age	37 ± 7	35 ± 10	32 ± 9	0.039
Gender	34M; 8F	26M; 3F	32M; 0F	0.032
EDUCATION				
General Education Diploma	0	2	2	*0.011*
High School Diploma	10	13	19	
Associate degree	12	6	8	
College Degree	8	4	3	
Postgraduate	12	4	0	
RACE				
Asian	0	0	0	0.213
American Indian or Alaska Native	0	1	1	
Black or African American	12	4	3	
Native Hawaiian or Other Pacific Islander	0	0	0	
White	29	22	24	
More than One Race	1	2	4	
ETHNICITY				
Hispanic or Latino	8	7	11	0.319
Not Hispanic or Latino	34	22	21	
MARITAL STATUS				
Single, Never Married	8	2	9	0.357
Married	32	23	20	
Separated	0	1	1	
Divorced	2	3	2	
MILITARY BRANCH				
Air Force	10	1	0	*0.011*
Army	28	28	29	
Navy	3	0	2	
Marine Corps	1	0	1	
Years served	16(6)	*13(10)*	*10(7)*	*0.006*
# of Deployments	2(1)	2(1)	2(1)	0.340

Table 3. Psychological and neuropsychological measures by group.

TEST	MEASURES	OC	mTBI	bmTBI
KBCI	Total Score	N/A	63 ± 6	60 ± 7
PCL-M	PTSD Symptom Severity [a]	27 ± 14	52 ± 16	46 ± 16
SCL-90-R	Current Anxiety [a]	48 ± 9	66 ± 11	62 ± 12
	Current Depression [a]	49 ± 10	64 ± 10	62 ± 11
PSAT	Sum of Trials 1-4	136 ± 30	112 ± 34	109 ± 29
DKEFS Verbal Fluency	Total Category [b]	11 ± 3	9 ± 3	9 ± 3
	Total Letter [b]	11 ± 4	10 ± 3	9 ± 3
	Averaged Category and Letter Fluency [c]	11 ± 3	10 ± 3	9 ± 3
DKEFS Trail Making	Trails Part A [e]	25 ± 10	35 ± 20	29 ± 13
	Trails Part B [e]	52 ± 20	66 ± 28	63 ± 20
WAIS-IV	Processing Speed Index [e]	107 ± 13	92 ± 13	92 ± 12
	Symbol Search [e]	11 ± 3	9 ± 3	9 ± 3
	Coding [e]	11 ± 3	8 ± 2	8 ± 3
	Working Memory Index [b]	104 ± 15	99 ± 15	94 ± 13
	Digit Span [b]	11 ± 3	10 ± 3	9 ± 3
	Sequencing [b]	11 ± 3	10 ± 3	9 ± 3
CVLT	Immediate Recall	11 ± 3	9 ± 3	10 ± 3
	Delayed Recall [f]	12 ± 3	9 ± 3	10 ± 4
	Recognition [f]	14 ± 2	13 ± 2	14 ± 2
WRAT	Total Standard Score [d]	104 ± 10	98 ± 11	95 ± 8
TOMM	Trial 1 [d]	48 ± 3	46 ± 4	45 ± 5
	Trial 2	50 ± 1	49 ± 2	49 ± 2

Note. Psychological and neuropsychological measures indicate significantly more symptoms of PTSD, anxiety, and depression in the TBI groups than in the OC. There are missing data for participants who did not complete certain neuropsychological measures.

[a] mTBI = bmTBI > OC.
[b] mTBI = OC > bmTBI.
[c] OC > mTBI > bmTBI
[d] mTBI > OC = bmTBI
[e] OC > mTBI = bmTBI
[f] bmTBI = OC < mTBI

Table 4. Modularity (Q) difference between groups and CE effort levels.

EFFORT LEVEL	**OC (n = 16)**	**mTBI (n = 29)**	**bmTBI (n = 32)**	**P-Value**
25%	.32 ± .08	.35 ± .09	.34 ± .06	F, p=.505
50%	.33 ± .07	.33 ± .07	.37 ± .07	F, p=.021
75%	.33 ± .07	.36 ± .09	.38 ± .09	F, p=.042

Note. Modularity (Q) values indicate significantly more modular structure in the bmTBI group than the mTBI group at the 50% effort level. Q values also indicate significantly more modular structure in the bmTBI group than the OC group at the 75% effort level.

Table 5. Pearson correlation values for associations between the neuropsychological test measures and the Q values by group and effort level.

TEST	*BLAST MTBI*			*MTBI*			*ORTHO CONTROLS*		
	Q 25%	Q 50%	Q 75%	Q 25%	Q 50%	Q 75%	Q 25%	Q 50%	Q 75%
DKEFS: TOTAL CATEGORY SCALED SCORE	-0.01	0.14	0.32	0.02	-0.07	0.16	-0.30	0.06	-0.13
DKEFS: TOTAL LETTER SCALED SCORE	0.09	-0.26	0.08	0.27	0.10	-0.01	-0.22	-0.11	0.02
DKEFS: AVG CATEGORY & LETTER FLUENCY SCALED SCORE	0.04	-0.04	0.23	0.15	0.01	0.08	-0.29	-0.03	-0.08
TRAIL MAKING: AGE - TRAILS PART A	-0.27	0.10	-0.04	.37*	-0.14	-0.21	0.06	0.20	-0.19
TRAIL MAKING: AGE - TRAILS PART B	-0.15	0.18	0.15	0.26	0.19	-0.07	0.18	0.10	-0.04
TRAIL MAKING: TIME - TRAILS PART A	0.27	-0.17	-0.02	-0.42*	0.06	0.12	-0.11	-0.09	0.21
TRAIL MAKING: TIME - TRAILS PART B	0.13	-0.11	-0.08	-0.32	-0.33	0.07	-0.22	-0.05	0.13
WAIS-IV: PROCESSING SPEED INDEX	-0.14	.41*	0.27	.37*	0.20	-0.09	-0.01	-0.01	-0.13
WAIS-IV: SYMBOL SEARCH SCALED SCORE	-0.07	.39*	0.32	.37*	0.13	-0.08	-0.01	-0.10	-0.17
WAIS-IV: CODING SCALED SCORE	-0.20	0.35	0.15	0.28	0.25	-0.08	0.00	0.08	-0.04
WAIS-IV: WORKING MEMORY INDEX	-0.11	0.15	-0.05	0.14	0.08	0.09	0.06	-0.02	0.02
WAIS-IV: DIGIT SPAN SCALED SCORE	-0.18	0.26	0.13	0.17	0.11	0.15	0.04	-0.05	-0.06
WAIS-IV: SEQUENCING SCALED SCORE	-0.01	-0.03	-0.26	0.10	0.04	0.01	0.06	0.03	0.13
CVLT: TRIAL 1 RAW	0.12	-0.12	0.07	0.23	-0.05	-0.17	-0.08	0.11	-0.03
CVLT: TRIAL 2 RAW	-0.08	-0.06	0.14	0.20	-0.15	-0.23	-0.04	-0.20	-0.04
CVLT: TRIAL 3 RAW	0.11	0.19	0.20	0.10	-0.12	0.06	-0.10	-0.10	-0.09
CVLT: TRIAL 4 RAW	-0.05	0.04	0.04	-0.15	-0.22	-0.11	-0.11	-0.09	-0.04
CVLT: TRIAL 5 RAW	-0.07	0.05	0.13	-0.06	0.01	-0.03	-0.02	-0.14	-0.10
CVLT: TRIALS (1-5) RAW	0.00	0.04	0.14	0.06	-0.13	-0.10	-0.08	-0.11	-0.07
CVLT: TRIALS (1-5) T-SCORE	-0.07	0.04	0.10	0.03	-0.16	-0.08	-0.14	-0.11	-0.06
CVLT: SHORT DELAY FREE RECALL RAW SCORE	-0.19	0.32	0.32	-0.12	-0.24	-0.17	-0.02	-0.07	-0.03

CVLT: LONG DELAY FREE RECALL RAW SCORE	-0.14	0.22	0.27	-0.05	-0.15	-0.09	0.00	-0.06	-0.02
CVLT: LONG DELAY CUED RECALL RAW SCORE	-0.04	0.16	0.26	-0.07	-0.07	-0.23	0.04	-0.11	0.05
CVLT: TOTAL PERSEVERATIONS	0.00	-0.05	0.25	0.13	-0.14	-0.30	-0.14	-0.08	-0.07
CVLT: TOTAL INTRUSIONS	0.07	0.16	-0.13	-0.40*	0.06	0.10	-0.03	0.14	0.06
CVLT: RECOGNITION HITS	-0.32	-0.06	0.04	-0.14	-0.12	0.09	0.05	-0.13	-0.13
CVLT: RECOGNITION FALSE POSITIVE ERRORS	0.09	0.28	0.03	0.04	-0.04	0.06	-0.02	-0.01	0.07
CVLT: LIST B TOTAL SCORE	-0.11	-0.26	-0.25	-0.17	0.19	-0.15	-0.15	0.07	-0.05
CVLT: SHORT DELAY CUED RECALL RAW SCORE	-0.09	0.25	0.16	-0.12	-0.11	-0.06	-0.03	-0.06	0.08
WRAT: STANDARD SCORE	-0.09	-0.04	-0.34	-0.03	-0.20	-0.06	0.19	0.07	0.01
TOMM: TRIAL 1	0.00	-0.04	-0.16	-0.04	0.08	0.26	0.12	-0.31	-0.09
TOMM: TRIAL 2	-0.18	.43*	0.22	-0.22	0.33	.41*	0.15	-0.17	-0.20

Note. * $p < .05$.

*Figure 1***.** Modularity (Q) Difference between Groups and CE effort levels.

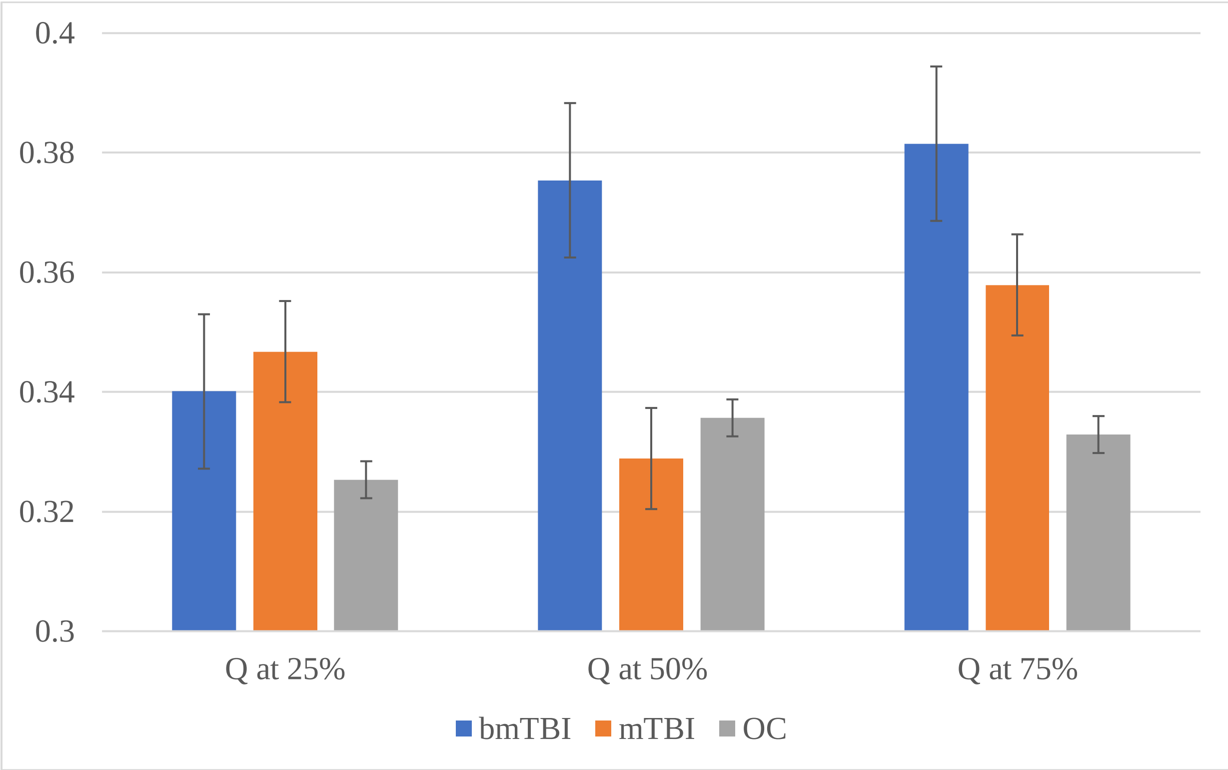

Figure 2. Modularity (Q) difference within groups and CE effort levels.