Journal of Neurotrauma
38:3332–3340 (December 1, 2021)

DOI: 10.1089/neu.2021.0200

Journal of Neurotrauma

ORIGINAL ARTICLE CLINICAL STUDIES

# Network Analysis of Neurobehavioral and Post-Traumatic Stress Disorder Symptoms One Year after Traumatic Brain Injury: A Veterans Affairs Traumatic Brain Injury Model Systems Study

Daniel W. Klyce,[1,*] Samuel J. West,[2] Paul B. Perrin,[3] Stephanie D. Agtarap,[4] Jacob A. Finn,[5] Shannon B. Juengst,[6,11] Kristen Dams-O'Connor,[7] CB Eagye,[4] Tiffanie A. Vargas,[8] Joyce, S. Chung,[9] and Charles H. Bombardier[10]



**Abstract**

Traumatic brain injury (TBI) is often experienced under stressful circumstances that can lead to symptoms of post-traumatic stress disorder (PTSD) and neurobehavioral symptoms of brain injury. There is considerable symptom overlap in the behavioral expression of these conditions. Psychometric network analysis is a useful approach to investigate the role of specific symptoms in connecting these two disorders and is well suited to explore their interrelatedness. This study applied network analysis to examine the associations among PTSD and TBI symptoms in a sample of Service Members and Veterans (SM/Vs) with a history of TBI one year after injury. Responses to the Neurobehavioral Symptom Inventory (NSI) and PTSD Checklist-Civilian version (PCL-C) were obtained from participants who completed comprehensive inpatient rehabilitation services across five Veterans Affairs polytrauma rehabilitation centers. Participants (N = 612) were 93.1% male with an average age of 36.98 years at injury. The analysis produced a stable network. Within the NSI symptom groups, the frustration symptom was an important bridge between the affective and cognitive TBI symptoms. The PCL-C nodes formed their own small cluster with hyperarousal yielding connections with the affective, cognitive, and somatic symptom groups. Consistent with this observation, the hyperarousal node had the second strongest bridge centrality in the network. Hyperarousal appears to play a key role in holding together this network of distress and thus represents a prime target for intervention among individuals with elevated symptoms of PTSD and a history of TBI. Network analysis offers an empirical approach to visualizing and quantifying the associations among symptoms. The identification of symptoms that are central to connecting multiple conditions can inform diagnostic precision and treatment selection.

**Keywords:** network analysis; post-traumatic stress disorder; traumatic brain injury; veterans

[1]Central Virginia Veterans Affairs Health Care System, Virginia Commonwealth University Health System, Sheltering Arms Institute, Central Virginia VA Health Care System, Richmond, Virginia, USA.
[2]Department of Surgery and Department of Psychology, Virginia Commonwealth University, Richmond, Virginia, USA.
[3]Central Virginia Veterans Affairs Health Care System, Department of Psychology and Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University, Richmond, Virginia, USA.
[4]Department of Research, Craig Hospital, Englewood, Colorado, USA.
[5]Rehabilitation & Extended Care Patient Service Line, Minneapolis VA Health Care System, Psychiatry and Behavioral Sciences, University of Minnesota–Twin Cities, Minneapolis, Minnesota, USA.
[6]Department of Physical Medicine and Rehabilitation, UT Southwestern Medical Center, Dallas, Texas, USA.
[7]Department of Rehabilitation and Human Performance, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA.
[8]Central Virginia Veterans Affairs Health Care System, Richmond, Virginia, USA.
[9]VA Palo Alto Health Care System, Polytrauma System of Care, Palo Alto, California, USA.
[10]Department of Rehabilitation Medicine, University of Washington, Seattle, Washington, USA.
[11]Brain Injury Research Center, TIRR Memorial Herman, Houston, Texas, USA.

*Address correspondence to: *Daniel W. Klyce, PhD, ABPP, Central Virginia VA Health Care System, 1201 Broad Rock Boulevard, Richmond, VA 23249, USA E-mail:* daniel.klyce@va.gov

## Introduction

Traumatic brain injury (TBI) is a priority focus within healthcare systems that serve Service Members and Veterans (SM/V).[1–4] As the ''signature injury'' of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND), more than 430,000 cases of TBI have been tracked by the TBI Center of Excellence since 2000.[5,6] Moderate-to-severe TBIs are often managed within acute care and rehabilitation settings.[7] The majority (80%) of TBIs among SM/Vs, however, are mild (mTBI) and are often identified through screening mechanisms or during evaluation for comorbidities such as pain or post-traumatic stress disorder (PTSD).[6,8–10] Surveillance systems implemented across military health systems track outcomes, advance understanding of TBI, and plan for long-term comprehensive care for SM/Vs.[11–14]

Among SM/Vs, TBI and PTSD are common comorbidities.[8–10,15,16] In a systematic review of mTBI and PTSD, Carlson and associates[15] found a wide range of mTBI and PTSD comorbidity across studies—i.e., 0% to 89%; however, among large studies of OEF/OIF/OND SM/Vs, the rates of probable PTSD among participants with mTBI ranged from 33% to 39%.[15] Both diagnoses have strong associations with other symptoms of physiological and psychological distress, including pain,[8,17–20] substance abuse,[21–23] anxiety and depression,[24,25] and suicidal behavior.[19,26–28] because of extensive symptom overlap, distinguishing the unique contributions of these two conditions to overall symptom presentation remains a challenge.

Behavioral manifestations of PTSD include symptoms that overlap with those commonly seen after TBI—i.e., depression/anxiety, insomnia, irritability/anger, trouble concentrating, fatigue, hyperarousal, and experiential avoidance.[29] Neurobehavioral symptoms of brain injury include fatigue, sleep problems, headaches, difficulty with concentration and memory, irritability, and changes in mood.[30,31] With uncomplicated mTBI, these symptoms typically resolve within three months, although the course of symptom evolution among SM/Vs varies.[32,33]

It is difficult to determine whether neurobehavioral symptoms of TBI and symptoms of PTSD represent overlapping manifestations of distinct etiologies or they are part of a larger clinical syndrome secondary to a traumatic event involving injury.[29] Studies have compared patterns of post-concussive symptoms among military populations to those with and without post-traumatic stress,[34,35] blast-related TBI,[36,37] and to healthy controls.[36] In all studies, the presence of post-traumatic stress was associated with greater cognitive, somatic, and emotional post-concussive symptoms. Hoge and colleagues,[38] however, have argued that in the context of mTBI, it is unhelpful to focus on assigning the manifestation symptoms to one etiology, because misattribution of symptoms to one condition or the other can result in stigmatization, inappropriate assessment, and misguided treatment.

Iverson[39] has argued that neurobehavioral symptoms of TBI commonly shared across multiple psychiatric conditions such as depression and PTSD are best understood in a personal biopsychosocial context; in this model, symptoms and problems can be amplified and reinforced by vulnerability factors, environmental stressors, and psychosocial and personality factors. Iverson[39] recommends psychometric network analysis as a methodology to understand the associations among symptoms of TBI and PTSD as a syndrome in and of itself rather than necessarily attributable to distinct, underlying etiologies.

Indeed, clinical research has benefited from applying network approaches to various syndromes or to disentangle commonly comorbid symptomologies.[40–43] One recent investigation provided network evidence that comorbid PTSD and depression have distinct network structures, identifying individual PTSD symptoms that were highly influential (i.e., re-experiencing) within their own symptom communities but did not overlap with depression, thus providing PTSD-distinct targets for intervention.[44]

Events such as head trauma—including repetitive injuries—often experienced under stressful circumstances can lead to both symptoms of PTSD and neurobehavioral symptoms of TBI. Given the challenge of distinguishing these overlapping symptoms, psychometric network analysis is well suited to investigate how the symptoms of these two conditions are interrelated or can be mutually reinforcing. The current study applied network analysis to examine the associations among PTSD and TBI symptoms in a sample of SM/Vs one year after TBI.

## Methods

### Participants

This study used data from the Department of Veterans Affairs TBI Model Systems (VA TBIMS) longitudinal study.[11] Participants were recruited from five VA Polytrauma Rehabilitation Centers (PRCs) after comprehensive inpatient rehabilitation. The inclusion criteria for the VA TBIMS study were: (1) diagnosis of TBI per case definition (i.e., a traumatically induced structural brain injury or physiological disruption of brain functioning due to external force, as evidenced by onset or worsening loss of and/or decreased consciousness, altered mental state, anterograde and/or retrograde amnesia, transient or stable neurological deficits, or intracranial lesion); (2) age ≥16 years at injury; and (3) admission to a PRC for TBI rehabilitation.

### Procedures

Study procedures were approved by the Institutional Review Boards at each site. All participants in the VA TBIMS database provided informed consent either directly or by legal proxy.[11] The study measures were collected directly from participants during a follow-up assessment by phone one year after injury.

### Measures

The Neurobehavioral Symptom Inventory (NSI) is a 22-item self-report measure of persistent post-concussion symptoms after TBI. Individuals rate the severity of symptoms during the past two weeks, ranging from 0 (none; rarely present) to 4 (very severe; almost always present).[45] Analyses of the NSI factor structure have yielded various solutions; the 3-factor (cognitive, affective, and somatosensory/vestibular) and 4-factor (cognitive, affective, somatosensory, and vestibular) solutions have tended to be stronger and replicable.[46] The NSI has demonstrated strong internal consistency and acceptable test-retest reliability.[46] The Cronbach $\alpha$ among the current sample was .94.

The PTSD Checklist-Civilian Version (PCL-C) is a 17-item self-report measure of PTSD symptoms.[47] Individuals rate how much each symptom has bothered them over the past month, ranging from 1 (not at all) to 5 (extremely). Although the PCL-C has likewise been found to have various factor structures, the original *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV)* three-factor model, which comprises re-experiencing, avoidance, and hyperarousal symptoms, has generally found broad support.[48] The PCL-C has demonstrated acceptable psychometric properties across trauma populations, including strong internal consistency.[49,50] The Cronbach $\alpha$ for the full scale among the current sample was .98; the $\alpha$s for the re-experiencing, avoidance, and hyperarousal subscales were .96, .94, and .93, respectively.

### Analytic approach

Psychometric network analysis is becoming a popular method to examine connections among individual symptoms as dynamic systems.[51] In our application of this analytic framework, *nodes* represented cross-sectional variables, and *edges* represented the partial correlations between any two given nodes. Indices of centrality provide further information about the degree of influence a given node has in a network. *Strength* centrality refers to the overall influence of a node within a network (i.e., the absolute sum of all edges connecting to a given node). *Bridge* centrality provides an index of how well a given node connects specified node communities.

Nodes with high bridge centrality values play a pivotal role in connecting node communities that are either detected automatically by applying a selected algorithm or are determined manually (e.g., placing all PTSD symptoms into their own community and neurobehavioral symptoms in another). We coded node communities such that each of the three PCL factor score variables made up the PCL community, and each NSI item variable belonged to the respective somatosensory, cognitive, or affective symptom community; this three-factor structure for the NSI has been validated among veterans with TBI.[52] We used a two-step index of expected influence (2EI) for bridge centrality estimates; this approach to bridge centrality produces estimates that indicate the extent to which a given node exerts influence on other communities directly and indirectly connected to their own.[53]

To standardize time since injury, this study analyzed participant responses one year post-injury using the raw values of the NSI items and the mean values of the PCL-C subscales as inputs to the network analysis. Given that our sample had a confirmed history of TBI, along with the opportunity to focus specifically on neurobehavioral symptoms, we elected to prioritize the NSI over the PCL-C by maximizing statistical power for item-level data with the former but subscale values for the latter. The sample size ($N = 612$) precluded the use of item-level responses to the PCL-C, because sample size must substantially exceed the number of estimated parameters to produce enough power to distinguish small coefficients consistently.[54,55]

We estimated a psychometric network using the *estimateNetwork* function in the bootnet package for R version 4.0.2.[55] We used the EBICglasso regularization procedure for estimation that implements a machine learning algorithm and attempts to reduce the smallest edges in the network to zero while examining model fit, ultimately selecting the network that is the best fit.[56] Bridge centrality was estimated using the *bridge* function from the networktools package for R.[53] To examine network stability and accuracy, we computed two 5000-sample bootstraps (a case-dropping bootstrap and a non-parametric bootstrap) using the *bootnet* function from the bootnet package.[55] Pairwise deletion was used for missing values (see Supplementary Table S1 for full missingness information).

## Results

### Characteristics of sample

A sample of 612 TBIMS participants who had at least one PCL subscale score or one NSI item score were included in the current analyses because of the pairwise deletion approach used in the network analysis. Missing data rates were extremely low, ranging from 2.8–3.3% for PCL subscales and 0.7–1.1% for NSI items. Sociodemographic and injury-related characteristics appear in Table 1.

### Network analysis

Descriptive statistics (Supplementary Table S1) and zero-order correlations (Supplementary Fig. S1) for the variables used in the current study are available as online supplements. Correlation stability coefficients were ideal for edge weights ($CS = 0.60$) and bridge centrality ($CS = 0.44$); they were lower (although still acceptable) for strength centrality estimates ($CS = 0.28$). The edges in the network were largely stable, because only one edge

**Table 1. Sample Characteristics (n = 612)**

| *Variable* | *M (SD) or* n *(%)* |
|---|---|
| Sex (%) | |
| Male | 567 (93.1%) |
| Female | 42 (6.9%) |
| Race/ethnicity | |
| Hispanic/Latino/Spanish | 81 (13.7%) |
| White | 468 (76.6%) |
| Black or African American | 73 (11.9%) |
| Asian | 27 (4.4%) |
| American Indian or Alaskan Native | 29 (4.7%) |
| Native Hawaiian or other Pacific Islander | 14 (2.3%) |
| Injury severity (GCS score) | |
| Mild (13–15) | 191 (37.7%) |
| Moderate (9–12) | 44 (8.7%) |
| Severe (3–8) | 151 (29.8%) |
| Chemically sedated | 52 (10.3%) |
| Intubated | 68 (13.4%) |
| Age at injury | 36.98 (16.14) |
| Time to follow commands (days) | 9.37 (16.36) |
| Post-traumatic amnesia (days) | 30.96 (47.06) |
| Cause of injury | 69.07 (16.16) |
| Vehicular | 307 (50.5%) |
| Gunshot wound | 25 (4.1%) |
| Assaults with blunt instrument | 25 (4.1%) |
| Other violence | 84 (13.8%) |
| Sports | 11 (1.8%) |
| Fall | 115 (18.9%) |
| Hit by falling/flying object | 8 (1.3%) |
| Pedestrian | 22 (3.6%) |
| Other | 8 (1.3%) |
| Unknown | 3 (.5%) |

SD, standard deviation; GCS, Glasgow Coma Scale.

in the network (connecting the ''headache'' and ''difficulty making decision'' nodes) was not included in the non-parametric bootstrap more than half (53.50%) of the time. Full edge weights and bootstrap estimates can be found in Supplementary Table S2).

The resultant network was relatively sparse (Fig. 1). Single keywords from items defined each node, as seen in Figure 1. The centrality estimates, along with the item content associated with single keywords for each node, appear in Table 2. Within the NSI communities, the frustrated node (i.e., the NSI item ''poor frustration tolerance'') was an important bridge node between the affective and cognitive TBI symptoms because it shared positive edges with three of the four cognitive nodes and yielded one of the strongest bridge centrality estimates in the network. The headaches node also served as a bridge node but shared more edges with the somatosensory community than the affective community, suggesting that headaches may not be appropriate to include as a symptom in affective factor scores.

The appetite node (i.e., ''changes in appetite'') was also an important bridge despite its modest bridge centrality values and shared edges with multiple nodes in the cognitive (i.e., difficult making decisions; poor concentration), affective (i.e., fatigue; feeling sad), and somatosensory (i.e., sensitivity to light; changes in taste/smell; nausea) node communities.

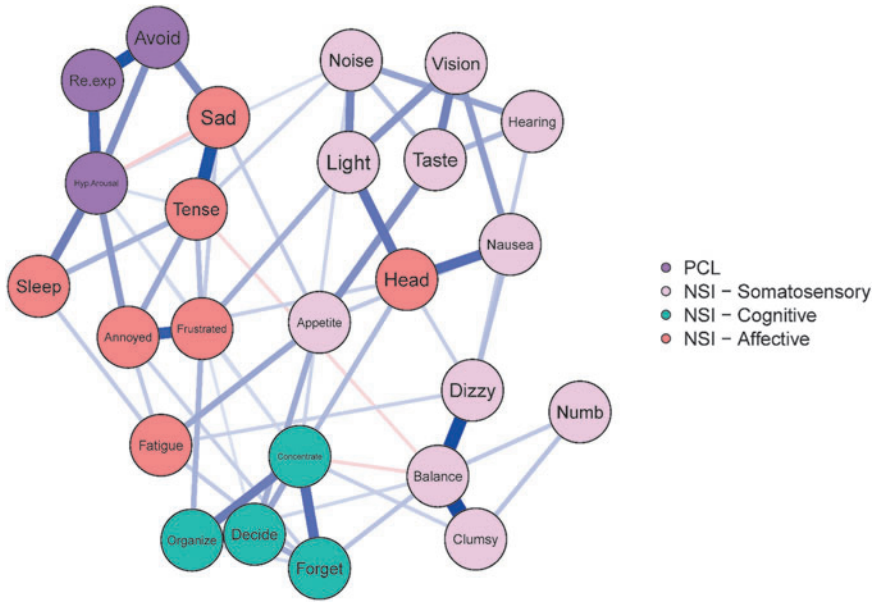


**FIG. 1.** Psychometric network of traumatic brain injury (TBI) symptoms measured via the Neurobehavioral Symptom Inventory (NSI) and post-traumatic stress disorder (PTSD) symptoms measured via the PTSD Checklist-Civilian version (PCL). Blue edges indicate positive associations and red edges indicate negative associations. Edge width and depth of color indicates the strength of associations. Hyp., Hyper; Re.exp, re-experience. An interactive version of this plot can be examined in greater detail online.[57] Color image is available online.

**Table 2. Strength and Bridge Centrality Estimates from All Nodes in the Network**

| *Node* | *Abridged Item Content* | *Community* | *2EI* | *Strength* |
|---|---|---|---|---|
| ***Neurobehavioral Symptom Inventory (NSI)*** | | | | |
| Annoyed | Irritability, easily annoyed | Affective | 0.86 | 1.06 |
| Frustrated | Poor frustration tolerance, overwhelmed | Affective | 1.06 | 1.14 |
| Head | Headaches | Affective | 1.25 | 1.04 |
| Sad | Feeling depressed or sad | Affective | 0.48 | 0.96 |
| Sleep | Difficulty falling asleep or staying asleep | Affective | 0.53 | 0.54 |
| Tense | Feeling anxious or tense | Affective | 0.40 | 1.16 |
| Concentrate | Poor concentration, inattentive, distracted | Cognitive | 0.93 | 1.36 |
| Decide | Difficulty making decisions | Cognitive | 0.49 | 1.02 |
| Forget | Forgetfulness, can't remember things | Cognitive | 0.79 | 0.91 |
| Organize | Slowed thinking, disorganized, can't finish | Cognitive | 0.67 | 0.96 |
| Appetite | Loss of appetite or increased appetite | Somatosensory | 0.75 | 0.80 |
| Balance | Loss of balance | Somatosensory | 0.18 | 1.47 |
| Clumsy | Poor coordination, clumsy | Somatosensory | 0.23 | 0.75 |
| Dizzy | Feeling dizzy | Somatosensory | 0.31 | 0.89 |
| Fatigue | Fatigue, loss of energy, tired easily | Somatosensory | 0.69 | 0.61 |
| Hearing | Hearing difficulty | Somatosensory | 0.07 | 0.45 |
| Light | Sensitivity to light | Somatosensory | 0.75 | 0.94 |
| Nausea | Nausea | Somatosensory | 0.46 | 0.78 |
| Noise | Sensitivity to noise | Somatosensory | 0.69 | 0.85 |
| Numb | Numbness or tingling on parts of the body | Somatosensory | 0.02 | 0.24 |
| Taste | Changes in taste or smell | Somatosensory | 0.14 | 0.77 |
| Vision | Vision problems, blurring, trouble seeing | Somatosensory | 0.17 | 0.68 |
| ***PTSD Checklist (PCL)*** | | | | |
| Avoid | Avoidance symptoms | PCL | 0.55 | 0.87 |
| Hyp.Arousal | Hyperarousal symptoms | PCL | 1.22 | 1.46 |
| Re.exp | Re-experiencing symptoms | PCL | 0.33 | 0.75 |

2EI, two-step expected influence; Hyp., hyper; Re.exp, Re-experience.



The three PCL nodes formed their own small cluster with the hyperarousal node yielding connections with the affective (i.e., feeling tense; irritable/annoyed; poor frustration; feeling sad; difficulty sleeping), cognitive (i.e., poor concentration), and somatic (i.e., sensitivity to noise) node communities. Consistent with this observation, the hyperarousal node had the second strongest bridge centrality in the network (Table 1). As such, PTSD symptoms comprising hyperarousal served as a crucial bridge among PTSD symptom and TBI symptoms. The avoidance node yielded an edge with the feeling sad node, whereas the re-experiencing node was only connected to the two PCL nodes. These findings suggest it is the affective symptoms of TBI and the affective content in hyperarousal that connect the clinical presentations/manifestations of TBI and PTSD.

## Discussion

Neurobehavioral symptoms after TBI reflect complex interactions among cognitive, affective, and physical consequences of injury.[58] Network analysis permits an examination of these dynamic connections to better understand how individual symptoms contribute to their domain (or ''community'') and how they overlap (or ''bridge'') one domain to another. The current psychometric network analysis examined regularized partial correlations among four communities (i.e., cognitive, somatosensory, and affective symptoms from the NSI, and PTSD symptoms from the PCL-C), along with the relative contributions of individual symptoms within their assigned community and as bridging symptoms to other communities.

A key finding from these analyses was the connection between symptoms of PTSD and affective symptoms of TBI (e.g., feeling annoyed, frustrated, sad, or tense). Given the rates of comorbidity between these two conditions, understanding the nature of overlapping symptoms is important, and the presence of affective distress might influence providers to focus on one diagnosis at the expense of the other. Such clinical confusion may be likeliest to occur when the frequency or intensity of affective symptoms is driving elevated total scores on measures like the PCL-C and NSI.

Within the community of PTSD nodes, re-experiencing and avoidance symptoms were relatively isolated from the symptoms of TBI. The relative lack of edges between the re-experiencing and avoidance nodes and those outside of the PTSD community is consistent with the well-established structure of the PTSD construct and supports clinical judgment that prominent experience of these symptoms is likely indicative of post-traumatic stress irrespective of whether there is a concurrent TBI. When such distinctions are possible, they can inform

the selection of an empirically supported intervention for PTSD, such as Cognitive Processing Therapy or Prolonged Exposure.[59–64]

Hyperarousal was a crucial bridge between symptoms of PTSD and TBI, suggesting hypotheses for future investigations of its role in connecting these two diagnoses and as a potential target for intervention. First, among SM/Vs with a history of TBI, hyperarousal could accentuate the experience of neurobehavioral symptoms, much as individuals with anxiety sensitivity tend to experience increased fearfulness or awareness of somatosensory symptoms.[65,66]

Second, given the association between hyperarousal and facets of irritability (e.g., feeling annoyed, frustrated, tense), hyperarousal might contribute to a cascading effect through the communities of TBI symptoms. Such downstream connections with cognitive symptoms could occur despite the modest number of direct connections between the cognitive TBI symptoms and hyperarousal. For example, the frustrated node, which shares an edge with hyperarousal, also shares edges with difficulty getting organized and difficulty making decisions—neither of which share an edge with hyperarousal.

Overall, hyperarousal appears to play a key role in holding together this network of distress through connecting post-traumatic stress and neurobehavioral symptoms of TBI. As such, hyperarousal could be an important target for intervention research among individuals with elevated symptoms of PTSD and a history of TBI. Although clinically intuitive, future research could clarify the conditions under which it is helpful to introduce strategies to reduce hyperarousal early in the course of treatment for either PTSD or TBI; given its role in the network of symptoms shown with the current data, addressing hyperarousal early could help to make other symptoms of PTSD and TBI more responsive to treatment. Fortunately, hyperarousal is readily amenable to cognitive-behavioral (e.g., psychoeducation; diaphragmatic breathing) or mindfulness-based interventions.[67–70]

Such interventions offer opportunities to disrupt these mutually reinforcing symptoms; they are face-valid, offer quick symptom reduction, and can serve as an entry into a holistic approach to care.

Although the PTSD and TBI communities were almost exclusively connected through hyperarousal and affective symptoms consistent with ''irritability,'' (e.g., tension, frustration, annoyance), there was one connection between avoidance and feeling sad. Compared with irritability, sadness represents an emotional state associated with lower arousal; this finding was accentuated by the negative edge shared by sadness with hyperarousal. For SM/Vs with elevated symptoms of PTSD whose presentation is more consistent with low arousal (vs. hyperarousal), clinicians might consider facilitating a therapeutic approach designed to target experiential avoidance through interventions such as prolonged exposure or acceptance and commitment therapy. Future applications of psychometric network analysis that include symptoms of depression along with PTSD and TBI could further characterize these associations.

### Limitations of data and analyses

Network analysis has been applied in diverse fields, yet its application to psychological research is relatively new; as such, its limitations in this area are still being explored.[71] The current sample size compelled a reduction in the number of PCL-C nodes by using subscale means instead of item-level data to conserve statistical power. A much larger sample size would have allowed the use of item-level data for the PCL-C, potentially resulting in more granular results. Sample size also influences the stability of the network and the estimation of edges, both of which increase along with sample size.[55]

Because the NSI and PCL-C data were cross-sectional, the results might erroneously imply a static relationship among nodes when they actually change over time or have some other dynamic component. This is a limitation of network analysis diagrams in general.[39] Further, when responding to the PCL-C, participants were not instructed to reference a specific stressor. Whether symptoms of post-traumatic stress are related to TBI or another stressful experience is unknown; nonetheless, the network analysis provides information about the associations among concurrent symptoms irrespective of the index trauma. The current analysis did not examine directionality, only strength of association. As such, these findings may be useful to generate hypotheses about causal relationships, and future studies might emphasize directional interactions as well as temporal ones.[54]

Important non-symptom variables were absent from the network that could influence both TBI and PTSD—e.g., age and gender.[72,73] Including non-symptom nodes could transform the results of the network and warrants further exploration.[74] Finally, the relative homogeneity of the participants in the VA TBIMS—predominantly male and White—precludes the results generalizing to larger, more heterogeneous TBI populations, despite their implications for SM/Vs.[13]

## Conclusion

The current study is among the first to perform a network analysis of neurobehavioral and PTSD symptoms as reported by individuals with TBI, and the first to examine this symptom network in a military cohort. Symptom overlap between these commonly co-occurring conditions posed challenges for diagnosis and treatment. As demonstrated herein, network analysis offers an empirical approach to visualizing and quantifying the relationships among symptoms that can improve diagnostic

precision, identify treatment targets, and inform treatment selection. Future extensions of these methods to include a broader range of symptoms experienced by individuals with TBI may yield novel insights into the ways in which co-occurring symptoms can serve to mutually exacerbate or maintain ongoing health problems in this population.

## Acknowledgments

The views expressed in this publication are those of the authors and do not necessarily represent the official policy or position of the Defense Health Agency, Department of Defense, or any other U.S. government agency.

## Authors' Contributions

Daniel Klyce conceived of the presented idea, contributed to data collection, organized the manuscript preparation, supervised the analyses, drafted sections of the manuscript, and performed final revisions.

Samuel West performed the analyses, prepared tables and figures, and drafted sections of the manuscript.

Paul Perrin assisted with conceptualizing the analyses plan, prepared tables, and drafted sections of the manuscript.

Stephanie Agtarap drafted sections of the manuscript.

Jacob Finn assisted with data collection and drafted sections of the manuscript.

Shannon Juengst drafted sections of the manuscript.

Kristen Dams-O'Connor drafted sections of the manuscript and assisted with revisions.

CB Eagye consulted on the data analyses plan and drafted sections of the manuscript.

Tiffanie Vargas assisted with data collection and drafted sections of the manuscript.

Joyce Chung assisted with data collection and drafted sections of the manuscript.

Charles Bombardier assisted with conceptualizing the analyses and drafted sections of the manuscript.

## Funding Information

This work was prepared under Contract HT0014-19-C-0004 with DHA Contracting Office (CO-NCR) HT0014 and, therefore, is defined as U.S. Government work under Title 17 U.S.C. §101. Per Title 17 U.S.C. §105, copyright protection is not available for any work of the U.S. Government. For more information, please contact dha.TBICOEinfo@mail.mil. UNCLASSIFIED

## Author Disclosure Statement

No competing financial interests exist.

## Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Figure S1

## References

1. The Management of Concussion-mild Traumatic Brain Injury Working Group. (2016). VA/DoD clinical practice guidlines for the management of concussion-mild traumatic brain injury (mTBI). Department of Veterans Affairs and Department of Defense; Washington, DC.
2. Scholten, J., Vasterling, J.J., and Grimes, J.B. (2017). Traumatic brain injury clinical practice guidelines and best practices from the VA state of the art conference. Brain Inj. 31, 1246–1251.
3. Armistead-Jehle, P., Soble, J.R., Cooper, D.B., and Belanger, H.G. (2017). Unique aspects of traumatic brain injury in military and veteran populations. Phys. Med. Rehabil. Clin. N. Am. 28, 323–337.
4. Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C., and Castro, C.A. (2008). Mild traumatic brain injury in U.S. soldiers returning from Iraq. N. Engl. J. Med. 358, 453–463.
5. Okie, S. (2005). Traumatic brain injury in the war zone. N. Engl. J. Med. 352, 2043–2047.
6. DoD TBI Worldwide Numbers. Mil. Health Syst. Available at: www.health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/DoD-TBI-Worldwide-Numbers. Last accessed October 17, 2021.
7. Armstrong, M., Champagne, J., and Mortimer, D.S. (2019). Department of Veterans Affairs Polytrauma Rehabilitation Centers: inpatient rehabilitation management of combat-related polytrauma. Phys. Med. Rehabil. Clin. N. Am. 30, 13-27.
8. Cifu, D.X., Taylor, B.C., Carne, W.F., Bidelspach, D., Sayer, N.A., Scholten, J., and Campbell, E.H. (2013). Traumatic brain injury, posttraumatic stress disorder, and pain diagnoses in OIF/OEF/OND Veterans. J. Rehabil. Res. Dev. 50, 1169–1176.
9. Lew, H.L., Cifu, D.X., Crowder, T., and Hinds, S.R. (2013). National prevalence of traumatic brain injury, posttraumatic stress disorder, and pain diagnoses in OIF/OEF/OND Veterans from 2009 to 2011. J. Rehabil. Res. Dev. 50, xi–xiv.
10. Brenner, L.A., Homaifar, B.Y., Olson-Madden, J.H., Nagamoto, H.T., Huggins, J., Schneider, A.L., Forster, J.E., Matarazzo, B., and Corrigan, J.D. (2013). Prevalence and screening of traumatic brain injury among veterans seeking mental health services. J. Head Trauma Rehabil. 28, 21–30.
11. Lamberty, G.J., Nakase-Richardson, R., Farrell-Carnahan, L., McGarity, S., Bidelspach, D., Harrison-Felix, C., and Cifu, D.X. (2014). Development of a traumatic brain injury model system within the Department of Veterans Affairs Polytrauma System of Care. J. Head Trauma Rehabil. 29, E1–E7.
12. Nakase-Richardson, R., Stevens, L.F., Tang, X., Lamberty, G.J., Sherer, M., Walker, W.C., Pugh, M.J., Eapen, B.C., Finn, J.A., Saylors, M., Dillahunt-Aspillaga, C., Adams, R.S., and Garofano, J.S. (2017). Comparison of the VA and NIDILRR TBI model system cohorts. J. Head Trauma Rehabil. 32, 221–233.
13. Ropacki, S., Nakase-Richardson, R., Farrell-Carnahan, L., Lamberty, G.J., and Tang, X. (2018). Descriptive findings of the VA Polytrauma Rehabilitation Centers TBI Model Systems National Database. Arch. Phys. Med. Rehabil. 99, 952–959.
14. Walker, W.C., Carne, W., Franke, L.M., Nolen, T., Dikmen, S.D., Cifu, D.X., Wilson, K., Belanger, H.G., and Williams, R. (2016). The Chronic Effects of Neurotrauma Consortium (CENC) multi-centre observational study: description of study and characteristics of early participants. Brain Inj. 30, 1469–1480.
15. Carlson, K.F., Kehle, S.M., Meis, L.A., Greer, N., Macdonald, R., Rutks, I., Sayer, N.A., Dobscha, S.K., and Wilt, T.J. (2011). Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. J. Head Trauma Rehabil. 26, 103–115.
16. O'Neil, M.E., Carlson, K., Storzbach, D., Brenner, L., Freeman, M., Quiñones, A., Motu'apuaka, M., Ensley, M., and Kansagara, D. (2013). Complications of mild traumatic brain injury in veterans and military personnel: a systematic review. Department of Veterans Affairs; Washington, DC.
17. Lew, H.L., Otis, J.D., Tun, C., Kerns, R.D., Clark, M.E., and Cifu, D.X. (2009). Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. J. Rehabil. Res. Dev. 46, 697–702.
18. Taylor, B.C., Hagel, E.M., Carlson, K.F., Cifu, D.X., Cutting, A., Bidelspach, D.E., and Sayer, N.A. (2012). Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran V.A. users. Med. Care 50, 342–346.

19. Blakey, S.M., Wagner, H.R., Naylor, J., Brancu, M., Lane, I., Sallee, M., Kimbrel, N.A., VA Mid-Atlantic MIRECC Workgroup, and Elbogen, E.B. (2018). Chronic pain, TBI, and PTSD in military veterans: a link to suicidal ideation and violent impulses? J. Pain 19, 797–806.
20. Seal, K.H., Bertenthal, D., Barnes, D.E., Byers, A.L., Strigo, I., Yaffe, K., and Chronic Effects of Neurotrauma Consortium Study Group. (2017). Association of traumatic brain injury with chronic pain in Iraq and Afghanistan veterans: effect of comorbid mental health conditions. Arch. Phys. Med. Rehabil. 98, 1636–1645.
21. Brady, K.T., Tuerk, P., Back, S.E., Saladin, M.E., Waldrop, A.E., and Myrick, H. (2009). Combat posttraumatic stress disorder, substance use disorders, and traumatic brain injury. J. Addict. Med. 3, 179–188.
22. Bowe, A., and Rosenheck, R. (2015). PTSD and substance use disorder among veterans: characteristics, service utilization and pharmacotherapy. J. Dual Diagn. 11, 22–32.
23. Petrakis, I.L., Rosenheck, R., and Desai, R. (2011). Substance use comorbidity among veterans with posttraumatic stress disorder and other psychiatric illness. Am. J. Addict. 20, 185–189.
24. Carlson, K.F., Nelson, D., Orazem, R.J., Nugent, S., Cifu, D.X., and Sayer, N.A. (2010). Psychiatric diagnoses among Iraq and Afghanistan war veterans screened for deployment-related traumatic brain injury. J. Trauma. Stress 23, 17–24.
25. Morissette, S.B., Woodward, M., Kimbrel, N.A., Meyer, E.C., Kruse, M.I., Dolan, S., and Gulliver, S.B. (2011). Deployment-related TBI, persistent postconcussive symptoms, PTSD, and depression in OEF/OIF veterans. Rehabil. Psychol. 56, 340–350.
26. Wisco, B.E., Marx, B.P., Holowka, D.W., Vasterling, J.J., Han, S.C., Chen, M.S., Gradus, J.L., Nock, M.K., Rosen, R.C., and Keane, T.M. (2014). Traumatic brain injury, PTSD, and current suicidal ideation among Iraq and Afghanistan U.S. veterans. J. Trauma. Stress 27, 244–248.
27. Brenner, L.A., Betthauser, L.M., Homaifar, B.Y., Villarreal, E., Harwood, J.E.F., Staves, P.J., and Huggins, J.A. (2011). Posttraumatic stress disorder, traumatic brain injury, and suicide attempt history among veterans receiving mental health services. Suicide Life. Threat. Behav. 41, 416–423.
28. Finley, E.P., Bollinger, M., Noël, P.H., Amuan, M.E., Copeland, L.A., Pugh, J.A., Dassori, A., Palmer, R., Bryan, C., and Pugh, M.J.V. (2015). A national cohort study of the association between the polytrauma clinical triad and suicide-related behavior among US Veterans who served in Iraq and Afghanistan. Am. J. Public Health 105, 380–387.
29. Stein, M.B., and McAllister, T.W. (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. Am. J. Psychiatry 166, 768–776.
30. American Medical Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* American Psychiatric Publishing, Washington, DC.
31. McCrea, M. (2008). *Mild Traumatic Brain Injury and Postconcussion Syndrome: The New Evidence Base for Diagnosis and Treatment.* Oxford University Press; New York, NY.
32. Alves, W., Macciocchi, S.N., and Barth, J.T. (1993). Postconcussive symptoms after uncomplicated mild head injury. J. Head Trauma Rehabil. 8, 48–59.
33. Lange, R.T., Brickell, T.A., Ivins, B., Vanderploeg, R.D., and French, L.M. (2013). Variable, not always persistent, postconcussion symptoms after mild TBI in U.S. military service members: a five-year cross-sectional outcome study. J. Neurotrauma 30, 958–969.
34. Aase, D.M., Babione, J.M., Proescher, E., Greenstein, J.E., DiGangi, J.A., Schroth, C., Kennedy, A.E., Feeley, S., Tan, M., Cosio, D., and Phan, K.L. (2018). Impact of PTSD on post-concussive symptoms, neuropsychological functioning, and pain in post-9/11 veterans with mild traumatic brain injury. Psychiatry Res. 268, 460–466.
35. Benge, J.F., Pastorek, N.J., and Thornton, G.M. (2009). Postconcussive symptoms in OEF–OIF veterans: factor structure and impact of posttraumatic stress. Rehabil. Psychol. 54, 270–278.
36. Kim, S.H., Lee, N., Martin, B., Suh, J., Walters, D., Silverman, D.H., and Berenji, G.R. (2020). Examining posttraumatic stress disorder as a key postinjury risk factor in OIF/OEF veterans with blast-induced mild traumatic brain injury. Neuropsychology 34, 713–725.
37. O'Neil, M.E., Callahan, M., Carlson, K.F., Roost, M., Laman-Maharg, B., Twamley, E.W., Iverson, G.L., and Storzbach, D. (2017). Postconcussion symptoms reported by Operation Enduring Freedom/Operation Iraqi Freedom veterans with and without blast exposure, mild traumatic brain injury, and posttraumatic stress disorder. J. Clin. Exp. Neuropsychol. 39, 449–458.
38. Hoge, C.W., Goldberg, H.M., and Castro, C.A. (2009). Care of war veterans with mild traumatic brain injury—flawed perspectives. N. Engl. J. Med. 360, 1588–1591.
39. Iverson, G.L. (2019). Network analysis and precision rehabilitation for the post-concussion syndrome. Front. Neurol. 10, 489.
40. Elliott, H., Jones, P.J., and Schmidt, U. (2020). Central symptoms predict posttreatment outcomes and clinical impairment in anorexia nervosa: a network analysis. Clin. Psychol. Sci. 8, 139–154.
41. Park, S.C., and Kim, D. (2020). The centrality of depression and anxiety symptoms in major depressive disorder determined using a network analysis. J. Affect. Disord. 271, 19–26.
42. Armour, C., Fried, E.I., Deserno, M.K., Tsai, J., and Pietrzak, R.H. (2017). A network analysis of DSM-5 posttraumatic stress disorder symptoms and correlates in U.S. military veterans. J. Anxiety Disord. 45, 49–59.
43. Weintraub, M.J., Schneck, C.D., and Miklowitz, D.J. (2020). Network analysis of mood symptoms in adolescents with or at high risk for bipolar disorder. Bipolar Disord. 22, 128–138.
44. Lazarov, A., Suarez-Jimenez, B., Levi, O., Coppersmith, D.D.L., Lubin, G., Pine, D.S., Bar-Haim, Y., Abend, R., and Neria, Y. (2020). Symptom structure of PTSD and co-morbid depressive symptoms—a network analysis of combat veteran patients. Psychol. Med. 50, 2154–2170.
45. Cicerone, K. and Kalmar, K. (1995). Neurobehavioral symptom inventory. J. Head Trauma Rehabil. 10, 1–17.
46. Silva, M.A. (2021). Review of the Neurobehavioral Symptom Inventory. Rehabil. Psychol. 66,170–182..
47. Weathers, F., Litz, B., Herman, D., Huska, J., and Keane, T. (1993). The PTSD Checklist: Reliability, validity and diagnostic utility. Presented at the Annual Convention of the International Society for Traumatic Stress Studies, San Antonio.
48. Armour, C., Műllerová, J., and Elhai, J.D. (2016). A systematic literature review of PTSD's latent structure in the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV to DSM-5. Clin. Psychol. Rev. 44, 60–74.
49. McDonald, S.D., and Calhoun, P.S. (2010). The diagnostic accuracy of the PTSD checklist: a critical review. Clin. Psychol. Rev. 30, 976–987.
50. Blanchard, E.B., Jones-Alexander, J., Buckley, T.C., and Forneris, C.A. (1996). Psychometric properties of the PTSD Checklist (PCL). Behav. Res. Ther. 34, 669–673.
51. Fried, E.I., Eidhof, M.B., Palic, S., Costantini, G., Huisman-van Dijk, H.M., Bockting, C.L.H., Engelhard, I., Armour, C., Nielsen, A.B.S., and Karstoft, K.I. (2018). Replicability and generalizability of posttraumatic stress disorder (PTSD) networks: a cross-cultural multisite study of PTSD Symptoms in four trauma patient samples. Clin. Psychol. Sci. 6, 335–351.
52. Dretsch, M., Bleiberg, J., Williams, K., Caban, J., Kelly, J., Grammer, G., and DeGraba, T. (2016). Three scoring approaches to the neurobehavioral symptom inventory for measuring clinical change in service members receiving intensive treatment for combat-related mTBI. J. Head Trauma Rehabil. 31, 23–29.
53. Jones, P. (2017). networktools: assorted tools for identifying important nodes in networks. R Package Version 100 HttpsCRANR-Proj.
54. Fried, E.I., and Cramer, A.O.J. (2017). Moving forward: challenges and directions for psychopathological network theory and methodology. Perspect. Psychol. Sci. 12, 999–1020.
55. Epskamp, S., Borsboom, D., and Fried, E.I. (2018). Estimating psychological networks and their accuracy: a tutorial paper. Behav. Res. Methods 50, 195–212.
56. Epskamp, S., and Fried, E.I. (2018). A tutorial on regularized partial correlation networks. Psychol. Methods 23, 617–634.
57. TBI Symptom Network https:tbi-ptsd-network.netlify.appr (Last accessed November 1, 2021).
58. Juengst, S.B., Switzer, G., Oh, B.M., Arenth, P.M., and Wagner, A.K. (2017). Conceptual model and cluster analysis of behavioral symptoms in two cohorts of adults with traumatic brain injuries. J. Clin. Exp. Neuropsychol. 39, 513–524.
59. Tanev, K.S., Pentel, K.Z., Kredlow, M.A., and Charney, M.E. (2014). PTSD and TBI co-morbidity: scope, clinical presentation and treatment options. Brain Inj. 28, 261–270.
60. Wolf, G.K., Kretzmer, T., Crawford, E., Thors, C., Wagner, H.R., Strom, T.Q., Eftekhari, A., Klenk, M., Hayward, L., and Vanderploeg, R.D. (2015). Prolonged exposure therapy with veterans and active duty personnel diagnosed with PTSD and traumatic brain injury. J. Trauma. Stress 28, 339–347.
61. Eftekhari, A., Ruzek, J.I., Crowley, J.J., Rosen, C.S., Greenbaum, M.A., and Karlin, B.E. (2013). Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. JAMA Psychiatry 70, 949–955.

62. Asmundson, G.J.G., Thorisdottir, A.S., Roden-Foreman, J.W., Baird, S.O., Witcraft, S.M., Stein, A.T., Smits, J.A.J., and Powers, M.B. (2019). A meta-analytic review of cognitive processing therapy for adults with post-traumatic stress disorder. Cogn. Behav. Ther. 48, 1–14.
63. Rauch, S.A.M., Defever, E., Favorite, T., Duroe, A., Garrity, C., Martis, B., and Liberzon, I. (2009). Prolonged exposure for PTSD in a Veterans Health Administration PTSD clinic. J. Trauma. Stress 22, 60–64.
64. Monson, C.M., Schnurr, P.P., Resick, P.A., Friedman, M.J., Young-Xu, Y., and Stevens, S.P. (2006). Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J. Consult. Clin. Psychol. 74, 898–907.
65. Reiss, S. (1991). Expectancy model of fear, anxiety, and panic. Clin. Psychol. Rev. 11, 141–153.
66. Marshall, G.N., Miles, J.N.V., and Stewart, S.H. (2010). Anxiety sensitivity and PTSD symptom severity are reciprocally related: evidence from a longitudinal study of physical trauma survivors. J. Abnorm. Psychol. 119, 143–150.
67. Mitchell, M.A., Capron, D.W., Raines, A.M., and Schmidt, N.B. (2014). Reduction of cognitive concerns of anxiety sensitivity is uniquely associated with reduction of PTSD and depressive symptoms: a comparison of civilians and veterans. J. Psychiatr. Res. 48, 25–31.
68. Smits, J.A.J., Berry, A.C., Tart, C.D., and Powers, M.B. (2008). The efficacy of cognitive-behavioral interventions for reducing anxiety sensitivity: a meta-analytic review. Behav. Res. Ther. 46, 1047–1054.
69. Schoorl, M., Van Mil-Klinkenberg, L., and Van Der Does, W. (2015). Mindfulness skills, anxiety sensitivity, and cognitive reactivity in patients with posttraumatic stress disorder. Mindfulness 6, 1004–1011.
70. Cabella, B., Donnelly, J., Cardim, D., Liu, X., Cabeleira, M., Smielewski, P., Haubrich, C., Hutchinson, P.J.A., Kim, D.J., and Czosnyka, M. (2017). An association between ICP-derived data and outcome in TBI patients: the role of sample size. Neurocrit. Care 27, 103–107.
71. Borsboom, D., and Cramer, A.O.J. (2013). Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 9, 91–121.
72. Konnert, C., and Wong, M. (2014). Age differences in PTSD among Canadian veterans: age and health as predictors of PTSD severity. Int. Psychogeriatr. 9, 1–8.
73. Lehavot, K., Katon, J.G., Chen, J.A., Fortney, J.C., and Simpson, T.L. (2018). Post-traumatic stress disorder by gender and veteran status. Am. J. Prev. Med. 54, e1–e9.
74. Jones, P.J., Heeren, A., and McNally, R.J. (2017). Commentary: A network theory of mental disorders. Front. Psychol. 8, 1305.