UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Neural Correlates of Working Memory Performance in Veterans with Mild Traumatic Brain Injury

A dissertation submitted in partial satisfaction
of the requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

Kelsey A. Holiday

Committee in charge:

University of California San Diego

Professor Dawn M. Schiehser, Chair
Professor Lisa T. Eyler, Co-Chair
Professor Scott F. Sorg

San Diego State University

Professor Paul E. Gilbert
Professor Jonathan Helm

2021

The dissertation of Kelsey A. Holiday is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Co-Chair

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Chair

University of California San Diego

San Diego State University

2021

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ACKNOWLEDGEMENTS

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I would also like to acknowledge the many members of "The TBI Lab," without whom my research would not have been possible. It is their support that helped me in an immeasurable way.

The entire dissertation document (including the introduction, methods, results, and discussion chapters) contains unpublished research co-authored by Holiday, Kelsey A.; Eyler, Lisa T; Sorg, Scott F.; and Schiehser, Dawn M. The dissertation author was the primary author of this work.

VITA

EDUCATION

Internship	West LA VA Healthcare Center	*Aug 2020 – Jul 2021*
Ph.D., Clinical Psychology	SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology Major Area of Study: Neuropsychology	*Sept. 2021*
M.S., Clinical Psychology	San Diego State University GPA 3.91	*May 2017*
B.S., Neuroscience and Psychology Minor: Biology	University of Delaware Honors Degree with Distinction Cumulative GPA 3.655, Neuroscience GPA 3.592 GRE: Verbal 163 (92%), Quantitative 164 (88%)	*May 2013*

FELLOWSHIPS, GRANTS, & AWARDS

Ruth L. Kirschstein National Research Service Award (NRSA) *Apr 2019-Mar 2021*
- Title: Neural correlates of working memory performance in mTBI
- Funding Agency: National Institute of Neurological Disorders and Stroke
- Grant Number: 1F31NS108573-01A1
- Percentile: 8; Impact Score: 22

National Science Foundation Graduate Research Fellowship *Sept 2015-Aug 2018*
- Title: Disruption of Distinct Visual Pathways for Encoding Dynamic and Static Emotional Faces
- Grant Number: DGE-1144086

Post-baccalaureate Intramural Research Training Award, NIH *Jul 2013-Jul 2015*

fMRI Visiting Fellowship, MGH/HST, Martinos Center, Boston, MA *Mar 2014*
- 5-day intensive introduction to the physics of MR imaging

Sigma Xi Undergraduate Thesis Award, University of Delaware *May 2013*

Donald W. Harward Fellows Award, University of Delaware *Jan 2013*
- Stipend Research Fellowship for an outstanding academic record

Science & Engineering Scholar Award, University of Delaware *Summer 2011*
- 10-week Full Time Experiential Learning Scholarship for research

General Honors Award Recipient, University of Delaware *Jan 2011*

Psi Chi – The International Honors Society in Psychology *2010-2013*

RESEARCH EXPERIENCE

Graduate Research Assistant

Veterans Medical Research Foundation, *Aug 2015–Present*
VA San Diego Healthcare System, San Diego, CA
Faculty Mentor: Dawn M. Schiehser, Ph.D.

Laboratory Emphasis: Elucidated the neural underpinnings of cognitive deficits associated with mild traumatic brain injuries (mTBI)

- Administered, Scored, & Interpreted neuropsychological assessments and clinical diagnostic techniques (i.e., BAT-L) to assess pathology in mTBI
- Analyzed fMRI data using Analysis of Functional NeuroImages (AFNI)
- Conducted volumetric analyses to examine the association between structural brain changes and neuropsychological symptoms in Veterans with mTBI
- Coordinated monthly laboratory meetings to foster collaboration between research scientists and to present research findings

Published Master's Thesis: Psychometric properties of the North-East Visual Hallucinations Interview in Parkinson's Disease (PD)

- Obtained mastery in psychometric assessment and validated clinical measure
- Proposed independent project for Master's Thesis
- Submitted and maintained Institutional Review Board (IRB) protocol
- Conducted statistical analyses of categorical data using SPSS
- Published first-author manuscript in peer-reviewed journal

Post-Baccalaureate Research Fellow

Laboratory of Brain and Cognition, National Institute of Mental Health *Jul 2013–Jul 2015*
National Institutes of Health (NIH), Bethesda, MD
Mentor: Leslie G. Ungerleider, Ph.D.

Project 1: Elucidated the temporal dynamics of memory and consolidation in higher order visual processing areas including the occipital face area (OFA)

- Designed original transcranial magnetic stimulation (TMS) experiment
- Programmed delayed match-to-sample task in E-Prime
- Used Brainsight™ to functionally localize TMS target sites

Project 2: Examined cognitive and attentional deficits in a patient with right middle frontal gyrus resection using fMRI and behavioral methods

- Recorded and analyzed eye movements with EyeTrak 6000
- Analyzed data in MATLAB and assisted in manuscript preparation

Project 3: Investigated the propagation of information in ventral visual pathway to higher order brain regions (*combined fMRI/TMS study*)

- Compared static vs. dynamic visual stimuli activation in right pSTS
- Administered thetaburst TMS to disrupt activity in two cortical regions
- Analyzed fMRI data using Analysis of Functional NeuroImages (AFNI) and created regions of interest to estimate the effects of TMS

Other responsibilities:

- Recruited and screened healthy control participants

- Coordinated weekly lab meetings and Annual Reports of current lab research
- Developed protocol amendments for Institutional Review Board approval

Undergraduate Research Assistant

Attention & Event-Related Brain Potentials Lab, University of Delaware *Jan 2012–May 2013*
Faculty Mentor: James Hoffman, Ph.D.

Laboratory Emphasis: Neural Basis of Attention During Emotional Image Processing

- Used electroencephalography (EEG) to examine the underlying ERPs involved in visual attention and emotion-induced blindness (EIB)

Published Senior Honors Thesis: Do negative emotional pictures automatically capture attention?

- Investigated the automaticity of impaired awareness elicited by an irrelevant negative image during a multiple object tracking task and modified attentional blink paradigm
- Drafted a protocol for the Institutional Review Board
- Performed principal component analysis of ERP components
- Conducted statistical analysis of data using SPSS and MATLAB
- Gained experience in "Eye-link" eye tracking, & Netlink ERP recording

Neural Basis of Learning and Memory Lab, University of Delaware *May 2011–Dec 2011*
Faculty Mentor: Amy Griffin, Ph.D.

Project: Effects of Hippocampal Inactivation on Working Memory Tasks

- Provided rodent training on T-maze working memory paradigms, such as continuous alternation and conditional discrimination of textures
- Performed perfusions, cryostat brain slicing, histology, and electrophysiology drive preparation and surgeries
- Induced temporary hippocampal inactivation through infusions of a $GABA_A$ receptor agonist (Muscimol)
- Evaluated cannulae placement in brain slices using Adobe Photoshop

Developmental Psychobiology Lab, University of Delaware *Feb 2011–May 2011*
Faculty Supervisor: Mark Stanton, Ph.D.

Project: Ontogeny of Associative Learning in the Brainstem-Cerebellar Circuit

- Utilized an eye-blink conditioning paradigm to explore the developmental detriments of fetal alcohol spectrum disorder in a rodent model
- Performed rodent surgeries for eye-blink conditioning experiments
- Collected eye-blink conditioning data collection and detected artifacts
- Conducted T-maze animal acclamation, data collection, and data analysis

CLINICAL EXPERIENCE

Neuropsychological Assessment

Neuropsychological Assessment Unit, West LA VA *Nov 2020-Present*
Supervisor: Charles Hinkin, Ph.D., ABPP-CN

- Conduct full chart review, clinical interview, neuropsychological evaluation, interpretation of neuropsychological data, integrative report writing, and patient/family feedback
- Patients include adult, often geriatric, veterans with a broad range of neurological, psychological, and general medical conditions

Inpatient Acute Physical Rehabilitation Unit, West LA VA *Aug 2020-Oct 2020*
Supervisor: Michelle Zeller, Psy.D., ABPP-CN

- Conducted diagnostic evaluation, psychological and neuropsychological assessment of veterans admitted for intensive physical rehabilitation
- Assessed decision-making capacity and communicate findings at interdisciplinary treatment rounds and family conferences
- Performed interpretation of neuropsychological data, and integrative report writing
- Supervised pre-intern on neuropsychological assessment cases
  - Patients included veterans in the acute phase of recovery from stroke, amputation, TBI, and neurological and orthopedic disorders

Polytrauma/TBI Program, West LA VA *Aug 2020-Oct 2020*
Supervisors: Anna Okonek, Ph.D. & Steve Castellon, Ph.D.

- Conducted neuropsychological assessment, interpretation of neuropsychological data, and integrative report writing
- Communicated findings at interdisciplinary treatment team rounds
  - Patients included veterans with multi-system injuries, including TBI

The Pain Clinic, West LA VA *Aug 2020-Oct 2020*
Supervisors: Katherine Bailey, Ph.D. & Morgan Kay, Ph.D.

- Conducted pre-surgical assessments with patients who are being considered for spinal cord stimulator or intrathecal drug pump implantation
  - Patients included veterans with chronic, complicated pain problems, along with co-morbid psychological conditions

Delis Neuropsychology Center, UC San Diego *July 2019-July 2020*
Supervisor: Dean C. Delis, Ph.D., ABPP-CN

- Neuropsychological assessment of adults, interpretation of neuropsychological data, and integrative report writing
  - Patients were predominantly former NFL players with sports-related concussions and other individuals with TBIs

Neuropsychological Assessment Clinic in Oncology at the Radiation Oncology PET/CT Center (ROPCC) *July 2019-July 2020*

Supervisor: Carrie McDonald, Ph.D., ABPP-CN

- Neuropsychological evaluation of adults, interpretation of neuropsychological data, and integrative report writing in a multidisciplinary outpatient hospital setting as part of a neuro-oncology treatment team
- Attended Brain Tumor Board to assist in patient care decisions
- Review patient MRIs with Dr. McDonald and the treatment team
  - Patients were individuals with cancer (e.g., primary and metastatic brain tumors) as well as presurgical epilepsy evaluations

Neuropsychological Assessment Unit, VA San Diego Healthcare System *Jul 2018-Jun 2019*

Supervisors: Mark W. Bondi, Ph.D., ABPP-CN, Lisa Delano-Wood, Ph.D., J. Vincent Filoteo, Ph.D., & Amy J. Jak, Ph.D.

- Conducted full chart review, clinical interview, neuropsychological evaluation, interpretation of neuropsychological data, integrative report writing, and patient/family feedback
  - Patients were adult, often geriatric, veterans with a broad range of neurological, psychological, and general medical conditions

UC San Diego Neuropsychology Laboratory *Jul 2018-Jun 2019*

Supervisor: Robert K. Heaton, Ph.D., ABPP-CN

- Neuropsychological test data interpretation, case formulations, and integrative report writing
- Conducted in-depth discussion of case details in a small group supervised setting with Dr. Heaton
  - Patients were primarily referred for litigation purposes and included adults from a variety of backgrounds with a wide range of neurological, psychological, and general medical conditions

Polytrauma & Inpatient Psychology Services, VASDHS *Jan 2019-Jun 2019*

Supervisor: Marc Jacobson, Ph.D.

- Neurocognitive and psychological assessment with a flexible battery to aid in differential diagnosis and treatment planning
  - Patients assessed included:
    - adult inpatient veterans hospitalized with acute psychiatric illnesses (e.g. PTSD, Bipolar, Addiction, Personality Disorders)
    - adult outpatient veterans with co-occurring cognitive difficulties due to neurological or developmental challenges (e.g., TBI, stroke, ADHD, Autism Spectrum, Neurocognitive Disorders, Learning Disorders) *and* co-morbid psychiatric overlay

Clinical Intervention

Mental Health Clinic, West LA VA *Aug 2020-Present*
Supervisor: Barbara Wettstein, Ph.D.

- Deliver long-term therapy and integrate EBPs with third-wave therapies such as acceptance and commitment therapy, dialectical behavior therapy skills, and mindfulness-based cognitive therapy.
- Provide integrative behavioral couple therapy (IBCT) to couples with reconcilable differences
- Patients include:
  - Individual veterans with a wide range of psychological conditions (e.g., anxiety, depression, PTSD, BPD, ADHD, SUD)
  - Couples experiencing marital distress

Inpatient Acute Physical Rehabilitation Unit, West LA VA *Aug 2020-Oct 2020*
Supervisor: Michelle Zeller, Psy.D., ABPP-CN

- Co-facilitated Rehabilitation Support Groups for veterans recovering from amputation or stroke and their family members
- Stroke Support Group: Topics included warning signs of stroke, risk factors, prevention of stroke, coping with depression and caregiver issues
- Amputee Support Group: Topics included risk factors for amputation, lifestyle change, coping with feelings, pain management, setting goals and discharge planning
- Provided consultation to interdisciplinary team members in all settings
- Provided brief supportive interventions on the Acute Rehabilitation Unit
  - Patients included veterans in the acute phase of recovery from stroke, amputation, TBI, and neurological and orthopedic disorders

The Pain Clinic, West LA VA *Aug 2020-Oct 2020*
Supervisors: Katherine Bailey, Ph.D. & Morgan Kay, Ph.D.

- Delivered national VA evidence-based psychotherapy (EBP) rollout of cognitive behavioral therapy for chronic pain (CBT-CP)
- Co-facilitated an interprofessional, 10-week Comprehensive Pain Rehabilitation Program (CPRP)
  - Patients included veterans with chronic, complicated pain problems, along with co-morbid psychological conditions such as anxiety, depression, PTSD, substance use disorder and borderline personality disorder

CogSMART, Neurocognition & Movement Lab *Jan 2019-Apr 2019*
UC San Diego School of Medicine | VA San Diego Healthcare System
Supervisor: Dawn Schiehser, Ph.D.

- Co-facilitated Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) group
- Delivered compensatory prospective memory, attention, learning, and executive functioning strategies to improve cognition
  - Patients included geriatric individuals with a diagnosis of Parkinson's disease and mild cognitive impairment

SARRTP PTSD Track, VA San Diego Healthcare System *Jul 2017-Jun 2018*
Supervisor: Moira Haller, Ph.D.

- Provided evidence-based PTSD intake evaluation and determine course of treatment (i.e., Prolonged Exposure, Cognitive Processing Therapy [CPT])
- Engaged patients in motivational interviewing regarding SUD and PTSD treatment
- Conducted *intensive* individual therapy (3x per week) to facilitate treatment completion prior to patient discharge
- Co-facilitated weekly PTSD/SUD group on in vivo exposure and CBT for PTSD
  - Substance Abuse Recovery and Rehabilitation Treatment Program (SARRTP) is a residential substance use treatment program

CPT Provider Training & Certification *Pending Licensure*
CPT Consultant: Ellen Healy, Ph.D., Training & Education Coordinator, CPT Training

- Participated in two-day onsite CPT training with treatment developers
- Attended 20 hours of sanctioned group CPT consultation
- Successfully completed three individual CPT cases including submission of redacted case notes, PCL and PHQ9 scores, and sample worksheets (e.g., stuck-point log)

Psychology Clinic, San Diego State University *Jul 2016-Jun 2017*
Supervisors: Nadar Amir, Ph.D., & Robin Weersing, Ph.D.

- Provided individual evidence-based assessment and therapy in a university-based outpatient treatment clinic serving community members
- Delivered intensive OCD exposure therapy (four hours per week)
  - Patients included children and adults presenting with a broad range of psychological diagnoses (e.g., OCD, anxiety, social anxiety, depression, bipolar disorder, PTSD, ADHD)

Psychosocial Rehabilitation & Recovery Center, VAMC, Perry Point, MD *Jan 2013–May 2013*
Supervisor: Mary Lambert, Ph.D.

- Facilitated skills training for veterans suffering from severe mental illnesses (i.e. schizophrenia, bipolar disorder, PTSD)
- Participated in patient evaluations with an interdisciplinary treatment team
- Assisted Veterans with community service projects
- Trained Veterans to become fully functional community members

LEADERSHIP & SERVICE

APA(Div 40) Association of Neuropsychology Students & Trainees Chapter Co-Representative *2017–2019*

- Elected to represent SDSU/UC San Diego JDP in Clinical Psychology Chapter
- Responsibilities: organized regular speakers and events that provide a forum for discussion of neuropsychology-related issues

Peer Clinical Supervisor
Neurocognition & Movement Lab *June 2016-2019*
UC San Diego School of Medicine | VA San Diego Healthcare System

- Provided peer supervision to post-baccalaureate and undergraduate research assistants
- Consulted with research assistants when challenges or clinical concerns arose in clinical research
- Revamped standardized procedures to assess suicidal ideation and risk in research participants
- Presented lectures and formalized training for assessing potential clinical concerns in research studies

Peer Clinical Supervisor
Psychology Clinic, San Diego State University *Mar 2016–June 2016*

- Provided peer supervision to more junior graduate students in clinical practicum placements

Student Research Mentor *2016–Present*

- Mentored undergraduate and post-baccalaureate research assistants in submission of scientific conference abstracts and presentations as well as career development
- Provided training and lectures in statistical methods
- Taught research assistants how to perform neuroimaging data collection and analysis as well as neuropsychological administration and scoring

Workshop Presenter *July 2016*

- "Camp Neuro": High School Student Outreach (http://www.campneuro.org/)
- Presented at 1-week summer day camp for high school students
- Responsibilities: provided information on brain health and career opportunities in neuroscience and psychology to high school students

PROFESSIONAL MEMBERSHIPS

Division 40 of The American Psychological Association, Student Member *Jan 2016–Present*
The Society for Neuroscience, Student Member *Feb 2013–Dec 2016*
Society for a Science of Clinical Psychology, Student Member *July 2016–2019*
Cognitive Neuroscience Society, Student Member *Oct 2014–2015*
Vision Sciences Society, Student Member *Nov 2013–2015*
Sigma Xi, The Scientific Research Society, Student Member *Jun 2013–Jun 2014*
Vice President of Psi Chi, University of Delaware *May 2012–May 2013*

PROFESSIONAL TRAINING

Mediation Analysis for Social Sciences Workshop, San Diego State University *Jan 2019*
Dialectical Behavior Therapy Training, UC San Diego Eating Disorders Center *Sept 2018*
Introduction to R Workshop, San Diego State University *Jun 2018*
CPR Certification, NIH, Bethesda, MD *Jun 2015*
Weschler Abbreviated Scale of Intelligence (WASI) Training, NIH *Aug 2014*
York Vision Science Summer School, Toronto, CA *Jun 2014*

- One week financed summer school on advances in vision science

Certification, AFNI Bootcamp, NIH, Bethesda, MD *Oct 2013*

- Intensive 5-day introduction to the use of AFNI for fMRI data analysis

BIO435: Current Trends in the Neurobiology of Mental Illness, NIH *Sept 2013–Dec 2013*
FMRI Summer Course, NIH, Bethesda, MD *Summer 2013*

- Introduction to fMRI and recent advances in neuroimaging at the NIH

Nuclear Magnetic Resonance Safety Training, NIH *Aug 2013*

COMPUTER SKILLS

Skilled at statistical data analysis using Excel and SPSS
Experienced in processing and analyzing fMRI data with AFNI
Adept in programming experiments with E-Prime, MATLAB, and Presentation
Proficient in Endnote and Zotero to manage citations

AD HOC STUDENT REVIEWER

Neuropsychology (2016)
Neuropsychological Rehabilitation (2015)

PEER-REVIEWED PUBLICATIONS

Sorg, S. F., Werhane, M. L., Clark, A. L., **Holiday, K. A.,** Merritt, V. C., Bondi, K. H., Jak, A. J., Schiehser, D. M., Delano-Wood, L. (*accepted*). PTSD Symptom Severity and Repetitive TBI Contribute to Elevated Memory Complaints in Veterans with Histories of Mild Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*

Nakhla, M. Z., **Holiday, K. A.,** Filoteo, J. V., Zlatar, Z. Z., Malcarne, V., Lessig, S., Litvan, I., & Schiehser, D. M. (2020). Informant-reported cognitive decline is associated with objective cognitive performance in Parkinson's disease. *Journal of the International Neuropsychological Society,* 1-11. doi:10.1017/S1355617720001137

Sorg, S. F., Merritt, V. C., Clark, A. L., **Holiday, K. A.,** Walsh, M., Werhane, M., Bondi, M., Schiehser, D. M., & Delano-Wood, L. (2020). Elevated Intra-individual Variability in Executive Functions in Veterans with Mild Traumatic Brain Injury and Associations with White Matter Microstructure. *Journal of the International Neuropsychological Society,* 1-10. doi:10.1017/S1355617720000879

Holiday, K. A., Clark, A. L., Merritt, V. C., Nakhla, M. Z., Sorg, S., Delano-Wood, L., & Schiehser, D. M. (2020) Response inhibition in Veterans with a history of mTBI: The role of self-reported complaints in objective performance. *Journal of Clinical and Experimental Neuropsychology*. doi: 10.1080/13803395.2020.1776847

Hoffman, J. E., Kim, M., Taylor, M., & **Holiday, K.** (2020). Emotional capture during emotion-induced blindness is not automatic. *Cortex,* 122, 140-158. doi: 10.1016/j.cortex.2019.03.013

Clark, A. L., Sorg, S. F., **Holiday, K. A.,** Bigler, E. D., Bangen, K. J., Bondi, M. W., Evangelista, N. D., Schiehser, D. M., & Delano-Wood, L. (2018). Fatigue is associated with global and regional thalamic morphometry in Veterans with history of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation, 33*, 382-392. doi: 10.1097/HTR.0000000000000377

Holiday, K. A., Pirogovsky-Turk, E., Malcarne, V. L., Filoteo, J. V., Litvan, I., Lessig, S. L., Song, D., & Schiehser, D. M. (2017). Psychometric properties and characteristics of the North-East Visual Hallucinations Interview in Parkinson's disease. *Movement Disorders Clinical Practice, 4*, 717-723. doi: 10.1002/mdc3.12479

Japee, S. A., **Holiday, K. A.**, Satyshur, M. D., Mukai, I., & Ungerleider, L. G. (2015). A role of right middle frontal gyrus in endogenous and exogenous visual attention: a case study. *Frontiers in Systems Neuroscience, 9*(23), 1-16. doi: 10.3389/fnsys.2015.00023

MANUSCRIPTS IN DEVELOPMENT

Holiday, K. A., Eyler, L. T., Sorg, S., Delano-Wood, L., & Schiehser, D. M. (*in preparation*). Cognitive Fatigue is Associated with Increased Neural Activation During Response Inhibition in Veterans with mild TBI.

Orff, H. J., **Holiday K. A.,** Kaufman C. N., Delano-Wood, L., & Schiehser D.M. (*in preparation*). Evaluation of Sleep Disturbance and Psychiatric, Health, and Quality of Life Functioning in Veterans with History of Mild Traumatic Brain Injury as Compared to Veteran Controls.

RESEARCH PRESENTATIONS

Holiday, K. A., Eyler, L. T., Sorg, S. F., Delano-Wood, L. D., & Schiehser, D. M. (2021). Cognitive Fatigue is Associated with Increased Neural Activation During Response Inhibition in Veterans with mild TBI. *JINS*. [*Accepted*].

Sorg, S. F., Merritt, V. C., Clark, A. L., **Holiday, K. A.,** Ozturk, E., Hanson-Bondi, K. L., Schiehser, D. M., & Delano-Wood, L. (2021) Greater Self-Reported Memory Difficulties are Associated with Lower Frontal and Temporal Lobe Cortical Thickness in Veterans with Histories of Mild Traumatic Brain Injury. *JINS*. [*Accepted*].

Vannini, M. B. N., **Holiday, K. A.,** Whiteley, N., Filoteo, J. V., & Schiehser, D. M. (2021) Sensitivity to Punishment and Reward in Non-Demented Individuals with Parkinson's Disease. *JINS*. [*Accepted*].

Holiday, K. A., Eyler, L. T., Sorg, S., Clark, A. L., Merritt, V. C., Delano-Wood, L., & Schiehser, D. M. (2020). Neural Correlates of Response Inhibition in Veterans with Mild-Moderate Traumatic Brain Injury with and without Subjective Complaints. *JINS*. [*Published Abstract*].

Nakhla, M. Z., **Holiday, K. A.,** Whiteley, N., Cabrera Tuazon, A. E., Mahmood, Z., Filoteo, J. V., Zlatar, Z. Z., & Schiehser, D. M. (2020). Parkinson's disease performance-based activities of daily living are associated with caregiver, not patient reports. *JINS*. [*Published Abstract*].

Walsh, M. J., **Holiday, K. A.**, Merritt, V. C., Clark, A. L., Sorg, S. F., Delano-Wood, L., & Schiehser, D. M. (2020). Cognitive and physical fatigue in Veterans with a history of mild Traumatic Brain Injury: Differential associations with regional gray matter volume. *JINS*. [*Published Abstract*].

Whiteley, N., Bashor, K. L., **Holiday, K. A.,** Cabrera Tuazon, A. E., Nakhla, M. Z., Das, A., Filoteo, J. V., Schiehser, D.M. (2020). Is fatigue associated with cognitive performance in Parkinson's disease? *JINS*. [*Published Abstract*].

Cabrera Tuazon, A. E., Whiteley, N., **Holiday, K. A.,** White B., Filoteo, J. V., Litvan I., & Schiehser, D. M. (2020). Novelty Seeking in Individuals with Parkinson's Disease with Mild Cognitive Impairment. *JINS*. [*Published Abstract*].

Holiday, K. A., Clark, A. L., Sorg, S. F., Merritt, V. C., Nakhla, M. Z., Delano-Wood, L., & Schiehser, D. M. (2019). The Relationship Between Subjective and Objective Disinhibition in Mild Traumatic Brain Injury. *Archives of Clinical Neuropsychology*. 34(6), 1021. [*Published Abstract*]. doi: 10.1093/arclin/acz034.156

Sorg, S. F., Walsh, M. J., Werhane, M., **Holiday, K.,** Clark, A. L., Merritt, V. C., Schiehser, D. M. & Delano-Wood, L. (2019). Clock-Checking During Prospective Memory Testing of Veterans with Blast-Related Mild Traumatic Brain Injury. *Archives of Clinical Neuropsychology*. 34(6), 999. [*Published Abstract*]. doi: 10.1093/arclin/acz034.136

Holiday, K. A., Eyler, L. T., Sorg, S. F., Clark, A. L., Merritt, V. C., Delano-Wood, L., & Schiehser, D. M. (2019). Neural activation during a working memory task in mild to moderate traumatic brain injury. *JINS*. 25(S1), 326. [*Published Abstract*]. doi: 10.1017/S1355617719000663

Sorg, S. F., Clark, A. L., Werhane, M., **Holiday, K. A.**, Merritt, V. C., Walsh, M. J., Jak, A. J., Hansen, K. L., Schiehser, D. M., & Delano-Wood, L. (2019). Reduced time-based prospective memory performance in Veterans with histories of mild traumatic brain injury and associations with white matter microstructure. *JINS*. 25(S1), 333. [*Published Abstract*]. doi: 10.1017/S1355617719000663

Walsh, M. J., Sorg, S. F., **Holiday, K. A.**, Werhane, M., Clark, A. L., Jessica L. Silverthorn, J. L., Merritt, V. C., Alexandra J. Weigand, A. J., Bondi, M. B., Schiehser, D. M., & Delano-Wood, L. (2019). Use of selective serotonin reuptake inhibitors moderates the relationship between hippocampal volume and verbal learning in mild traumatic brain injury. *JINS*. 25(S1), 336. [*Published Abstract*]. doi: 10.1017/S1355617719000663

Holiday, K. A., Clark, A. L., Merritt, V. C., Sorg, S., Delano-Wood, L., & Schiehser, D. M. (2018). Blast exposure moderates the association between post-traumatic stress disorder and cognition in

Veterans with mild or moderate traumatic brain injury. *Archives of Clinical Neuropsychology.* 33(6), 703–794. [*Published Abstract*]. doi: 10.1093/arclin/acy061.53

Holiday, K. A.,* Sorg, S., Clark, A. L., Evangelista, N. D., Delano-Wood, L., & Schiehser, D. M. (2018). Mild or moderate TBI moderates the relationship between depression symptoms and response inhibition in Veterans. *The Clinical Neuropsychologist.* 32(4), 548. [*Published Abstract*]. doi: 10.1080/13854046.2018.1453949
***Recognized with Griffenstein-Kaplan Merit Award for student presentation**

Sorg, S. F., Clark, A. L., Werhane, M., **Holiday, K. A.,** Walsh, M., Merritt, V. C., Bondi, M., Schiehser, D. M., & Delano-Wood, L. (2018). Reduced decision making in military Veterans with a history of mild blast-related Traumatic Brain Injury: Results from the Iowa Gambling Task**.** *The Clinical Neuropsychologist.* 32(4), 547. [*Published Abstract*]. doi: 10.1080/13854046.2018.1453949

Orff, H. J., Sorg, S. F., **Holiday, K. A.,** Clark, A. L., Delano-Wood, L., & Schiehser, D. M. (2018). Comparison of sleep disturbance and quantitative volumetric MRI measures in Veterans with and without history of mild traumatic brain injury (mTBI). *Sleep.* 41(S1). [*Published Abstract*]. doi: 10.1093/sleep/zsy061.299

Holiday, K. A., Clark, A. L., Sorg, S. F., Walsh, M. J., Strom, J., Delano-Wood, L., & Schiehser, D. M. (2018). Hippocampal volume independently predicts subjective memory complaints in mild traumatic brain injury. *JINS*. 24(S1), 137. [*Published Abstract*]. doi: 10.1017/S1355617718000528

Clark, A. L., Sorg, S. F., Merritt, V. C., Bangen, K. J., Bondi, M. W., **Holiday, K. A.,** Evangelista, N. D., Schiehser, D. M., & Delano-Wood, L., (2018). Blast exposure is associated with anterior cortical thinning in Veterans with mild traumatic brain injury. *JINS*. 24(S1), 219. [*Published Abstract*]. doi: 10.1017/S1355617718000528

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ABSTRACT OF THE DISSERTATION

Neural Correlates of Working Memory Performance in Veterans with Mild Traumatic Brain Injury

by

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Rationale. Mild traumatic brain injury (mTBI), identified as the "signature" wound of U.S. veterans, is often associated with cognitive complaints, which have been inconsistently linked to working memory (WM) deficits. Moreover, the relationship between WM and brain function in mTBI veterans is understudied. The overarching aim of the study was to examine WM performance and underlying neural mechanisms via fMRI in mTBI veterans.

Design. The study aimed to investigate: (1) whether veterans with mTBI demonstrated worse WM performance than veteran controls (VC); (2) whether brain activation in anterior cingulate cortex (ACC) and bilateral dorsolateral prefrontal cortex (DLPFC) during the WM task was

higher in veterans with mTBI compared to VC; and (3) whether greater brain activation was associated with better WM performance in veterans with mTBI. Seventy-eight veterans (44 mTBI; 34 VC) completed neuroimaging, a WM task (modified Paced Auditory Serial Addition Test), and neuropsychiatric symptom measures. Hierarchical linear regression models including demographic and psychiatric variables were employed.

Results. Veterans with and without mTBI did not differ in WM performance. However, groups differed in ACC activation during correct-incorrect trials (p=.003) after accounting for depression with lower activation in the mTBI group. Within veterans with mTBI, ACC correct-incorrect activation (p=.031) significantly predicted WM, controlling for education, such that higher activation was associated with higher false-alarm rate (worse performance). In VC, ACC activation (p=.030) during correct trials significantly predicted WM, such that higher ACC activation was associated with poorer performance; PTSD symptoms attenuated these associations, however.

Conclusions & Implications. Despite similar WM performance, veterans with mTBI exhibited relatively higher ACC activation on incorrect trials than veterans without mTBI. Greater ACC activation was associated with worse WM performance in both groups. Elevated ACC activation was evident only during correct-incorrect trials; thus, the ACC may act as a salience detector signaling increased activation to errors in mTBI. This project enhances our knowledge of WM and brain activation in veterans with mTBI. Findings from this study contribute to our understanding of chronic sequelae following mTBI, which could ultimately be utilized in intervention studies to decrease distress and disability following mTBI in this vulnerable population.

1. INTRODUCTION

1.1 Long-term Clinical and Cognitive Sequelae of Mild Traumatic Brain Injury

Traumatic brain injury (TBI) has been identified as the "signature" wound of military service members involved in the U.S. conflicts in Iraq and Afghanistan (Hoge et al., 2008). Estimates indicate 17-25% of deployed veterans sustained a concussion/mild TBI (mTBI) (Helmich et al., 2015). Veterans with mTBI often report multiple cognitive, emotional, and/or physical symptoms in the acute phase following injury (Iverson, 2005). Traditionally, the clinical course of mTBI was thought to result in full symptom recovery within days to months following the injury (Bigler, 2008). However, in some individuals, these injuries have been linked to chronic (> three months post injury) cognitive, psychiatric symptoms, and physical post-concussive symptoms (PCS) (Schwab et al., 2017). These symptoms, particularly cognitive and emotional symptoms, have been associated with poorer health outcomes, worse quality of life, and increased healthcare costs in mTBI veterans (Schiehser et al., 2015; Williams, McDevitt-Murphy, Murphy, & Crouse, 2017). Specifically, treatment of mTBI is exorbitantly expensive, with 1-year cost estimates at $32,000 per person with mTBI (Rosenfeld & Ford, 2010), and this cost increases for individuals with mTBI who endure persisting cognitive and emotional symptoms beyond the initial year. Further study of potential etiology of these persisting cognitive symptoms is vital to developing future treatment targets and decreasing health care costs associated with chronic mTBI.

1.2 Working Memory and mTBI

One of the most frequent cognitive complaints by mTBI veterans is poor working memory (McDonald, Saykin, & McAllister, 2012; Vanderploeg, Curtiss, & Belanger, 2005). Working memory (WM) is a multi-dimensional cognitive process that includes the ability to

continuously control, regulate, and actively maintain mental representations of task-relevant information (Baddeley, 1992; Miyake & Shah, 1999; Thomas et al., 2017). WM evolved from the concept of unitary short-term memory, which referred to the temporary storage of information over brief periods of time (Baddeley, 1992; Linden, 2007). The current definition of WM, however, includes the necessity for both simultaneous storage and processing of information (Baddeley, 1992). Baddeley and Hitch (1974) proposed the seminal multi-component WM model, suggesting that WM can be divided into three subcomponents: (1) the visuospatial sketch pad, which manipulates visual images, (2) the phonological loop, which stores and rehearses speech-based information, and (3) the central executive, which serves as an attentional control system for the other two subsystems. In addition to controlling these two subsystems, the central executive is essential for integrating stored material into long term memory and executive functions responsible for comparison, manipulation, and storage of this material (Rottschy et al., 2012). Importantly, the central executive is evoked during *tasks with high cognitive demands* and is instrumental in attentional focusing, divided attention, and attentional switching (Baddeley, 2002).

Most measures designed to examine the central executive of WM simultaneously tap into various component processes, and performance on such tasks has been directly associated with disability in chronic mTBI (McAllister, Flashman, McDonald, & Saykin, 2006). Previous research suggests that WM is particularly vulnerable to mTBI (Bigler & Maxwell, 2012; McDonald, Flashman, & Saykin, 2002), and WM tasks may be one of the most sensitive measures of cognitive dysfunction in the chronic phase following mTBI (Cicerone & Azulay, 2002; Frencham, Fox, & Maybery, 2005). Due to the demands that it places on the central executive, one WM task called the Paced Auditory Serial Addition Test (PASAT), has

demonstrated sensitivity to cognitive impairments following mTBI (Cicerone & Azulay, 2002; Dean & Sterr, 2013; O'Jile et al., 2006; Vanderploeg et al., 2005). One of the brain regions that plays a critical role in the central executive of WM, the dorsolateral prefrontal cortex (DLPFC), is often impacted by mTBI and thought to be instrumental to performance on the PASAT (Hillary, 2008; McAllister et al., 1999; McAllister et al., 2001). The DLPFC is thought to underlie the central executive component of WM that allocates processing resources to adequately match processing load (McAllister et al., 2001). It has been suggested that injuries to the DLPFC as a result of mTBI may diminish the central executive's capacity to appropriately allocate resources to cognitively demanding WM tasks (McAllister et al., 2001). According to this theory, the WM problems in chronic mTBI may actually be related to difficulties with adequately matching cognitive resources to processing load (McAllister et al., 2001).

Despite these vulnerabilities and frequently endorsed difficulties with WM in individuals with chronic mTBI (denoted as mTBI herein), considerable debate exists regarding whether chronic objective cognitive deficits result from mTBI compared to those without a history of mTBI (Carroll et al., 2014; Rohling et al., 2011). In civilians, several studies have failed to find differences in WM performance between individuals with mTBI and healthy controls (Chen et al., 2012; Chen et al., 2004; Dean, Sato, Vieira, McNamara, & Sterr, 2015; van der Horn et al., 2016; Wylie et al., 2015). However, other civilian studies have found that mTBI is associated with diminished WM performance (Bohnen, Jolles, & Twijnstra, 1992; Dean & Sterr, 2013; Helmich et al., 2015; Kumar, Rao, Chandramouli, & Pillai, 2013; McAllister, Flashman, Sparling, & Saykin, 2004; Smits et al., 2008). According to McAllister's theory, these discrepant findings may be due to differences in task demand that require varying allocation of resources.

1.3 WM Task Demands

Test selection and associated task demand appear to be critical to WM assessment. Previous studies in chronic mTBI have demonstrated that WM deficits were only detected with highly demanding tasks (Bryer, Medaglia, Rostami, & Hillary, 2013; Dean & Sterr, 2013). Furthermore, complex measures that combined demands on WM and processing speed were found to be the most sensitive to deficits following post-acute mTBI (Cicerone & Azulay, 2002). One such widely used and well-validated test of WM and processing speed with high cognitive demand is the PASAT (Gronwall, 1977; Tombaugh, 2006). The PASAT has demonstrated clinical validity (Cicerone & Azulay, 2002; Dean & Sterr, 2013; O'Jile et al., 2006; Vanderploeg et al., 2005) and relationship to functional outcomes in mTBI (Gronwall, 1977; Woods, Wyma, Herron, Yund, & Reed, 2018). The design of this task does not isolate component processes within WM, per se, but rather focuses on the entire WM-related neural system governed by the central executive in order to better identify brain regions likely related to task performance deficits in mTBI. A previous study implemented a modified version of the PASAT and found that chronic mTBI civilians, both with and without PCS, performed significantly worse on the PASAT than civilian controls (Dean & Sterr, 2013). Indeed, the PASAT has demonstrated the highest overall efficiency, or balance between sensitivity and specificity, for identifying clinically impaired functioning in mTBI (Cicerone & Azulay, 2002), and the PASAT is routinely used to guide clinical decisions, such as return to work post-injury (Gronwall, 1977; Woods et al., 2018). The traditional PASAT involves auditory perception of numbers and production of verbal responses. Unfortunately, movement of the jaw required to speak aloud in the scanner has been shown to result in artifacts in fMRI signal (Seto et al., 2001). In order to avoid these potentially confounding signal artifacts, a version of the task was modified for visual

presentation with responses via button box. This visually presented PASAT task has been evaluated in comparison to the traditional auditory PASAT, and the visually modified version demonstrated comparable results (Fos, Greve, South, Mathias, & Benefield, 2000). Therefore, a version of the PASAT modified for visual presentation (mPASAT) was selected as the cognitively demanding measure to examine WM performance in mTBI veterans in the current study.

1.4 Clinical Characteristics of Veterans

Assessments of objective WM deficits in veterans following combat-related chronic mTBI are complicated by challenges that are not often encountered in civilian studies. Combat-related mTBI frequently occurs in the context of psychological trauma (Hoge et al., 2008; Lew et al., 2008). Not surprisingly, veteran mTBI has a high incidence of comorbidity with psychiatric disorders, especially post-traumatic stress disorder (PTSD; Lew et al., 2008) and depression (Hoge et al., 2008; Spencer, Drag, Walker, & Bieliauskas, 2010). In fact, many studies with mTBI veterans suggest that discrepancies in WM task performance between mTBI veterans and veteran controls may actually reflect psychiatric comorbidity as opposed to mTBI status (Dolan et al., 2012; Simmons & Matthews, 2012). Therefore, it is vital to account for the influences of psychiatric distress (e.g., PTSD, depression) when examining cognition, specifically WM, associated with mTBI in a veteran population.

Only a handful of studies have examined WM in mTBI veterans, with inconsistent results (Dolan et al., 2012; Vanderploeg et al., 2005). A recent study found that mTBI veterans without psychiatric diagnoses demonstrated diminished WM accuracy and slower reaction time on trials with increased WM demand in comparison to veteran controls (Huang et al., 2018). Another study found that veterans with mild-to-moderate TBI (mmTBI) performed significantly worse on

a highly-demanding WM task, but not a low-demand task, compared to mmTBI civilians; the latter performed similarly to veterans and civilians without a history of TBI (Newsome et al., 2015). These findings underscore the necessity of evaluating WM task performance in veterans and matched comparison participants with particular attention to task demand. Importantly, assessing characteristics that are unique to veteran mTBI in conjunction with WM is essential to identify potential mechanisms of WM deficits in addition to potential treatment targets.

Another confounding factor in assessing cognition, specifically WM, in mTBI veterans is the heterogeneity of TBI injury characteristics (e.g., injury mechanism). The majority of mTBI studies have been conducted on civilians with blunt force injuries, such as motor vehicle accidents or sports concussions (Andriessen et al., 2011; Newsome et al., 2015). It has been established that head impact, or blunt-force injury, causes a rapid acceleration/deceleration of the head that may result in coup-contrecoup contusions to the frontal lobes (MacDonald, 2012). In addition to these direct insults, the forces associated with head impact may induce mechanical deformation of the vulnerable axons of the brain through stretching, shearing, and twisting actions (Bigler & Maxwell, 2012; McDonald et al., 2002). Some of the brain's most vulnerable axons subserve the frontal-subcortical systems responsible for WM, and the majority of mTBIs involve disruption of these axons at some level (Bigler & Maxwell, 2012; McDonald et al., 2002).

In addition to the blunt-force trauma described above, combat-related mTBI frequently results from blast-force injury, specifically improvised explosive devices or grenades (Hoge et al., 2008; Tanielian et al., 2008). According to the Department of Veteran's Affairs, the majority of mTBIs reported by combat veterans are associated with blast exposure, yet research on blast-exposed mTBI in humans is limited (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009;

Karr, Areshenkoff, Duggan, & Garcia-Barrera, 2014), particularly in relation to long-term cognitive outcomes of blast mTBI (Greer, Sayer, Koeller, Velasquez, & Wilt, 2018). Blast explosions induce a myriad of injuries: primary blast injuries occur when the over-pressurization wave hits the body impacting the brain and transmitting pressure through the skull and cervical blood vessels after compression of the thorax (Mu, Catenaccio, & Lipton, 2017), secondary blast injuries may be induced by wind propelling shrapnel or debris likely to cause blunt or penetrating head injuries, tertiary blast injuries result from the body being propelled by a blast into other objects, quaternary blast injuries denote the side effects of these explosions including environmental toxins, bodily injuries, and infections (Greer et al., 2018). Although animal studies have examined the isolated effects of these four mechanisms of blast injury, these mechanisms are not mutually exclusive and rarely occur in isolation in humans (Mu et al., 2017). For the purposes of clinical studies in humans, mechanism of mTBI is typically characterized into three categories: blast only, blunt only, or blast and blunt. A systematic review of the blast-related mTBI literature found the clinical and functional outcomes to be comparable between blast and non-blast-related mTBI (Greer et al., 2018), but additional research on the relationship between blast exposure and cognition is necessary.

A meta-analysis of the effects of blast-related mTBI found deficits in cognitive domains including WM, inhibition, set-shifting, verbal learning and memory, complex attention, and processing speed (Karr et al., 2014). Additionally, another study compared blast to blunt injury in mTBI veterans and found that the blast group demonstrated poorer WM as measured by PASAT performance than the blunt mTBI veterans (Mendez et al., 2013). These findings demonstrate that mTBI in veteran populations may be unique and associated with clinical injury characteristics (e.g., injury mechanism, psychiatric comorbidity) that differ from civilian mTBI.

Thus, further study examining these characteristics in a purely mild TBI veteran sample is needed. Importantly, if clinical injury characteristics differentially influence long-term negative outcomes in veteran compared to civilian samples, assessing these characteristics in a veteran population may be vital as these characteristics are likely to influence cognitive rehabilitation strategies and treatment outcomes.

1.5 Neural Activation as a Measure of WM in mTBI

In addition to clinical injury characteristics, the neural mechanisms of WM performance also merit exploration. Functional magnetic resonance imaging (fMRI) provides the opportunity to elucidate neural correlates of WM performance in mTBI (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; McDonald et al., 2012; Wilde et al., 2015). Through fMRI, the activation of certain brain regions can be detected by measuring the ratio of deoxygenated to oxygenated blood, or blood-oxygen-level-dependent (BOLD) response (Graner, Oakes, French, & Riedy, 2013). This BOLD response can be utilized as a measure of engagement of a brain region during a WM task.

Previous neuroimaging studies reveal substantial overlap between the neural circuitry involved in regions most vulnerable to TBI and those underlying WM performance (Bigler & Maxwell, 2012; McDonald et al., 2002). A large body of fMRI literature has examined the neural correlates of WM, yet the field has not reached a consensus regarding the regions consistently involved in WM (Rottschy et al., 2012). It is generally accepted that WM activates a frontoparietal network involving the DLPFC, anterior cingulate cortex (ACC), and posterior parietal cortex (Chai, Abd Hamid, & Abdullah, 2018). The DLPFC is thought to serve as an executive control region, instrumental in integrating information for decision making as well as maintaining and updating temporarily stored information during WM (Chai et al., 2018; Kim,

Kroger, Calhoun, & Clark, 2015). The ACC has been implicated in attentional control and conflict monitoring, and it has been shown to adjust and adapt to received input based on task demands (Chai et al., 2018; Hillary, 2008). The posterior parietal cortex has been associated with mediating information storage during WM (Smith & Jonides, 1998). Although these three brain regions are most commonly referenced in regard to WM, many brain areas outside of these regions are integral to the WM network.

Additional regions with important implications for WM include frontal cortex regions such as the ventrolateral prefrontal cortex as well as the superior, middle, and inferior frontal gyri (IFG) (Emch, von Bastian, & Koch, 2019; Linden, 2007; Rottschy et al., 2012; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). The ventrolateral prefrontal cortex is often associated with maintenance of information in WM (Graner, 2013). Activation of the superior frontal gyrus has also been associated with WM high task load in addition to spatial cognition (Boisgueheneuc et al., 2006). The right middle frontal gyrus is thought to be a site of convergence between the ventral and dorsal attention networks and play a role in reorienting attention from bottom-up to top-down attentional control (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). The dorsal attention network has been localized to dorsal frontoparietal regions, and it is generally accepted as the network responsible for top-down or goal directed spatial attention (Corbetta, Patel, & Shulman, 2008). Less information is known about the ventral attentional network, which has been localized to ventral fronto-parietal brain regions and is thought to be responsible for signals that interrupt ongoing processes and divert attention to an environmental stimulus (Japee et al., 2015). Thus, the right middle frontal gyrus may be particularly involved in tasks invoking the visuospatial sketchpad, and it has been proposed as the circuit breaker that switches attentional control from a bottom-up stimulus driven attention

back to a top-down, goal directed attentional focus (Japee et al., 2015). The IFG is thought to be influential in the ventral attentional network, and increased activation of the IFG has been associated with increased task load in healthy controls (Emch et al., 2019; Rottschy et al., 2012). In addition to these regions generally activated by WM tasks, an fMRI study using a visually modified version of the PASAT, similar to the task implemented in the current study, revealed activations in the DLPFC, ACC, ventrolateral prefrontal cortex, left intraparietal sulcus, and left inferior parietal lobule (Audoin et al., 2005). Notably, there is evidence to suggest that these brain regions critical for WM are also quite susceptible to damage from mTBI (Bigler & Maxwell, 2012; McDonald et al., 2002). Specifically, Hillary (2008) conducted a review of fMRI studies examining WM dysfunction following TBI, which revealed increased activation in the DLPFC and ACC as a primary finding.

1.6 Neuroimaging of High WM Task Demand

The majority of WM fMRI studies in chronic mTBI have been conducted in civilians and have observed discrepant findings, revealing predominantly increased (Dean et al., 2015; Hillary, 2008; McAllister et al., 1999; McAllister et al., 2001; Pardini et al., 2010; Woytowicz, Sours, Gullapalli, Rosenberg, & Westlake, 2018), and occasionally decreased (Chen, Johnston, Collie, McCrory, & Ptito, 2007; Chen et al., 2004; Gosselin et al., 2011), activation in WM regions compared to controls. One proposed explanation for the discrepant activations detected using fMRI during WM tasks is due to differing task demand (Bryer et al., 2013). Few fMRI studies in mTBI have explicitly examined the relationship between task load and BOLD activation within the same study (Bryer et al., 2013). However, a meta-analysis that examined task load across three different mTBI studies revealed that hyperactivation was associated with cognitively demanding tasks whereas hypoactivation was observed in studies with lower cognitive demands

(Bryer et al., 2013). Thus, implementing a task with high cognitive demand is crucial to not only detect possible WM deficits as described above, but also to examine neural activation during the WM task and relationship to performance accuracy. Importantly, neural activation associated with WM tasks with *high cognitive load,* such as the mPASAT, have yet to be explored in mTBI veterans.

When cognitively demanding tasks were implemented in civilian studies, the most common findings included higher activation in the ACC (Pardini et al., 2010) and DLPFC (Dean et al., 2015; Hillary, 2008; McAllister et al., 1999; McAllister et al., 2001; Woytowicz et al., 2018) among individuals with mTBI compared to controls. Specifically, Dean et al. (2015) examined fMRI during presentation of a modified PASAT with varying levels of task demand in eight mTBI civilians with PCS and nine civilian controls. They found higher activation in bilateral IFG, right DLPFC, and ACC as well as lower activation in posterior cingulate cortex, medial frontal cortex, and bilateral parietal regions in the mTBI civilians in comparison to civilian controls (Dean et al., 2015). Importantly, these group differences were only observed at high levels of task demand.

In contrast, one cohort of researchers (Chen et al., 2007; Chen et al., 2004; Gosselin et al., 2011) has consistently found decreased activation in the DLPFC in mTBI civilians in comparison to controls. However, these studies implemented visual and verbal WM tasks with low cognitive demand, which likely tapped the visuospatial sketch pad and phonological loop respectively, rather than the central executive that is presumed to be recruited during tasks of high cognitive demand.

The increased activation often detected in mTBI is hypothesized to serve as a compensatory mechanism to facilitate adequate WM performance, even when task performance

is equivalent across groups (Chen et al., 2012; McAllister et al., 1999; McAllister et al., 2001). Moreover, it is postulated that at higher WM task loads, those with a history of mTBI and presumably damaged neural circuits require the recruitment of additional processing reserves to compensate for processing inefficiencies (McAllister et al., 2001). Those without a history of TBI, however, are not as challenged by the task demands and thus, do not require processing reserves to complete the task (McAllister et al., 2001). Another theory suggests that there may be a dedifferentiation, or decrease in the specialization of brain networks following TBI (Bernier et al., 2017). As a result of this dedifferentiation, there may be increased recruitment of neural resources outside of brain regions anticipated for task involvement. Despite the prevalence of these theories, direct correlations of brain activation and task performance are rarely conducted in mTBI (Bryer et al., 2013; Hillary, 2008). Examining the association between brain activation and task performance is crucial to determining whether neural recruitment may serve as a compensatory mechanism as opposed to dedifferentiation or poor regulation of neural resources following mTBI (Bryer et al., 2013; Hillary, 2008).

1.7 Neuroimaging and mTBI Clinical Characteristics

In addition to examining brain-behavior relationships, accounting for the unique clinical characteristics (e.g., psychiatric distress, injury mechanism) of veteran populations could augment our understanding of the underlying neural mechanisms associated with WM task performance deficits in mTBI. Despite high levels of comorbidity between psychiatric symptoms (i.e., PTSD, depression) and mTBI (Fonda et al., 2017; Lippa et al., 2015), very few of the previous neuroimaging studies in mTBI have examined PTSD or depressive symptoms. Previous fMRI studies in mTBI have found that co-occurring PTSD (Scheibel et al., 2012; Scheibel et al., 2015; Simmons & Matthews, 2012) and depressive symptoms (Chen, Johnston, Petrides, &

Ptito, 2008; Matthews et al., 2011) are associated with diminished activation in WM regions, predominantly the DLPFC. Thus, it is essential to account for psychiatric symptoms when determining unique neural correlates of WM deficits in mTBI.

As described in detail above, the blast exposures associated with combat and subsequent mTBIs involve an entirely different mechanism of injury than blunt mTBIs and may impact different brain regions. Previous neuroimaging studies have found that blast forces impact similar regions as blunt forces with heightened impact on frontal brain regions, anterior temporal lobes, and frontal-subcortical circuits (Bogdanova & Verfaellie, 2012; Mendez et al., 2013). A review of the limited neuroimaging literature in blast-related mTBI found that fMRI studies generally reported diffuse changes in frontal, parietal, temporal, and cingulate changes (Mu et al., 2017). A positron emission tomography study that compared blast to blunt mTBI veterans found that the blast group demonstrated poorer PASAT performance as well as hypometabolism in the right superior parietal cortex and left medial frontal cortex than blunt mTBI veterans, thought to reflect degradation of a frontal-parietal attentional network (Mendez et al., 2013). Due to the paucity of blast-related mTBI studies, the influence of blast on cognition and brain activation merits further exploration (Greer et al., 2018; Mu et al., 2017).

Prior studies have found that mTBI civilians with self-reported PCS performed significantly worse on WM tasks than mTBI civilians without self-reported PCS, who performed similarly to civilian controls (Chamelian & Feinstein, 2006; Smits et al., 2009; Sterr, Herron, Hayward, & Montaldi, 2006). Smits et al. (2009) found hyperactivation in mTBI with PCS in comparison to mTBI without PCS, and the hyperactivation was that activation was associated with increased WM loads and greater severity of PCS. The civilian studies discussed above examined general measures of PCS; however, psychometric studies of general PCS measures in

veterans revealed that these measures were more strongly associated with psychiatric symptoms levels (i.e., PTSD, depression) than TBI status (Franke, Czarnota, Ketchum, & Walker, 2015; King et al., 2012). Thus, the use of the FrSBe, a comprehensive measure specifically designed to assess subjective complaints of executive dysfunction, could enable selection of a subgroup of mTBI veterans with subjective complaints of executive function that will be supported by objective WM performance above and beyond the influence of psychiatric symptom levels.

To our knowledge, only one fMRI study has examined brain activation in mTBI veterans during a WM task (Newsome et al., 2015), and this delayed match-to-sample task was of low cognitive demand. Specifically, Newsome and colleagues found decreased activation in the caudate, which is functionally connected to the DLPFC, in mild-moderate TBI veterans compared to mild-moderate TBI civilians (Newsome et al., 2015). These findings support the necessity of studying WM and task-related neural activation in mTBI veterans in parallel to the existing civilian studies. To our knowledge, the current study is the first to use fMRI to examine neural correlates of a WM task with high cognitive demand in mTBI veterans.

1.8 Specific Aims

The overarching aim of this project was to examine the relationship between WM performance and underlying neural mechanisms via fMRI in mTBI veterans. Specific aims and hypotheses are detailed below.

Aim 1: To investigate WM performance using a cognitively demanding task in mTBI veterans compared to veteran controls (VC).

Hypothesis 1: mTBI veterans would perform significantly worse on a WM task (mPASAT) than VC while controlling for psychiatric symptom levels.

Aim 2: To examine brain activation in mTBI compared to VC during the WM task.

Hypothesis 2: mTBI veterans would demonstrate *increased* levels of brain activation (BOLD response) in WM regions (DLPFC, ACC) compared to VC during the mPASAT while controlling for psychiatric symptom levels.

Aim 3: To evaluate the association between brain activation and WM (mPASAT) performance in mTBI veterans compared to VC.

Hypothesis 3: *Greater* WM region activation (DLPFC, ACC) would be associated with *better* WM performance in mTBI while controlling for psychiatric symptom levels.

Exploratory Aim: To explore the relationship between clinical injury characteristics (e.g., psychiatric comorbidity, mechanism of injuries) and neural activation as well as the association of neural activation with WM performance in mTBI. Furthermore, we proposed to explore brain activation in these *a priori* regions as mediators of any relationship between group and mPASAT accuracy.

INTRODUCTION ACKNOWLEDGEMENTS

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2. METHODS

2.1 Participants & Recruitment

The proposed study utilized baseline data from an existing larger longitudinal study that examined the neurocognitive effects of fatigue in traumatic brain injury (VA CSR&D CDA-2-065-10S [PI: Schiehser] 11/01/2010–10/31/2015). Although the parent project is a longitudinal cohort design, the proposed project examined only baseline data (acquisition completed), to ensure feasibility and timely completion of all data analyses. Seventy-eight Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) service members between the ages of 18 and 50 were recruited for this study. Participants were recruited primarily from the VASDHS Polytrauma Clinic, the Center of Excellence for Stress and Mental Health (CESAMH), Physical Medicine & Rehabilitation (PM&R) service, the Neuropsychological Assessment Unit, and the TBI/Cognitive Rehabilitation Clinic. Study groups included veterans with a history of mTBI (n=44) and veterans without a history of TBI (VC; n=34).

2.1.1 Inclusion Criteria

The following Department of Defense and VA TBI Task Force guidelines (Management of Concussion/mTBI Working Group, 2009) were used to determine eligibility for the mTBI group: (1) presence and duration of loss of consciousness (LOC) ≤ 30 minutes; (2) presence and duration of alteration of consciousness (AOC) ≤ 24 hours; and/or (3) presence and duration of post-traumatic amnesia (PTA) of ≤ 24 hours. Glasgow Coma Scale (GCS) of no less than 13 for all injuries is also listed in the Department of Defense guidelines. However, the majority of veteran mTBIs occurred during military deployments, and physicians were rarely available or able to perform an evaluation including GCS at the time of injury in this setting. Consequently,

duration of LOC and/or AOC was used to determine TBI severity for the current study. Both primary blunt-force and blast-force trauma mTBIs were included. VC were included in the study only if they had no history of head injury.

2.1.2 Exclusion Criteria

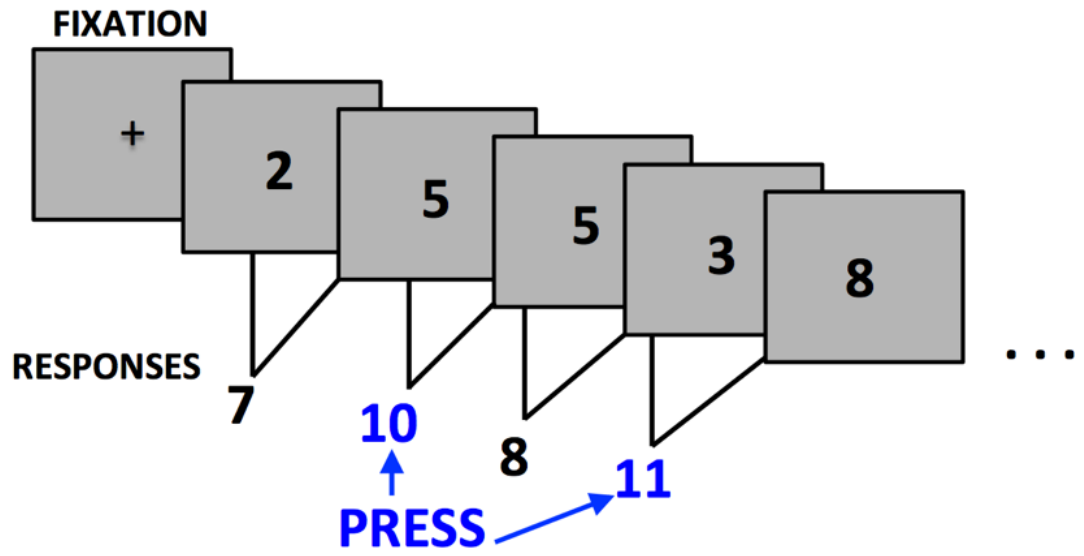
All participants were excluded if they met guidelines (Management of Concussion/mTBI Working Group, 2009) for moderate or severe TBI: (1) LOC > 30 minutes; (2) AOC or PTA > 24 hours. Additional exclusion criteria for the entire sample included the following: (1) current active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; (2) current or past history of a significant medical condition (e.g., seizures, multiple sclerosis); (3) hearing or vision impairment that interferes with testing; (4) any contraindications to magnetic resonance scanning (MRI; e.g., shrapnel, ferromagnetic implants); (5) failure to complete or pass effort testing as measured by the Test of Memory Malingering (TOMM; Tombaugh, 1996) using the criteria of Trial 2 score < 45 (Haber & Fichtenberg, 2006); (6) current substance/alcohol abuse or dependence as indicated by diagnostic clinical interview; and (7) a positive toxicology or psychostimulant screen as measured by the Rapid Response 10-drug Test Panel.

2.2 Measures

2.2.1 mPASAT: Primary Outcome Measure of WM

We administered a version of the PASAT (Gronwall, 1977) modified for visual presentation (mPASAT) to facilitate administration during fMRI data collection. Single digit numbers between 1 and 9 inclusive were presented on the screen one at a time during an fMRI scan (see Figure 1). Participants were instructed to add the first number to the second and the second number to the third and so on, and rapidly press one of two buttons if the sum equaled one of the target numbers (i.e., 10 or 11). The mPASAT consisted of 3 runs, each lasting 4 min

32 seconds, with 120 trials per run. Accuracy and reaction time data were logged with a button box designed for MRI studies. mPASAT performance was measured by d-prime (d'), which was calculated as the z-score of the hit rate minus the z-score of the false alarm rate.



Participants instructed to mentally add sequentially presented numbers and press a button (**blue**) in response to sum equating to target number.

Figure 1. Schematic representation of mPASAT.

2.2.2 Visual Monitoring: Control Task

The Visual Monitoring task presentation and data recording was identical to the mPASAT, and visual monitoring was performed immediately prior to the mPASAT in the scanner. Participants were instructed to press a button every time the digit 7 was presented on the screen. The visual monitoring task consisted of 1 run lasting 3 min 30 seconds with 60 trials and a rest/fixation period per run. Performance in the form of percentage correct button presses during the visual monitoring control task were examined for each participant, and any participant who performed at less than 75% accuracy (n = 4) were excluded from analyses due to low task engagement.

The following measures were obtained as part of a standard assessment battery under the parent study.

2.2.3 TBI History and Severity

TBI diagnosis was verified via the modified version of the VA's semi-structured clinical interview for TBI identification (Vanderploeg, Groer, & Belanger, 2012). All participants were comprehensively assessed for head injuries with this measure. Key aspects of traumatic events including mechanism of injury (i.e., blunt or blast force), number of head injuries sustained, and important diagnostic data (e.g., duration of LOC, AOC, PTA) were obtained with this measure. Blast and blunt force mechanisms of injury were assessed separately for any military-related head injuries. For all blast injuries, participants were asked to estimate distance and direction from which the blast was initiated (e.g., front, back, left right) as well as total number of blast exposures.

2.2.4 Neuropsychiatric Symptom Measures

Neuropsychiatric symptomatology was assessed via various psychiatric self-report measures, which corresponded to criteria in the Diagnostic and Statistical Manual or Mental Disorders – Fourth Edition (DSM-IV). Higher scores are suggestive of worse outcomes.

<u>The PTSD Checklist – Military Version (PCL-M)</u>

The PCL-M is a 17-item questionnaire that was specifically designed to assess PTSD symptoms related to stressful military experiences in service members (Weathers, Litz, Herman, Huska, & Keane, 1993). Participants were instructed to provide ratings for the severity of each symptom on a 5-point scale, ranging from "not at all" (1) to "extremely" (5). The Interagency TBI Outcomes Workgroup recommended the PCL-M as a reliable and valid measure of

assessing PTSD in veterans with mTBI to address primary clinical research outcomes (Wilde et al., 2010).

The Beck Depression Inventory-II (BDI-II)

The BDI-II is a 21-item questionnaire of depression severity, in which participants were asked to rate how strongly they have identified with each symptom over the past two weeks (Beck, Steer, & Brown, 1996). For each symptom, four statements were sequenced by increasing severity on a scale of 0 to 3. Research has demonstrated support for the clinical utility of the BDI-II in the identification of depressive symptoms in acute and chronic TBI (Homaifar et al., 2009; Rowland, Lam, & Leahy, 2005).

The Frontal Systems Behavior Scale (FrSBe)

The FrSBe – self report version is a 46-item questionnaire that examines self-reported cognitive complaints (Grace & Malloy, 2001) and was developed to assess disturbances in frontal systems behavior (i.e., frontal dementia, brain injury, stroke). Participants were instructed to provide ratings for how much they have identified with each symptom on a scale ranging from "almost never" (1) to "almost always" (5). The FrSBe contains three subscales: Apathy, Disinhibition, and Executive Function, and the Executive Function subscale may be analyzed in an alternative strategy of this study. FrSBe subscale development was driven by theory, and the Executive Function subscale was designed to measure behaviors associated with frontally-mediated brain circuits governed by the DLPFC (Cummings, 1993). Thus, the Executive Function items assess behaviors characterized by difficulties with WM, sustained attention, organization, planning, and problem solving (Carvalho, Ready, Malloy, & Grace, 2013; Cummings, 1993). The FrSBe has also demonstrated validity for behavioral symptoms corresponding with chronic TBI (Juengst, Kumar, Arenth, & Wagner, 2014; Reid-Arndt, Nehl, &

Hinkebein, 2007). Although the FrSBe has not been directly compared to mPASAT performance in mTBI, elevations in the Executive Function subscale of the FrSBe have been significantly negatively associated with PASAT performance in patients with a neurological disease that is thought to impact the frontal lobes (i.e., multiple sclerosis) (Goverover, Chiaravalloti, & DeLuca, 2005).

2.2.5 Neuropsychological Measures

A neuropsychological battery containing the following measures was administered: Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-III/IV) Coding and Digit Span (Wechsler, 2008) as well as Delis-Kaplan Executive Function System (D-KEFS) TMT (Delis, 2001). Given that the mPASAT used in the current study is a novel task, correlations between performance on the mPASAT and traditional neuropsychological measures were conducted. The above measures were selected based on findings from a previous study by Tombaugh (2006), who performed a similar analysis using a visually modified PASAT and found significant correlations with Digit Span (forward, backward, and total) as well as Trails A and B. Additionally, the neural activation during the mPASAT was correlated with these other neuropsychological measures that tap similar domains of WM, sustained attention, and processing speed to examine whether cognitively demanding WM tasks are required to detect brain changes in mTBI.

2.2.6 Participant Screening

Effort/Validity

The TOMM (Tombaugh, 1996) was administered to ensure optimal effort (Trial 2 score ≥ 45). This cutoff score has demonstrated adequate sensitivity to effort regardless of cognitive impairment in individuals with TBI (Haber & Fichtenberg, 2006).

Drug Screen

All participants provided a urine sample for confidential drug toxicology screening measured by a Rapid Response 10-drug Test Panel. Participants who tested positive for drug use were excluded from study. Four participants were excluded from the study due to recent drug use. Two of these veterans self-reported this use during clinical interview, and two participants were excluded due to positive toxicology screening.

Demographic Information

Employment history, medical history, and demographic information were collected for each participant via a demographic/background history questionnaire.

2.3 Scanning Parameters

Three-plane Localizer

Mid-sagittal and axial localizer slices confirmed whole brain coverage prior to imaging.

Structural MRI

A whole brain (1.2 mm slice thickness, FOV=24 cm) T1-weighted (3D inversion recovery fast spoiled gradient echo, TE=min/full, flip angle=8°, matrix=192) sequence was sagittally acquired. The presence of any gross structural defects was ruled out in all participants.

fMRI

BOLD functional activity was acquired using an 8-channel brain array coil during a series of T2* weighted axially acquired echo-planar imaging (EPI) sequences (TE=30ms, TR=2s, flip angle 90°, FOV=24 cm, 64x64 matrix, 3.43 x 3.43 x 2.6 mm voxels with 1.4 mm gap, 30 slices). Tasks were synchronized with the scanner.

Field Maps

Field maps were acquired to correct field inhomogeneities in fMRI acquisitions by minimizing warping and signal dropouts (Jezzard & Balaban, 1995; Reber, Wong, Buxton, & Frank, 1998).

2.4 Image Processing.

All data were processed and analyzed using Analysis of Functional NeuroImages (AFNI).

2.4.1 fMRI Preprocessing

The first 2 unwanted TRs were removed, and field map correction was performed. Slice timing correction aligned all volumes to one time point and extract the volume registration base. The individual anatomical scan was aligned with the EPI registration base and then registered to standard atlas space. The EPI data was motion corrected and transformed into standard space. Spatial smoothing to enable group comparison of EPI data was conducted by blurring each volume by 4.0mm. A full mask of the data set was created. Each voxel in the time series was scaled to have a mean of 100. Individual time series data for each participant was processed using a multiple regression model with a generalized least-squares time series fit with temporal auto-correlation structure. Regression analyses included stimulus timing and motion parameters as regressors. Each trial was coded individually for each subject depending on the participant's behavioral response to the stimulus. Thus, four orthogonal regressors of response types were included: (1) correct (hits), (2) null (no button pressed when no button press required), (3) missed (omitted button press when button press required), and (4) error (incorrect button pressed or button press on null trial). The incorrect trials were examined and were composed of both missed and error trials. The contrast containing correct and null responses (i.e., correct+null) served as the primary outcome measure of interest. This contrast was selected because it contains

all trials in which the participants provided (or withheld) a response accurately. Trials in which participants incorrectly responded, either through missed responses or errors, were explored separately in alternative analyses. Additionally, six nuisance regressors were used to account for residual motion (i.e., roll, pitch, and yaw; x, y, and z). Changes from the baseline established in the BOLD signal during the mPASAT trials were calculated at each voxel.

2.4.2 Functional Activation Analyses

First, we manually selected anatomical regions of interest (ROIs; DLPFC, ACC) *a priori*. The ACC and DLPFC were selected as the primary ROIs for this study due to their vulnerability to TBI, central role in WM, and previous fMRI findings suggesting that these regions are the primary areas that demonstrate differences between individuals with and without a history of brain injury (Hillary, 2008). We selected coordinates for ROIs using Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011), an automated brain mapping framework based on meta-analysis and machine learning techniques. Functional activation in these *a priori* defined ROIs were measured using the mean response level (as indexed by the fit coefficients for the correct+null contrast) across the ROI. The *β coefficients* then were exported to statistical software.

2.5 Data Analysis

2.5.1 Data Screening

Participants were screened based on the aforementioned exclusion criteria. Out of the one-hundred three participants who consented to participate in the study, twenty-five participants were excluded from analyses based on the exclusion criteria. Specifically, five participants were excluded due to moderate TBI and three participants were excluded for severe TBI. Although not specifically detailed in study exclusion criteria, five participants were excluded for childhood

TBI of unclear severity due to age of injury. One participant was excluded for a diagnosis of bipolar disorder with psychotic features. Four participants were excluded from the study due to recent drug use; two of these veterans self-reported this use during clinical interview, and two participants were excluded due to positive toxicology screening. Finally, seven participants were excluded for "effort" or "task engagement;" three of these participants evidenced scores < 45 on Trial 2 of the TOMM, and four of these participants demonstrated visual monitoring performance below 75% accuracy. Thus, a total of 78 participants were included in the study analyses.

All variables were examined for possible outliers due to invalid or implausible values in the raw data form. Given that the hierarchical linear regression models proposed in the current study rely on the assumption that the dependent variable scores are normally distributed, the data were checked for normality via skewness and kurtosis. Visual inspection of the shape of the distribution of the dependent variables was performed using histograms and normal probability plots. The same process was performed for the residuals of each regression model to ensure that the residuals of the regression also followed a normal distribution (see residual plots in Appendix). All of the analyzed variables were deemed to follow a normal distribution and have normally-distributed residuals, so parametric statistics were used and no transformations were required.

2.5.2 Participant Demographics

Independent samples t-tests were used to examine group differences (mTBI vs. VC) in demographic characteristics for continuous variables. Chi-squared tests (or Fischer's exact test for cell sizes fewer than five) were utilized to explore group differences in categorical variables.

2.5.3 Covariates

All analyses included examination of demographic variables (e.g., age, education, sex, ethnicity) as covariates in step 1 of hierarchical models (Cohen, Cohen, West, & Aiken, 2003) when there was a demonstrated relationship between the covariate and the dependent variable of interest. The relationship between participant characteristics and outcome variables was examined using Pearson correlations for continuous variables and point-biserial correlations for dichotomous variables. Neuropsychiatric factors (i.e., PTSD, depression) were selected *a priori* based on evidence from the existing literature, and each was examined in step 1 of a regression model to explore their influence on the relationship between the independent and dependent variables. Independent variables were assessed for multicollinearity and, when present, appropriate adjustments to model complexity were performed. When demographic or mood covariates did not display a significant relationship with the outcome variable, a backwards elimination approach was employed as an alternative strategy such that covariates were eliminated from the model in order of descending p-value until only significant predictors remained in the model.

2.5.4 Hypothesis Testing

Hypothesis 1. A hierarchical linear regression model was used to test whether group (mTBI vs. VC) predicted mPASAT performance above and beyond the influence of covariates.

Hypothesis 2. Mean functional activation in the mPASAT for voxels defined within *a priori* ROIs (e.g., DLPFC, ACC) was compared between groups using a hierarchical linear regression model. Simulation techniques sensitive to spatial correlations helped control familywise error rate.

Hypothesis 3. Separate hierarchical linear regression models for each ROI were fitted to data in order to determine whether there was a significant linear relationship between BOLD activation and mPASAT accuracy within each group.

Exploratory Aims. Within the mTBI group, clinical injury characteristics (e.g., injury mechanism, time since injury, level of psychiatric distress) were examined using multiple regression to determine (1) their potential influence on neural activation, and (2) whether they moderated brain-behavior relationships explored in Aim 3. Demographic characteristics (i.e., age) that displayed a significant relationship with the outcome variable were explored as a moderator of performance and brain-behavior relationships. Moderators were examined by creating interaction terms with neural activation in ROIs (β coefficients) and candidate moderator variables such as LOC duration, injury mechanism, and number of injuries. Following regression models that did not evidence a significant relationship, independent samples t-tests were explored to better understand the role of the covariates and whether groups differed without the inclusion of these covariates. Similarly, Pearson correlations were examined following brain-behavior regression models to explore the nature of bivariate relationships and the role of covariates. Effect sizes were reported.

2.5.5 Power Analysis

G-Power (Cohen, 1992) was used to calculate the estimated effect size with 78 participants, power of 1-β = .80, and a two-tailed α = .05. Assuming two covariates in multiple regression analyses, we could detect small to medium main effects (f^2 = .1474). Observed effect sizes were examined using Cohen's f^2 on the scale of $\geq$ .02 (small), $\geq$ .15 (medium) and $\geq$ .35 (large; Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012).

2.6 Alternative Strategies

We anticipated that we might not see a significant difference in WM performance or neural activation between mTBI and VC. Given that we did not find group differences in *a priori* ROIs based on our hypothesis-driven approach, we explored a whole-brain voxel-wise approach to examine BOLD responses. Although we had proposed to compare the hyperactivation or hypoactivation detected using the whole brain approach to behavioral performance, there were no ROIs that survived whole-brain comparisons. Therefore, we did not detect potential activation differences outside of the *a priori* defined ROIs, and we were unable to explore the nuances of compensation vs. dedifferentiation using this approach.

In addition to the whole brain approach, we also examined BOLD activation and performance over the duration of the task. This allowed us to determine if veterans with mTBI exhibited greater difficulty performing the cognitively demanding task in the last run in comparison to the first run due to increased mental load of maintaining attention for an extended period of time. Furthermore, we explored whether veterans with mTBI displayed increased variability in performance and neural activation throughout the task.

Additionally, we conducted alternative contrasts designed to isolate WM processes after accounting for visual and motor system involvement. The mPASAT taps into several subdomains, such as goal maintenance, processing speed, sustained attention, and executive function. In order to better distinguish the processes unique to WM from more general task demands (e.g., processing speed, sustained attention), we contrasted the mPASAT activation to activation during a control task. The contrast of the mPASAT to the visual monitoring task may help detect subtle differences in brain activation not evident during the examination of the entire task. Furthermore, the contrast of correct and incorrect responses (i.e., correct – incorrect) was

also explored as an alternative outcome measure of interest, given that the comparisons of the correct+null contrasts yield similar activations in each group. The correct-incorrect contrast enabled isolation of brain activity during accurate WM performance from incorrect trials, which revealed group differences not observed in our primary brain imaging contrast.

We also explored the presence of self-reported cognitive complaints of executive function (as measured by the FrSBe) in our mTBI group, which was used to delineate our mTBI group for additional subgroup analyses. The use of the FrSBe, a comprehensive measure specifically designed to assess subjective complaints of executive dysfunction, could enable selection of a subgroup of mTBI veterans with subjective complaints of executive function that will be supported by objective WM performance above and beyond the influence of psychiatric symptom levels. These analyses provided additional strategies to examine BOLD responses and characteristics of WM performance in mTBI veterans.

Finally, in exploratory analyses of brain-behavior relationships, the neural activation during the mPASAT was correlated with other neuropsychological measures that tap similar domains of WM, sustained attention, and processing speed including WAIS-III/IV Digit Span, WAIS-III/IV Digit Symbol Coding, and D-KEFS TMT. The above measures were selected based on findings from a previous study by Tombaugh (2006), who performed a similar analysis using a visually modified PASAT and found significant correlations with Digit Span (forward, backward, and total) as well as Trails A and B. For the neuropsychological tests that demonstrated a significant relationship with brain activation, we explored brain activation in the *a priori* regions as mediators of the relationship between group and performance. These analyses were performed to determine whether cognitively demanding WM tasks are required to detect brain changes in mTBI. The relationship between the neural activation and psychiatric measures

(i.e., PTSD, depression) was also examined to explore the independent influences of mTBI and psychiatric symptoms.

METHODS ACKNOWLEDGEMENTS

The Methods chapter contains unpublished research co-authored by Holiday, Kelsey A.; Eyler, Lisa T; Sorg, Scott F.; and Schiehser, Dawn M. The dissertation author was the primary author of this work.

3. RESULTS

3.1 Data Screening

All variables were examined for possible outliers in raw data form, and no invalid or implausible values were identified. Measures of mPASAT performance (e.g., d') and brain activation (i.e., ACC, DLPFC) fell within acceptable values of skew and kurtosis (George & Mallery, 2011).

3.2 Sample Demographics and Clinical Characteristics

Participant demographics and mTBI characteristics are presented in Table 1. The entire sample included 78 military veterans (78% male), who were, on average, 31.28 years old (*SD* = 6.55) and who completed 14.58 years of education (*SD* = 1.73). Veterans with mTBI significantly differed from VC in sex, with a greater proportion of female participants in the VC group. We examined relationships of these variables with dependent variables and included as covariates where necessary. In comparison to the VC group, the mTBI group had greater levels of combat exposure and more severe depressive and PTSD symptoms. The mTBI and VC samples did not significantly differ on any other demographic variables.

With regard to the entire mTBI sample (*n* = 44), the median number of mTBIs sustained was 2 (*SD* = 1.49). On average, mTBI participants were tested 68.23 months following their most recent mTBI (*SD* = 44.05). In reference to their most significant mTBI, 61 percent reported LOC, 39 percent endorsed AOC, and 55 percent experienced PTA. Regarding the mechanism of their most significant injury, 66 percent experienced only blunt injuries and 34 percent experienced blast injuries. These mTBI characteristics are consistent with a national random sample of post-9/11 military veterans (Lindquist, Love, & Elbogen, 2017).

Table 1. Participant Characteristics: mTBI vs. VC

Variables	mTBI (n = 44)	VC (n = 34)	t or χ^2	p	η_p^2 or Cramer's V
Age (years)	31.4 (6.8)	31.2 (6.4)	.16	.874	<.001
Sex (Males:Females)	38:6	23:11	3.94	**.047**	**.05**
Education (years)	14.3 (1.6)	14.9 (1.8)	-1.66	.101	.04
Ethnicity					
Hispanic/Latino	13	6	1.47	.225	.14
Not Hispanic/Latino	31	28			
BDI-II Total Score (Out of 63)	20.6 (11.6)	6.4 (8.9)	5.88	**<.001**	**.31**
PCL-M Total Score (Out of 85)	43.8 (17.3)	24.0 (12.7)	5.59	**<.001**	**.29**
CES Total Score (Out of 41)	15.8 (12.1)	7.0 (8.6)	3.47	**0.001**	**.15**
Months since most recent mTBI	68.2 (44.0)	-	-	-	-
Number of mTBIs	2.5 (1.4)	-	-	-	-
mTBI Mechanism*		-	-	-	-
Blunt injury	29	-	-	-	-
Blast injury	15	-	-	-	-
LOC:AOC	27:17	-	-	-	-
PTA (Yes:No:Unsure)	24:19:1	-	-	-	-

All values listed are means (standard deviations) unless otherwise indicated.

Abbreviations: mTBI, mild traumatic brain injury; BDI-II, Beck Depression Inventory-II; PCL-M, Posttraumatic Stress Disorder (PTSD) Checklist - Military Version; CES, Combat Exposure Scale; LOC, loss of consciousness; AOC, alteration of consciousness; PTA, post-traumatic amnesia.

*most significant injury

3.3 Covariate Determination

Correlations between demographic characteristics (i.e., age, sex, years of education, ethnicity) and performance (d') on the mPASAT were examined in the overall veteran sample (n = 78). In regard to behavioral models, age (r = .17, p = .143), sex (r = .06, p = .591), and ethnicity (r = -.05, p = .657) were not significantly correlated with d'. However, years of education demonstrated a significant association with d' (r = .35, p = .002) and therefore, was examined as a covariate in behavioral models. In some exploratory models, components of d' (i.e., hit rate, false alarm rate) were examined as outcome variables. Correlations between

demographic characteristics (i.e., age, sex, years of education, ethnicity) and components of d' were examined in the overall veteran sample (n = 78). Similar to d', age (r = .088, p = .443), sex (r = .112, p = .329), and ethnicity (r = -.084, p = .467) were not significantly correlated with hit rate. Moreover, age (r = -.185, p = .105), sex (r = -.077, p = .502), and ethnicity (r = .006, p = .956) were not significantly correlated with false alarm rate. However, years of education were significantly correlated with hit rate (r = .337, p = .003) and false alarm rate (r = -.288, p = .011) and therefore, were included in all behavioral models.

Brain activation (i.e., ACC, DLPFC) during the mPASAT was also examined for correlations with demographic characteristics (i.e., age, sex, years of education, ethnicity) in the overall veteran sample (n = 78). Age (r = -.07, p = .540), sex (r = .10, p = .402), ethnicity (r = .08, p = .481), and years of education (r = -.08, p = .512) were not significantly correlated with brain activation in the ACC. Furthermore, brain activation in the DLPFC was not significantly correlated with age (r = .08, p = .465), sex (r = -.08, p = .480), ethnicity (r = .08, p = .465), or years of education (r = -.05, p = .661). Therefore, demographic characteristics were not included as covariates in models with brain activation as outcome measures.

As expected, depression (r = -.28, p = .013) and PTSD (r = -.26, p = .024) were significantly associated with mPASAT performance (d') in the overall sample. The psychiatric measures (i.e., depression and PTSD) were highly correlated with each other in the overall sample (r = .82, p < .001), and depression evidenced a numerically higher correlation with mPASAT performance than PTSD. In the interest of parsimony, only one measure of psychiatric distress (i.e., depression) was included as a covariate in subsequent analyses; follow-up analyses tested models that included only PTSD as a covariate. Even though depression was not significantly correlated with brain activation in the ACC (r = .14, p = .220) or DLPFC (r = .09, p

= .435), depression was included in brain activation models as a covariate based on *a priori* hypotheses discussed above. Moreover, PTSD was not significantly correlated with brain activation in the ACC (r = .05, p = .669) or DLPFC (r = .17, p = .131).

3.4 Aim 1: Working Memory Performance

After adjusting for covariates including years of education (β = .290, t = 2.590, p = .012) and depressive symptoms (β = -.258, t = -1.946, p = .055), a hierarchical regression analysis revealed group (mTBI vs. VC; β = -.121, t = -.941, p = .350) did not account for a significant proportion of variance in mPASAT performance as measured by d', $F(3, 74) = 4.819$, p = .004, R^2 = .163. Average performance in each group is presented in Table 2. The residual plots of the regression model were examined and determined to approximate a normal distribution (see Appendix). Of note, results do not significantly change when PTSD is examined in lieu of depression. Specifically, a hierarchical regression analysis revealed group (mTBI vs. VC; β = -.102, t = -.803, p = .424) did not account for a significant proportion of variance in mPASAT performance as measured by d', $F(3, 74) = 4.553$, p = .006, R^2 = .156, after controlling for years of education (β = .305, t = 2.742, p = .008) and PTSD symptoms (β = -.228, t = -1.757, p = .083). We conducted an independent samples t-test to explore whether groups significantly differed in mPASAT performance without the inclusion of education or mood symptoms. This exploratory t-test revealed that groups did not significantly differ in mPASAT performance (d'), $t(76) = -.680$, p = .499, η_p^2= .006.

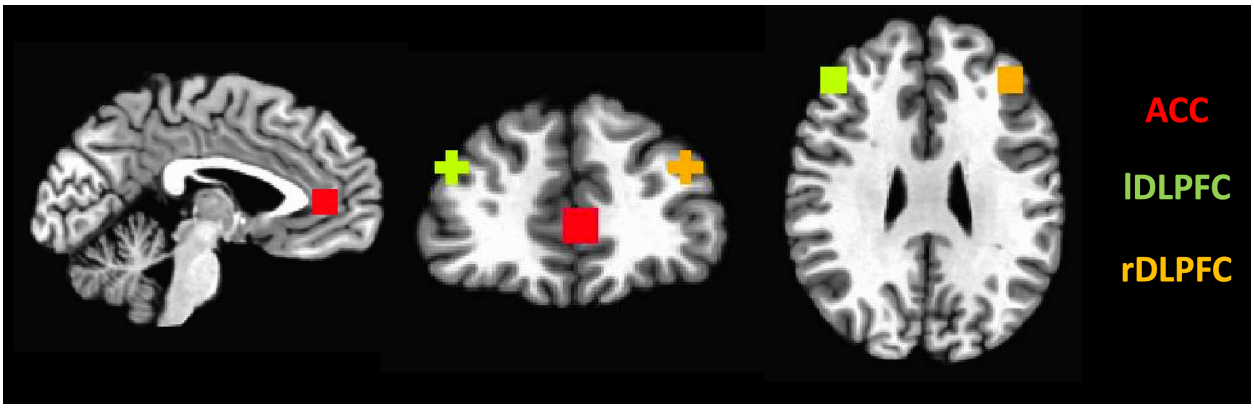
Table 2. mPASAT performance of mTBI and VC

Group	d'	Hit Rate	False Alarm Rate
mTBI	3.185 (.668)	.709 (.190)	.043 (.030)
VC	3.289 (.641)	.750 (.167)	.039 (.024)

All values reflect mean (SD).

3.5 Aim 2: Functional Brain Activation

Anatomical ROIs were manually selected *a priori* using Neurosynth (Yarkoni et al., 2011) (see ROIs in Figure 2). Functional activation in these *a priori* defined ROIs was measured using the mean response level (as indexed by the fit coefficients for the correct+null contrast) across the ROI for the ACC, right DLPFC, and left DLPFC. After *β coefficients* were exported to statistical software, activation in the right and left DLPFC were averaged to create one DLPFC region for analyses. Of note, exploratory analyses confirmed that results did not significantly differ when right and left DLPFC regions were examined independently.



AFNI coordinates determined by Neurosynth of the a priori selected ROIs. Anterior cingulate cortex (ACC) = red; left dorsolateral prefrontal cortex (lDLPFC) = light green; right dorsolateral prefrontal cortex (rDLPFC) = gold. AFNI coordinates (X, Y, Z) = ACC (2, -40, 8), lDLPFC (40, -34, 30), rDLPFC (-40, -34, 30).

Figure 2. Visual representation of the a priori selected ROIs.

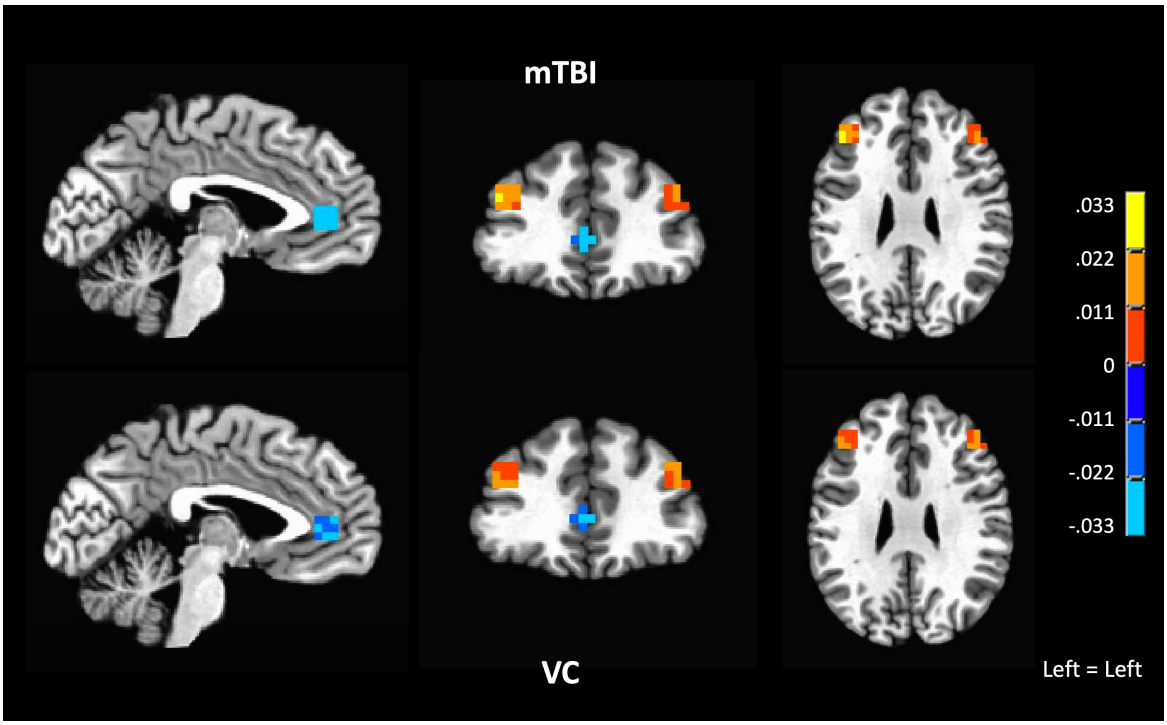
After adjusting for depressive symptoms (β = .282, t = 2.095, p = .040), a regression analysis revealed group (mTBI vs. VC; β = .253, t = 1.880, p = .064) did not account for a significant proportion of variance in ACC correct+null activation during an mPASAT, $F(2, 75)$ = 2.559, p = .084, R^2 = .064. When PTSD was included in lieu of depression, results were similar, $F(2, 75)$ = .900, p = .411, R^2 = .023. Another regression analysis revealed that group (mTBI vs. VC; β = .034, t = .224, p = .808) did not account for a significant proportion of variance in bilateral DLPFC activation during correct+null trials of a mPASAT, $F(2, 75)$ = .334, p = .717,

R^2 = .009, after accounting for depressive symptoms (β = .109, t = .783, p = .436). The residual plots of the regression models were examined and determined to approximate a normal distribution (see Appendix). Of note, results did not significantly change when PTSD was examined in lieu of depression, $F(2, 75) = 1.397$, $p = .254$, $R^2 = .036$. We also conducted independent samples t-tests to explore whether groups significantly differed in brain activation without the inclusion of mood symptoms. Results revealed that groups did not significantly differ in ACC, $t(76) = -.837$, $p = .405$, $\eta_p^2 = .009$, or bilateral DLPFC, $t(76) = .234$, $p = .815$, $\eta_p^2 = .001$, activation during correct+null trials of the mPASAT. The average activation in each ROI during the correct+null contrast is presented in Table 3 and depicted in Figure 3, and a box plot of the data is presented in Figure 4.

Table 3. Neural activation of the ACC and bilateral DLPFC of mTBI and VC during correct+null trials.

Correct+Null	ACC activation	Bilateral DLPFC activation
mTBI	-0.009 (0.011)	0.017 (0.015)
VC	-0.007 (0.009)	0.016 (0.012)

Values reflect mean (SD) fit coefficients for this contrast.



Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation.

Figure 3. Neural activation in the ACC and bilateral DLPFC during correct+null mPASAT trials in mTBI and VC.

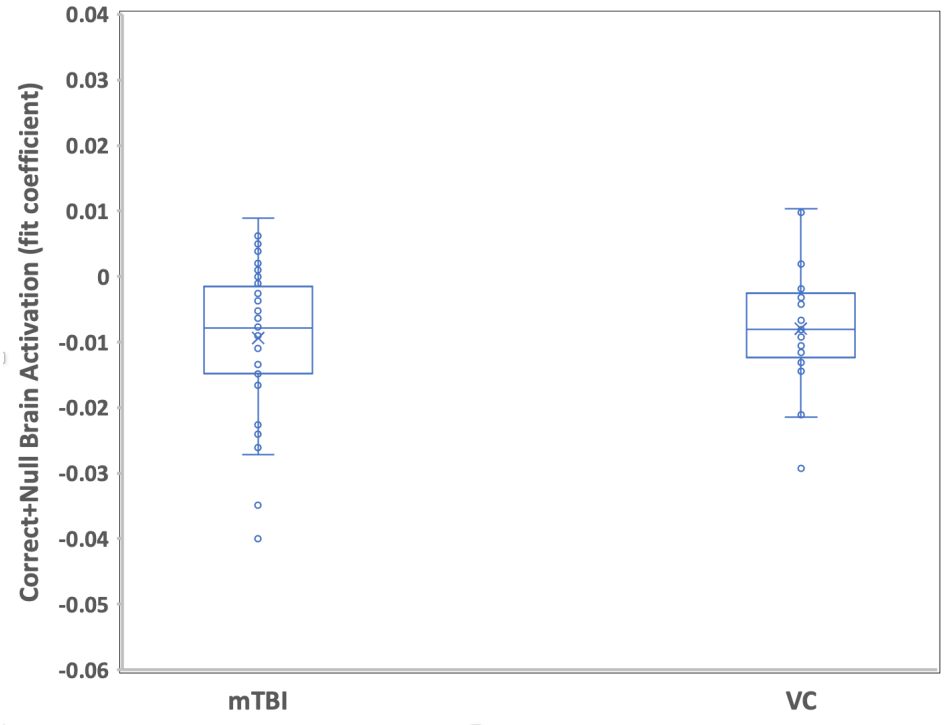


Figure 4. Box plot representing ACC activation during correct+null trials in mTBI and VC.

3.6 Aim 3: Brain-Behavior Associations

Separate hierarchical linear regression models for each ROI examined whether there was a significant linear relationship between BOLD activation during the correct+null contrast and mPASAT performance within each group. Within mTBI, ACC correct+null activation (β = -.007, t = -.044, p = .965) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 40) = 2.401$, $p = .082$, $R^2 = .153$, after controlling for years of education (β = .307, t = 2.056, p = .046) and depressive symptoms (β = -.181, t = -1.175, p = .247). Of note, results did not significantly change when PTSD was examined in lieu of depression, $F(3, 40) = 2.327$, $p = .089$, $R^2 = .149$. After accounting for years of education (β = .296, t = 2.025, p = .050) and depressive symptoms (β = -.219, t = -1.473, p = .149), bilateral DLPFC activation (β = .195, t = 1.345, p = .186) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 40) = 3.112$, $p = .037$, $R^2 = .189$, in the mTBI group. When PTSD was included in lieu of depression, results were similar, $F(3, 40) = 2.594$, $p = .066$, $R^2 = .163$. Using Pearson correlations, we explored whether brain activation significantly predicted mPASAT performance without the inclusion of mood symptoms. Results revealed that ACC (r = -.080; p = .604) and bilateral DLPFC activation (r = .162; p = .293) were not significantly associated with mPASAT performance (d') in mTBI.

Within VC, ACC activation (β = -.340, t = -2.174, p = .038) significantly predicted mPASAT performance (d'), $F(3, 30) = 4.148$, $p = .014$, $R^2 = .293$, after accounting for years of education (β = .228, t = 1.410, p = .169) and depressive symptoms (β = -.222, t = -1.354, p = .186). Similarly, when PTSD was included instead of depression, ACC activation significantly predicted mPASAT performance. Specifically, ACC activation (β = -.324, t = -2.159, p = .039) accounted for a significant proportion of variance in mPASAT performance (d'), $F(3, 30)$ =

5.666, $p = .003$, $R^2 = .362$, after controlling for years of education ($\beta = .148$, t = .923, $p = .363$) and PTSD symptoms ($\beta = -.371$, t = -2.291, $p = .029$) in VC. ACC activation during correct+null trials was negatively related to performance ($r = -.406$; $p = .017$), such that higher ACC activation (less deactivation) was associated with poorer mPASAT performance (d'; see Figure 5).

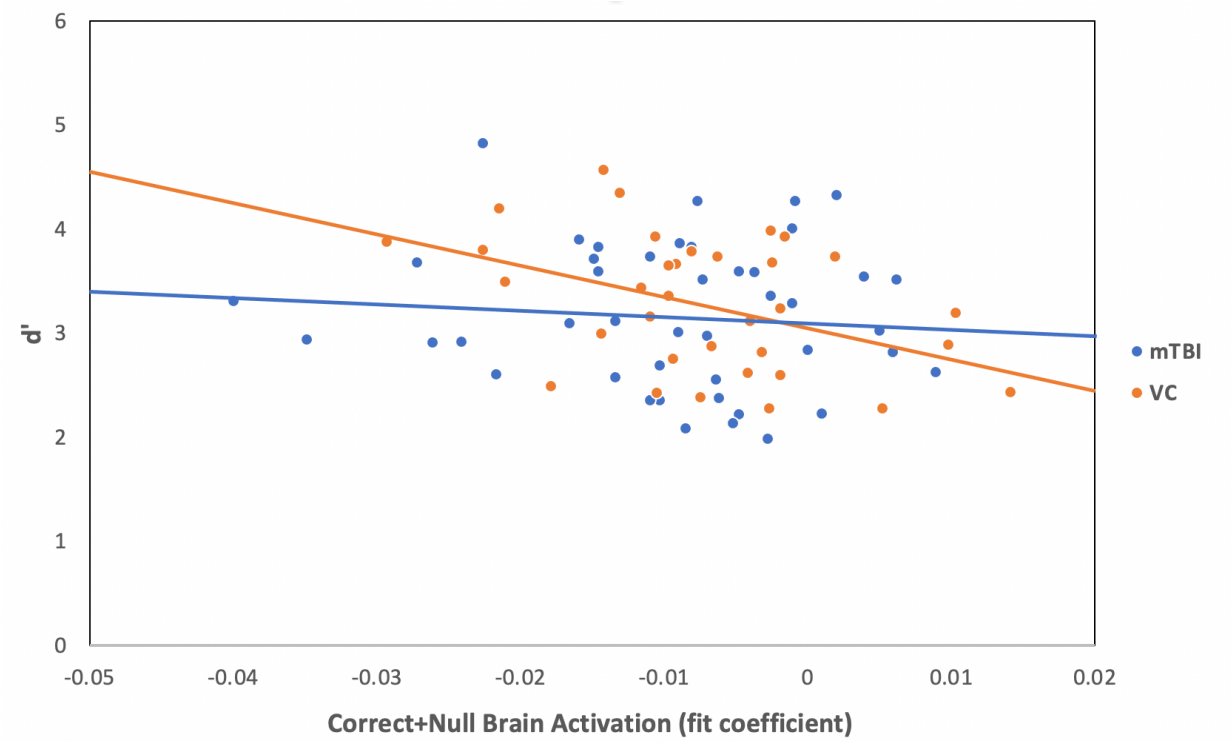


Figure 5. Scatterplot depicting the relationship between ACC activation during correct+null trials and mPASAT performance as measured by d'.

In contrast, bilateral DLPFC activation ($\beta = .109$, t = .651, $p = .520$) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 30) = 2.385$, $p = .088$, $R^2 = .193$, after accounting for years of education ($\beta = .267$, t = 1.524, $p = .138$) and depressive symptoms ($\beta = -.264$, t = -1.515, $p = .140$) in the VC group. Of note, results did not significantly change when PTSD was examined in lieu of depression, $F(3, 30) = 4.521$, $p = .010$, $R^2 = .311$. The bivariate relationship between brain activation and mPASAT performance was explored, and bilateral DLPFC activation during correct+null trials was not associated with mPASAT

performance (r = .094; p = .597). The residual plots of the regression models were examined and determined to approximate a normal distribution (see Appendix).

3.7 Exploratory Analyses

Clinical injury characteristics (e.g., injury mechanism, time since injury, level of psychiatric distress) were examined using multiple regression to determine their potential association with neural activation within *a priori* defined ROIs. Months since most recent injury did not significantly predict bilateral DLPFC activation $F(1, 42) < .001$, $p = .991$, $R^2 < .001$, $\beta = -.002$, $t = -.012$, or ACC activation $F(1, 42) = .141$, $p = .709$, $R^2 = .003$, $\beta = .058$, $t = .375$. Similarly, months since most significant injury did not significantly predict bilateral DLPFC activation, $F(1, 42) = .703$, $p = .407$, $R^2 = .016$, $\beta = -.838$, $t = -.128$, or ACC activation, $F(1, 42) = .226$, $p = .637$, $R^2 = .005$, $\beta = -.073$, $t = -.476$. Number of TBIs did not significantly predict bilateral DLPFC activation, $F(1, 42) = .986$, $p = .326$, $R^2 = .023$, $\beta = .151$, $t = .993$, or ACC activation, $F(1, 42) = .521$, $p = .475$, $R^2 = .012$, $\beta = -.111$, $t = -.721$. Furthermore, the presence of LOC in comparison to AOC did not significantly predict bilateral DLPFC activation, $F(1, 42) = .519$, $p = .475$, $R^2 = .012$, $\beta = -.110$, $t = -.720$, or ACC activation, $F(1, 42) = 2.516$, $p = .120$, $R^2 = .057$, $\beta = -.238$, $t = -1.586$. Moreover, depressive symptoms did not significantly predict bilateral DLPFC activation, $F(1, 42) = 1.265$, $p = .267$, $R^2 = .029$, $\beta = .171$, $t = 1.125$, or ACC activation, $F(1, 42) = 3.081$, $p = .086$, $R^2 = .068$, $\beta = .261$, $t = 1.755$. Likewise, PTSD symptoms did not significantly predict bilateral DLPFC activation, $F(1, 42) = 1.217$, $p = .276$, $R^2 = .054$, $\beta = .168$, $t = 1.103$, or ACC activation, $F(1, 42) = .326$, $p = .571$, $R^2 = .035$, $\beta = .088$, $t = .571$.

Although it was proposed to examine whether clinical injury characteristics mediate or moderate brain-behavior relationships explored in Aim 3, no such brain-behavior relationships were found within the mTBI group. Furthermore, clinical injury characteristics did not

significantly predict brain activation or behavior within the mTBI group. Specifically, clinical injury characteristics including time since most recent injury (r = .206, p = .181), total number of mTBIs (r = -.163, p = .291), presence of LOC or AOC (r = .023, p = .885), presence of PTA (r = .022, p = .887), and mTBI injury mechanism (blast vs. blunt; r = -.142, p = .356) were not significantly correlated with mPASAT performance (d'). Additionally, clinical injury characteristics such as time since most recent injury (r = .058, p = .709), total number of mTBIs (r = -.111, p = .475), presence of LOC or AOC (r = -.122, p = .430), presence of PTA (r = .014, p = .929), and mTBI injury mechanism (blast vs. blunt; r = -.238, p = .120) were not significantly correlated with ACC activation. Furthermore, clinical injury characteristics including time since most recent injury (r = -.002, p = .991), total number of mTBIs (r = .151, p = .326), presence of LOC or AOC (r = -.004, p = .981), presence of PTA (r = -.089, p = .568), and mTBI injury mechanism (blast vs. blunt; r = -.110, p = .475) were not significantly correlated with DLPFC activation. Thus, subsequent moderation analyses were not performed.

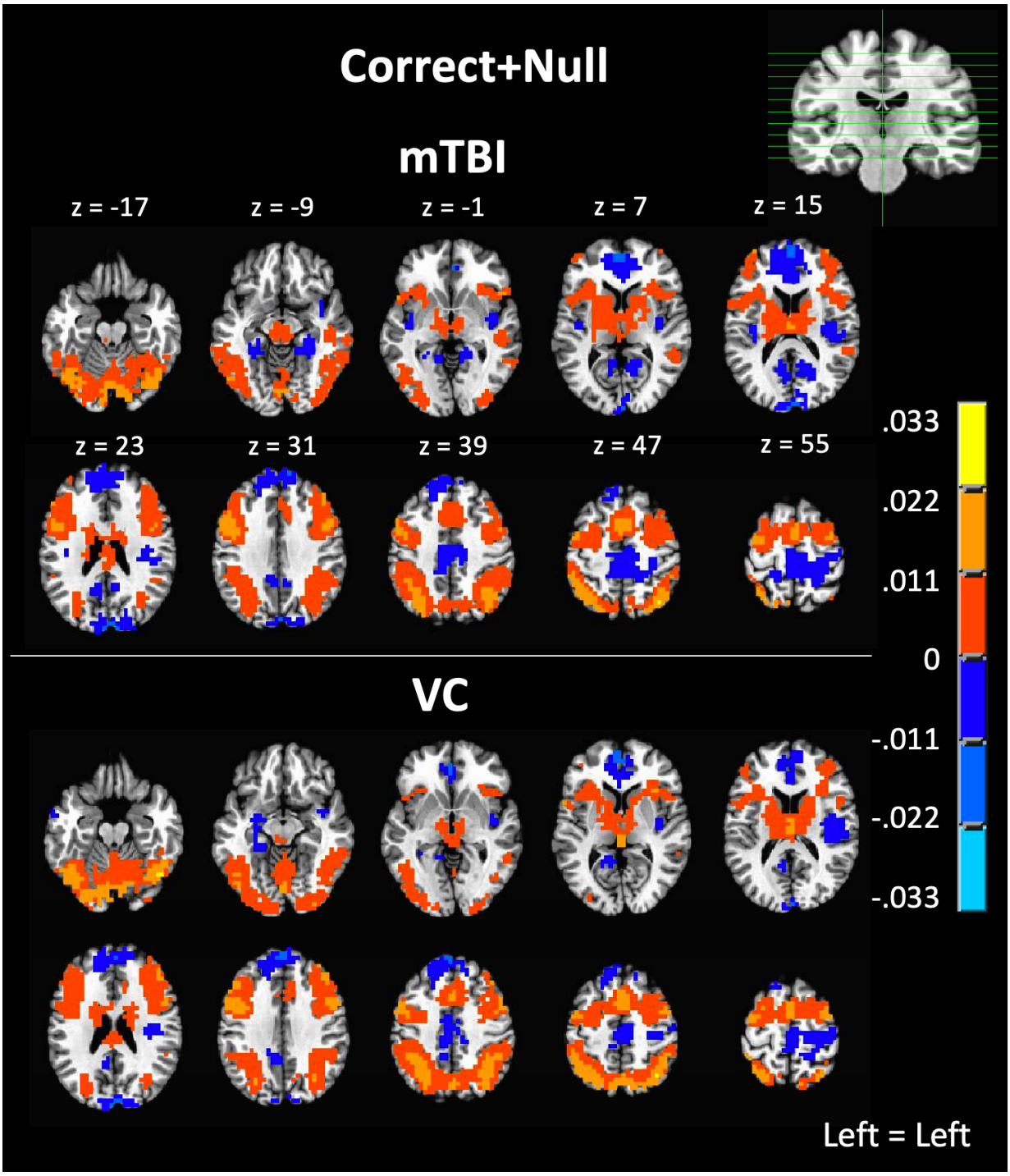
Demographic characteristics (e.g., age, years of education) that displayed a significant relationship with the outcome variable were also explored as a moderator of significant performance and brain-behavior relationships. As mentioned above, age (r = .17, p = .143), sex (r = .06, p = .591), and ethnicity (r = -.05, p = .657) were not significantly correlated with d', but years of education demonstrated a significant association with d' (r = .35, p = .002). Therefore, years of education was examined as a moderator (i.e., interaction term) in significant models with mPASAT performance as the outcome variable. The only significant relationship detected within the primary aims was the relationship between ACC activation during correct+null trials and performance (d') in VC. Within VC, education (β = -.056, t = -.146, p = .885) did not moderate the relationship between ACC correct+null activation (β = -.366, t = -2.081, p = .046)

and mPASAT performance (d'), $F(4, 29) = 3.015$, $p = .034$, $R^2 = .294$, after accounting for years of education ($\beta = .181$, $t = .499$, $p = .622$) and depressive symptoms ($\beta = -.213$, t = -1.197, $p = .241$). No demographic characteristics (i.e., age, sex, years of education, ethnicity) were significantly associated with brain activation in the ACC or bilateral DLPFC.

3.8 Alternative Strategies

3.8.1 Whole Brain Analyses

Given that we did not find that group predicted *a priori* ROI activation based on our hypothesis-driven approach, we explored a whole-brain voxel-wise approach to examine BOLD responses. Figure 6 illustrates the high level of similarity of significant whole brain response to the mPASAT correct+null contrast between the mTBI and VC groups. Significant clusters of activation are listed in Table 4. Whole-brain findings for incorrect-only and correct-incorrect contrasts also reveal broadly similar regions of activation within mTBI and VC groups (Figures 7 & 8). Consistent with this impression, after accounting for multiple comparisons (Cox, Chen, Glen, Reynolds, & Taylor, 2017), no ROIs survived whole-brain voxel-wise group comparison for any contrast (e.g., correct+null, correct-incorrect, incorrect-only, run3-run1, mPASAT trials minus visual monitoring). Therefore, we were unable to relate any hyperactivation or hypoactivation detected among mTBI participants using the whole brain approach to behavioral performance in that group.



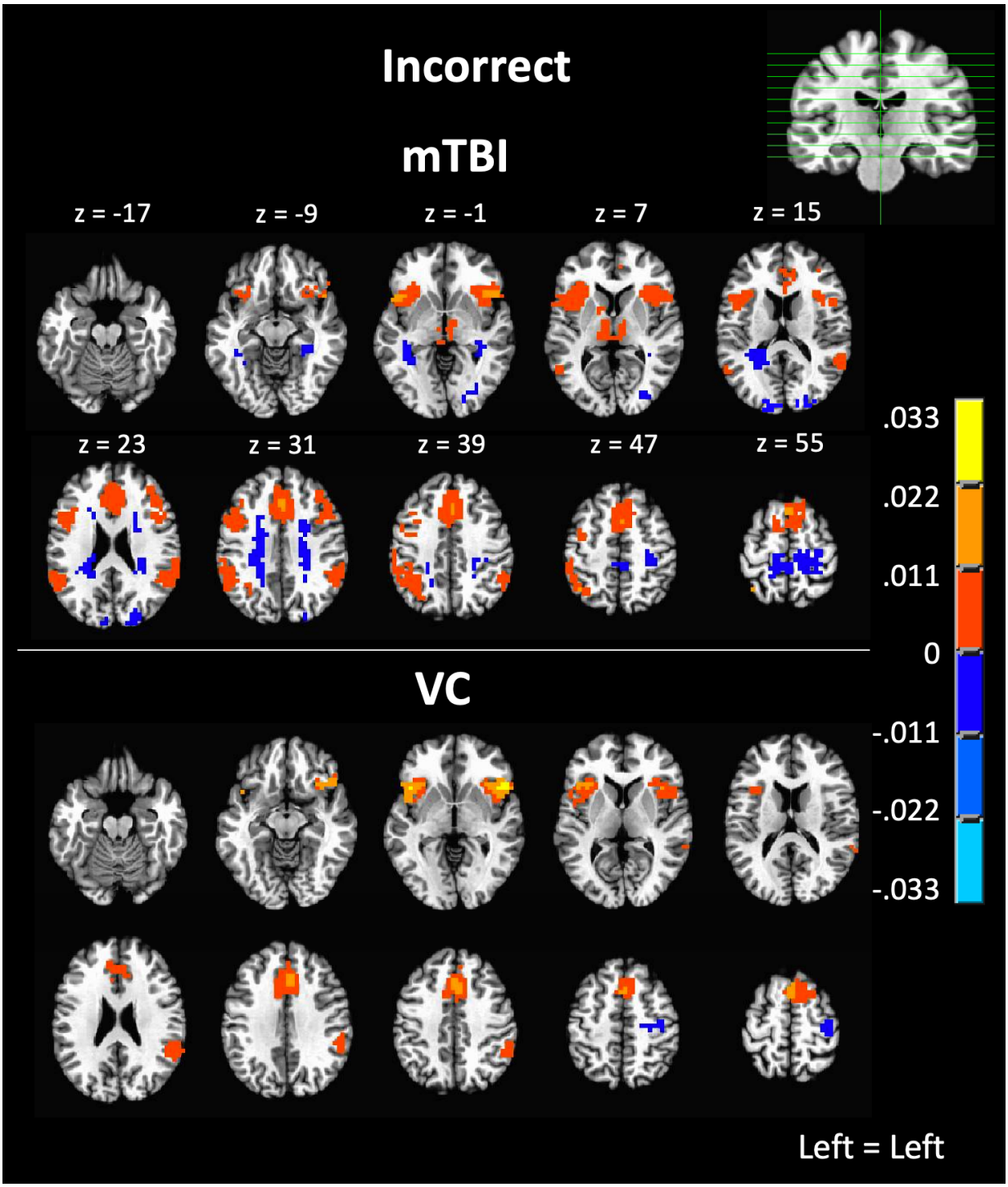
Activations displayed above reflect clusters that survived thresholding correcting for multiple comparisons (-ETAC; $p < .0018$). Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation. z-coordinates for each slice are depicted above the brain image in mTBI and identical coordinates were used for the VC. A cross-section of the distribution of montage slices is depicted in lime green on the coronal slice in the upper right corner.

Figure 6. Montage of whole brain neural activation during correct+null mPASAT trials in mTBI and VC.

Table 4. Coordinates of brain activation during the mPASAT in VC.

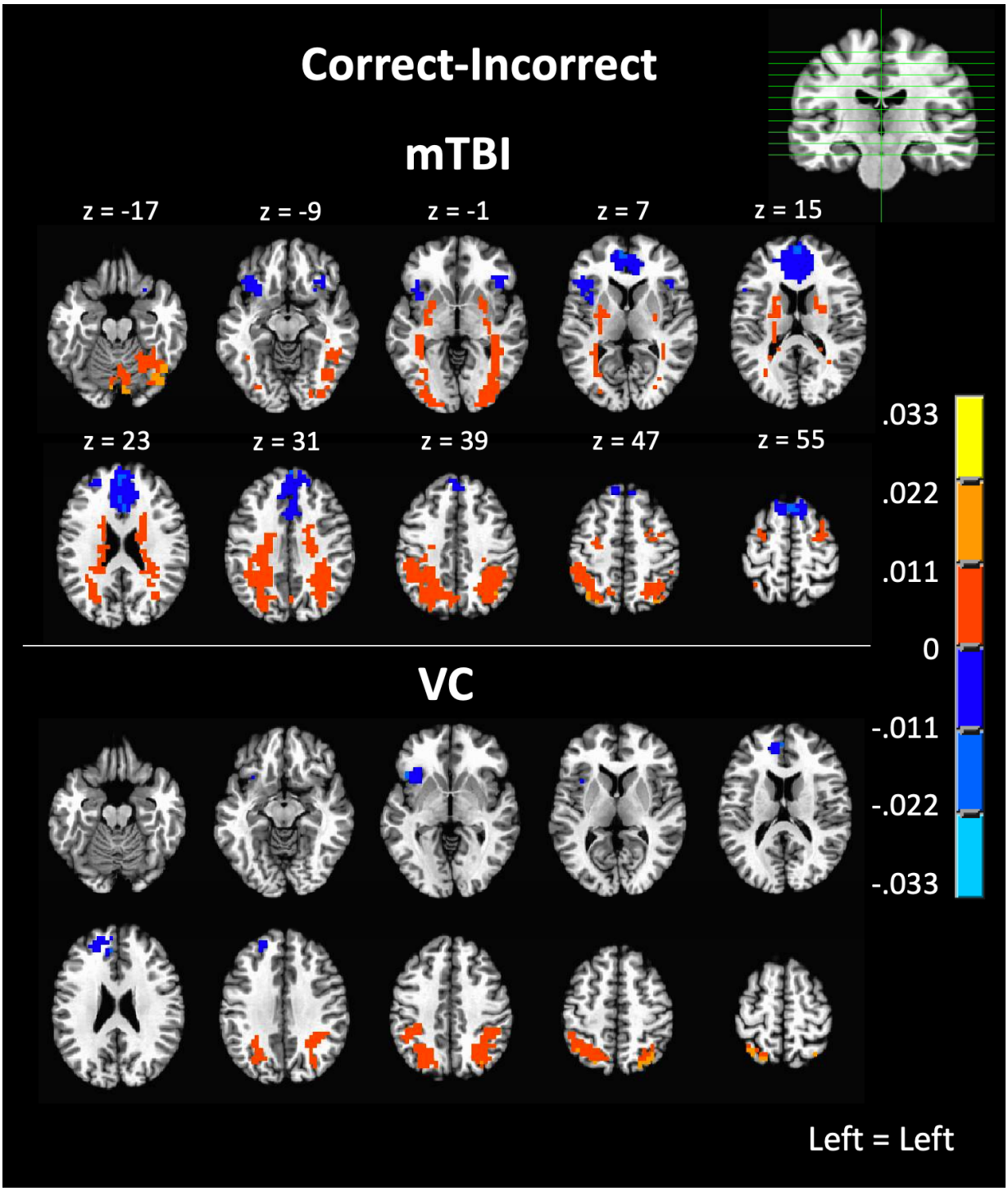
Cluster #	# of Voxels	AFNI Coordinates (Peak)	Peak Brain Activation	AFNI Coordinates (Center of Mass)	Brain Regions (survive -ETAC thresholding, p = .0018)
1	1871	-34, 5, 56	.0204	-.3, -6.8, 31.5	R&L middle frontal gyrus, R&L precentral gyrus, R&L medial frontal gyrus, R&L thalamus, R&L inferior frontal gyrus, R&L insula, R&L caudate, R&L anterior cingulate, R&L superior frontal gyrus, R&L claustrum, posterior commisure
2	1037	-42, 61, -16	.0247	3.1, 66.4, -14	R&L fusiform gyrus, R&L cerebellum, R&L middle occipital gyrus, R&L inferior occipital gyrus, R&L inferior temporal gyrus, R&L middle temporal gyrus, R&L lingual gyrus
3	961	-34, 61, 48	.0224	.4, 57.1, 42.6	R&L superior parietal lobule, R&L precuneus, R&L inferior parietal lobule, R&L supramarginal gyrus, R&L angular gyrus, R&L middle yemporal gyrus
4	415	-2, -51, 4	-.0195	3.8, -44.4, 23.1	R&L anterior cingulate cortex, R&L medial frontal gyrus, R&L superior frontal gyrus
5	369	-34, 25, 64	-.0094	-10.4, 28.9, 49.3	R precentral gyrus, R postcentral gyrus, R&L medial frontal gyrus, R&L paracentral lobule, L precuneus, L posterior cingulate gyrus, L parahippocampal gyrus, L lingual gyrus
6	121	-38, 17, 12	-.0068	-40.3, 16.4, 13.8	R insula, R precentral gyrus, R postcentral gyrus
7	62	38, -15, -24	-.0132	42, -5, -24.8	L superior temporal gyrus, L middle temporal gyrus
8	53	-42, -15, -24	-.0116	-36.7, -8.6, -25.6	R superior temporal gyrus, R middle temporal gyrus
9	53	-6, 85, 24	-.0131	-3.1, 87.3, 23.1	R&L cuneus
10	38	26, 17, -8	-.0094	23.2, 23.8, -8.2	L lentiform nucleus, L parrahippocampal gyrus

Abbreviations. R = right, L = left, # = number, p = p-value, AFNI = Analysis of Functional Neuroimages, ETAC = Equitable Thresholding and Clustering.



Activations displayed above reflect clusters that survived thresholding correcting for multiple comparisons (-ETAC; $p < .0018$). Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation. *z*-coordinates for each slice are depicted above the brain image in mTBI and identical coordinates were used for the VC. A cross-section of the distribution of montage slices is depicted in lime green on the coronal slice in the upper right corner.

Figure 7. Montage of whole brain neural activation during incorrect-only mPASAT trials in mTBI and VC.



Activations displayed above reflect clusters that survived thresholding correcting for multiple comparisons (-ETAC; $p < .0018$). Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation. *z*-coordinates for each slice are depicted above the brain image in mTBI and identical coordinates were used for the VC. A cross-section of the distribution of montage slices is depicted in lime green on the coronal slice in the upper right corner.

Figure 8. Montage of whole brain neural activation during the contrast of correct-incorrect mPASAT trials in mTBI and VC.

In addition to the whole brain approach, we also examined BOLD activation and performance over the duration of the task by comparing behavioral performance and neural activation between the last and first run of the task to assess the possible effects of sustained attentional load over time. In regard to behavior, a regression analysis revealed group (mTBI vs. VC; β = -.052, t = -.373, p = .710) did not account for a significant proportion of variance in mPASAT performance across the task, as measured by the difference in d' for run3-run1, $F(3, 74) = .261$, $p = .854$, $R^2 = .010$, after adjusting for covariates including years of education (β = .050, t = .409, p = .684) and depressive symptoms (β = -.094, t = -.651, p = .517). Another regression analysis revealed group (mTBI vs. VC; β = .011, t = .080, p = .936) did not account for a significant proportion of variance in ACC activation in run3-run1, $F(2, 75) = .090$, $p = .914$, $R^2 = .002$ after adjusting for depressive symptoms (β = .054, t = .389, p = .698). A third regression analysis revealed group (mTBI vs. VC; β = -.133, t = -.973, p = .334) did not account for a significant proportion of variance in bilateral DLFPC activation in run3-run1, $F(2, 75) = 1.737$, $p = .183$, $R^2 = .044$, after adjusting for depressive symptoms (β = .105, t = .773, p = .442). We conducted t-tests to explore whether groups significantly differed in mPASAT performance or brain activation during the contrast of run3-run1 without the inclusion of covariates. Results revealed that groups did not significantly differ in mPASAT performance, $t(76) = -.085$, $p = .933$, $\eta_p^2 < .933$, ACC, $t(76) = .167$, $p = .868$, $\eta_p^2 < .009$, or bilateral DLPFC, $t(76) = 1.700$, $p = .093$, $\eta_p^2 = .037$, activation during run3-run1 of the mPASAT. Furthermore, results did not change when PTSD was included in lieu of depression or alternative contrasts were examined as exploratory analyses (i.e., correct-incorrect, incorrect-only). Therefore, we did not detect any group differences in changes in behavior or brain activation due to sustained attentional load over time.

3.8.2 Alternative Behavioral Outcome Measures

Given that d', the main behavioral outcome measure of this study, did not yield significant results, components of d' (i.e., hit rate, false alarm rate) were explored as alternative outcome measures for aim 1 and 3 (see Table 2 for specific values). After adjusting for covariates including depressive symptoms (β = -.343, t = -2.634, p = .010) and years of education (β = .254, t = 2.312, p = .024), a regression analysis revealed group (mTBI vs. VC; β = -.126, t = -.999, p = .321) did not account for a significant proportion of variance in mPASAT performance as measured by hit rate, $F(3, 74) = 5.860$, $p = .001$, $R^2 = .438$. When PTSD was included in lieu of depression, results were similar, $F(3, 74) = 5.451$, $p = .002$, $R^2 = .181$. Likewise, a regression analysis revealed that group (mTBI vs. VC; β = .054, t = .405, p = .687) did not account for a significant proportion of variance in mPASAT performance as measured by false alarm rate, $F(3, 74) = 2.572$, $p = .061$, $R^2 = .307$, after accounting for covariates including years of education (β = -.257, t = -2.211, p = .030) and depressive symptoms (β = .132, t = .957, p = .342). Of note, results do not significantly change when PTSD is examined in lieu of depression, $F(3, 74) = 2.435$, $p = .071$, $R^2 = .090$. We conducted t-tests to explore whether groups significantly differed in alternative measures of mPASAT performance without the inclusion of education or mood symptoms. Results revealed that groups did not significantly differ in hit rate, $t(76) = -.996$, $p = .322$, $\eta_p^2 = .013$, or false alarm rate, $t(76) = .593$, $p = .555$, $\eta_p^2 = .005$, without accounting for the influence of covariates.

3.8.2.1 Correct+Null ACC Activation & Hit Rate

In regard to aim 3, separate hierarchical linear regression models for each ROI examined whether there was a significant linear relationship between BOLD activation during the correct+null contrast and components of mPASAT performance (i.e., hit rate, false alarm rate)

within each group. Within mTBI, ACC correct+null activation (β = -.029, t = -.187, p = .853) did not account for a significant proportion of variance in mPASAT hit rate, $F(3, 40) = 1.772$, $p = .168$, $R^2 = .117$, after controlling for years of education (β = .199, t = 1.307, p = .199) and depressive symptoms (β = -.229, t = -1.453 p = .154). Of note, results do not significantly change when PTSD is examined in lieu of depression, $F(3, 40) = 1.158$, $p = .338$, $R^2 = .080$. Exploratory analyses revealed that ACC correct+null activation was not significantly associated with mPASAT performance as measured by hit rate (r = .495; p = -.106; see Figure 9).

Within VC, ACC correct+null activation (β = -.269, t = -1.844, p = .075) did not significantly predict mPASAT hit rate, $F(3, 30) = 6.285$, $p = .002$, $R^2 = .386$, after accounting for years of education (β = .283, t = 1.877, p = .070) and depressive symptoms (β = -.348, t = -2.281, p = .030). When PTSD was included in lieu of depression, ACC activation (β = -.235, t = -1.944, p = .061) did not significantly predict mPASAT hit rate, $F(3, 30) = 13.641$, $p < .001$, $R^2 = .577$, after accounting for years of education (β = .148, t = 1.135, p = .266) and PTSD symptoms (β = -.605, t = -4.594, $p < .001$) in VC. Exploratory analyses revealed that ACC correct+null activation was significantly associated with mPASAT performance as measured by hit rate (r = -.364; p = .034) in VC such that greater ACC activation (less deactivation) was associated with lower hit rates (see Figure 9).

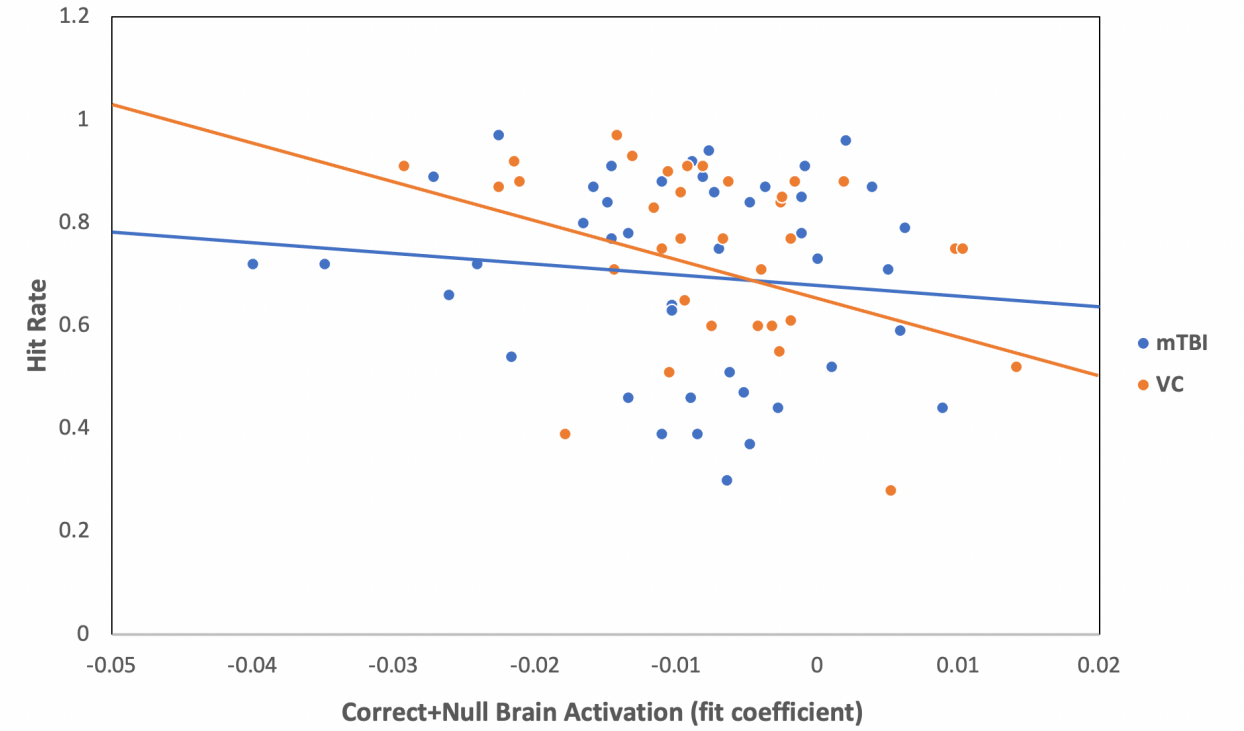


Figure 9. Scatterplot depicting the relationship between ACC activation during correct+null trials and mPASAT performance as measured by hit rate.

3.8.2.2 Correct+Null ACC Activation & False Alarm Rate

In mTBI, ACC correct+null activation (β = .056, t = .355, p = .725) did not account for a significant proportion of variance in mPASAT false alarm rate, $F(3, 40) = 1.140$, $p = .345$, $R^2 = .079$, after controlling for years of education (β = -.245, t = -1.573, p = .124) and depressive symptoms (β = .066, t = .409 p = .685). Results remained similar when PTSD was included in lieu of depression, $F(3, 40) = 1.110$, $p = .356$, $R^2 = .077$. Exploratory analyses revealed that ACC correct+null activation was not significantly associated with mPASAT performance as measured by false alarm rate (r = .094; p = .544) in mTBI (see Figure 10).

In VC, ACC correct+null activation (β = .291, t = 1.757, p = .089) did not significantly predict mPASAT false alarm rate, $F(3, 30) = 2.647$, $p = .067$, $R^2 = .209$, after accounting for years of education (β = -.245, t = -1.430, p = .163) and depressive symptoms (β = .127, t = .736, p = .468). When PTSD was included as a measure of mood symptoms instead of depression,

results were similar, $F(3, 30) = 2.668$, $p = .065$, $R^2 = .211$. In contrast to the regression analyses, exploratory analyses revealed that ACC correct+null activation was significantly associated with mPASAT performance as measured by false alarm rate ($r = .341$; $p = .048$) in VC. Specifically, greater ACC activation (less deactivation) was associated with higher false alarm rates in VC (Figure 10). The residual plots of the regression models were examined and determined to approximate a normal distribution (see Appendix).

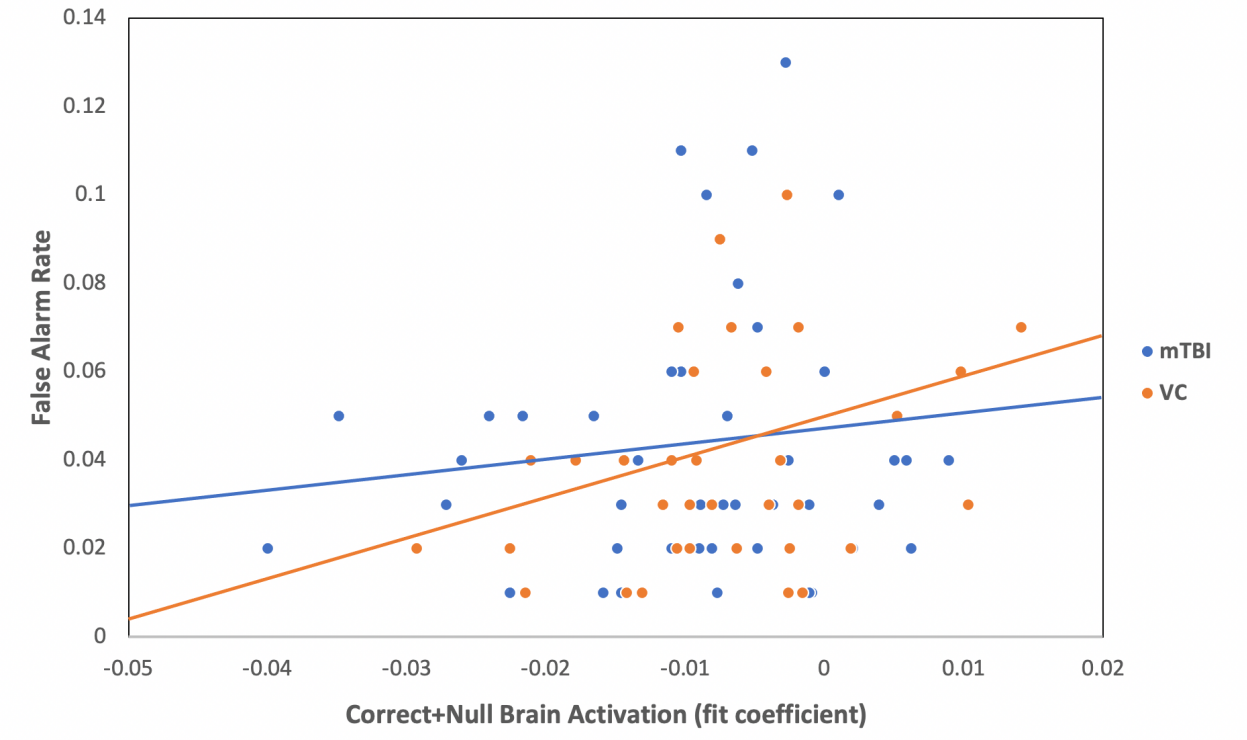


Figure 10. Scatterplot depicting the relationship between ACC activation during Correct+Null trials and mPASAT performance as measured by false alarm rate.

3.8.2.3 Correct+Null Bilateral DLPFC Activation

In mTBI, bilateral DLPFC activation ($\beta = .236$, t = 1.616, $p = .114$) did not account for a significant proportion of variance in mPASAT hit rate, $F(3, 40) = 2.743$, $p = .056$, $R^2 = .171$, after accounting for years of education ($\beta = .187$, $t = 1.026$, $p = .215$) and depressive symptoms ($\beta = -.279$, $t = -1.861$, $p = .070$). Results remained similar when PTSD was included in lieu of

depression, $F(3, 40) = 1.773$, $p = .168$, $R^2 = .117$. Furthermore, bilateral DLPFC activation ($\beta = -.120$, $t = -.783$, $p = .438$) did not account for a significant proportion of variance in mPASAT false alarm rate, $F(3, 40) = 1.316$, $p = .283$, $R^2 = .090$, after accounting for years of education ($\beta = -.240$, $t = -1.547$, $p = .130$) and depressive symptoms ($\beta = .102$, $t = .648$, $p = .520$) in the mTBI group. Of note, results did not significantly change when PTSD symptoms were added to models instead of depressive symptoms, $F(3, 40) = 1.237$, $p = .309$, $R^2 = .085$. Exploratory analyses revealed that bilateral DLPFC correct+null activation was not significantly associated with mPASAT performance as measured by hit rate ($r = .192$; $p = .212$) or false alarm rate ($r = -.107$; $p = .491$) in mTBI.

In VC, bilateral DLPFC activation ($\beta = -.098$, t = -.641, $p = .526$) did not explain a significant proportion of variance in mPASAT hit rate, $F(3, 30) = 4.829$, $p = .007$, $R^2 = .326$, after controlling for years of education ($\beta = .281$, $t = 1.753$, $p = .090$) and depressive symptoms ($\beta = -.407$, $t = -2.554$, $p = .016$). Results remained similar when PTSD symptoms were included instead of depressive symptoms, $F(3, 30) = 11.217$, $p < .001$, $R^2 = .529$, in the VC group. Bilateral DLPFC activation ($\beta = -.261$, t = -1.564, $p = .128$) did not explain a significant proportion of variance in mPASAT false alarm rate, $F(3, 30) = 2.402$, $p = .087$, $R^2 = .194$, after accounting for years of education ($\beta = -.308$, $t = -1.759$, $p = .089$) and depressive symptoms ($\beta = .140$, $t = .805$, $p = .427$) in the VC group. When PTSD was included instead of depression in the VC group, results did not significantly change, $F(3, 30) = 2.972$, $p = .047$, $R^2 = .229$. Exploratory analyses revealed that bilateral DLPFC correct+null activation was not significantly associated with mPASAT performance as measured by hit rate ($r = -.103$; $p = .563$) or false alarm rate ($r = -.231$; $p = .198$) in VC.

3.8.3 Visual Monitoring Contrast

In order to better distinguish the processes unique to WM from more general task demands (e.g., processing speed, sustained attention), we contrasted the mPASAT activation to activation during a visual monitoring control task. After adjusting for covariates including depressive symptoms (β = .130, t = .993, p = .354), a hierarchical regression analysis revealed that group (mTBI vs. VC; β = .166, t = 1.192, p = .237) did not account for a significant proportion of variance in bilateral DLPFC activation during the contrast between correct+null mPASAT runs and visual monitoring, $F(2, 75) = .763$, $p = .470$, $R^2 = .020$. When PTSD was included in lieu of depression, results remained similar, $F(2, 75) = 1.706$, $p = .189$, $R^2 = .045$.

Another regression analysis revealed group (mTBI vs. VC; β = .288, t = 2.127, p = .037) did account for a significant proportion of variance in ACC activation during the contrast between mPASAT runs and visual monitoring, $F(2, 75) = 2.976$, $p = .057$, $R^2 = .075$ after adjusting for depressive symptoms (β = .295, t = 2.178, p = .033). However, the overall model was not statistically significant, and thus it would be inappropriate to interpret the predictors in this model. When PTSD was included in lieu of depression, a regression analysis revealed group (mTBI vs. VC; β = .182, t = 1.328, p = .188) did not account for a significant proportion of variance in ACC activation during the contrast between mPASAT runs and visual monitoring, $F(2, 75) = .886$, $p = .417$, $R^2 = .024$, after adjusting for PTSD symptoms (β = .109, t = .793, p = .430). Exploratory analyses revealed that groups did not significantly differ in ACC, $t(76) = -1.072$, $p = .287$, $\eta_p^2 = .015$, or bilateral DLPFC, $t(76) = -.809$, $p = .421$, $\eta_p^2 = .009$, activation during the contrast between correct+null mPASAT runs and visual monitoring.

3.8.4 Correct-Incorrect Contrast

Given that we did not find that group predicted brain activation in the ACC or DLPFC during correct+null contrasts, we explored the contrast of correct and incorrect responses (i.e., correct–incorrect) as an alternative outcome measure of interest. After adjusting for depressive symptoms (β = .127, t = .970, p = .335), a regression analysis revealed group (mTBI vs. VC; β = .405, t = 3.101, p = .003) accounted for a significant proportion of variance in ACC activation during the contrast between correct-incorrect trials, $F(2, 75) = 5.235$, $p = .007$, $R^2 = .123$ (Figures 11, 12, 13, 14). When PTSD was included in lieu of depression, results were similar, $F(2, 75) = 6.414$, $p = .003$, $R^2 = .146$. The residual plots of the regression models were examined and determined to approximate a normal distribution (see Appendix).

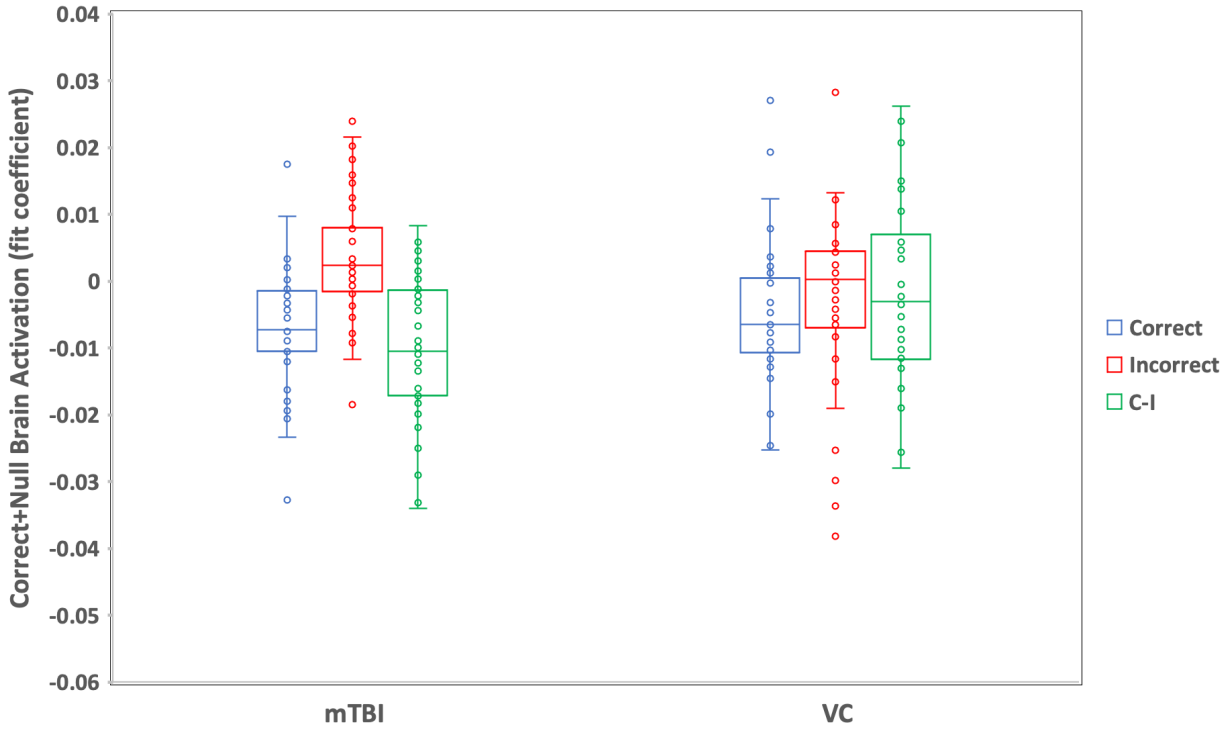


Figure 11. Box plot representing ACC activation during correct-only (**blue**), incorrect-only (**red**), and correct-incorrect trials (**green**) in mTBI and VC.

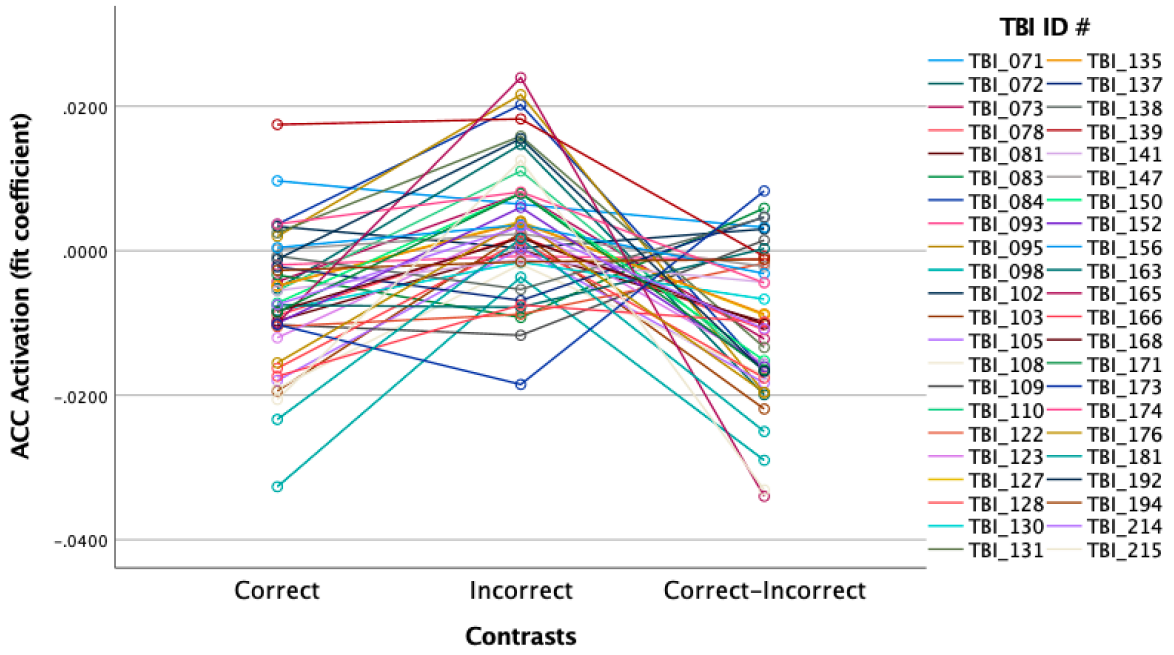


Figure 12. Spaghetti plot representing ACC activation during correct-only, incorrect-only, and correct-incorrect trials for each individual in the mTBI group.

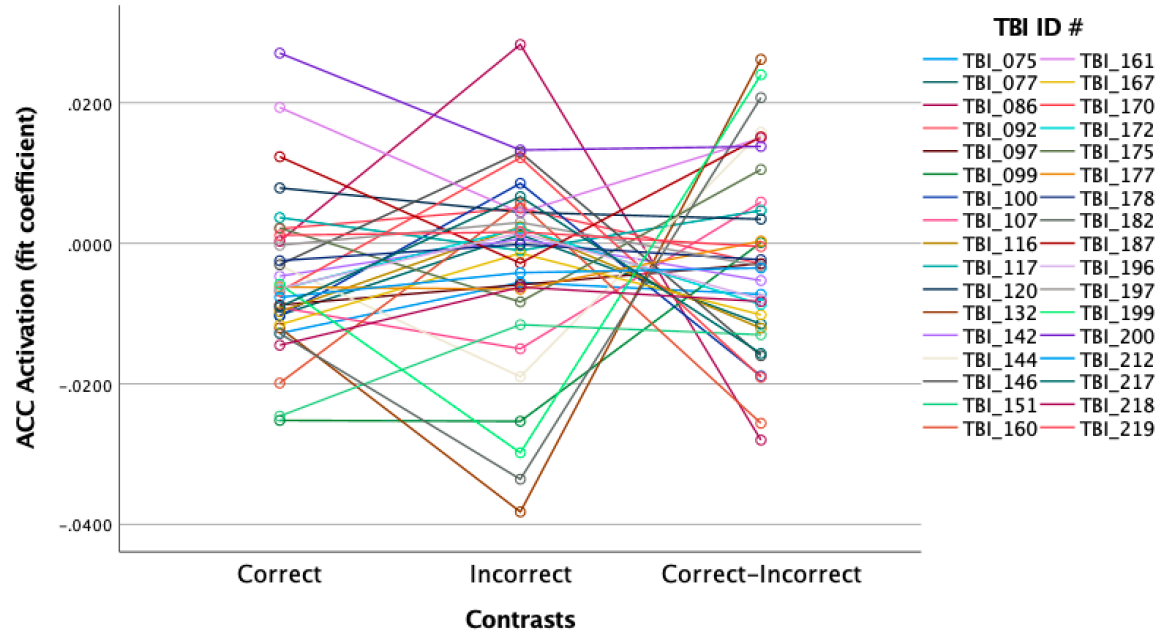
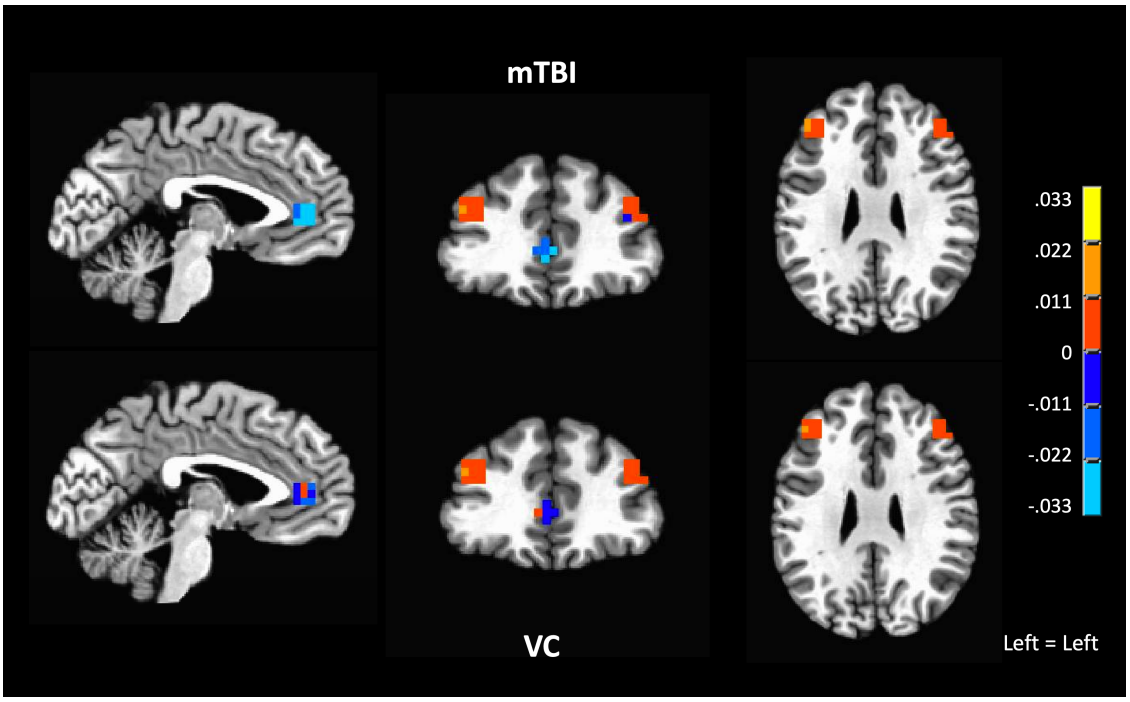
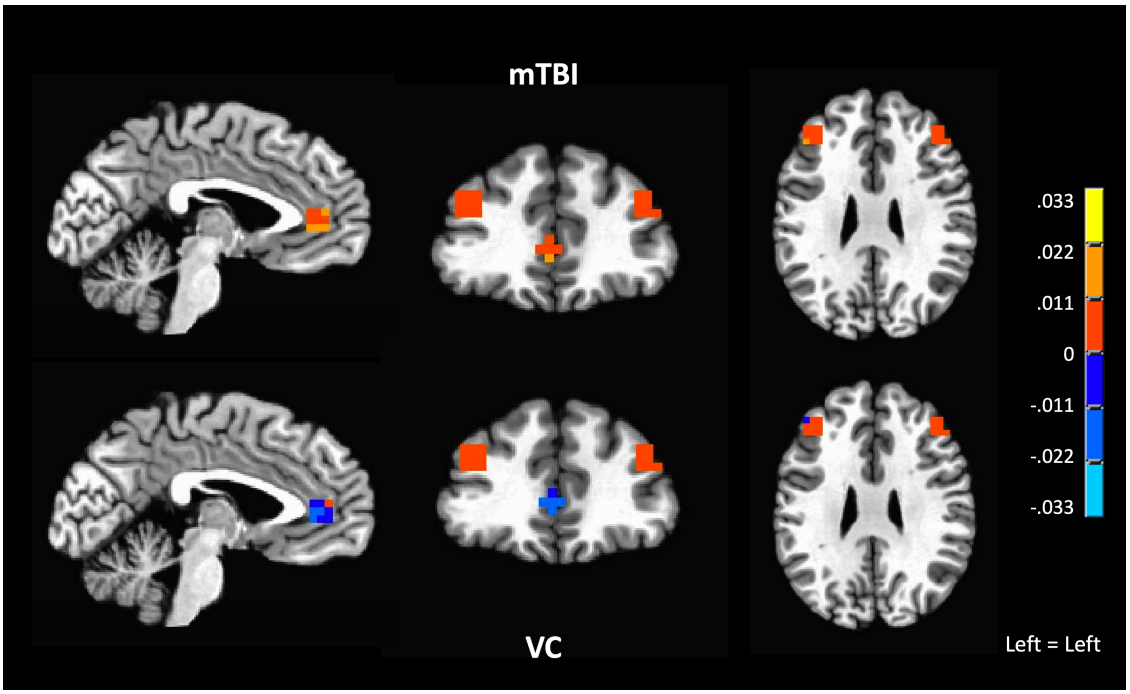


Figure 13. Spaghetti plot representing ACC activation during correct-only, incorrect-only, and correct-incorrect trials for each individual in the VC group.



Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation.

Figure 14. Neural activation in the ACC and bilateral DLPFC during Correct-Incorrect mPASAT trials in mTBI and VC.



Blue/cooler colors represent lower brain activation as measured by the fit coefficient (β), and red/warmer colors indicate higher brain activation.

Figure 15. Neural activation in the ACC and bilateral DLPFC during Incorrect-only mPASAT trials in mTBI and VC.

The individual trial types (i.e., correct, incorrect) were explored to more fully understand the nature of these group differences in the contrast (Figures 11, 12, 13, 14). The investigation of these contrasts revealed that both groups demonstrated deactivation of the ACC during correct trials, but the veteran controls evidenced ACC *deactivation* during incorrect trials while the mTBI veterans evidenced *increased* ACC activation during incorrect trials (Table 5). Thus, the *more negative* ACC activation in the veterans with a history of mTBI on correct vs. incorrect trial contrast is actually the mathematical product of subtracting ACC deactivation during correct trials minus *positive* ACC activation during incorrect trials (please see Table 5 for details). Consistent with this finding, groups significantly differed in the ACC activation during incorrect trials, $F(1, 76) = 5.834$, $\beta = -.267$, $t = -2.415$, $p = .018$, $R^2 = .071$, but not during correct trials, $F(1, 76) = .895$, $\beta = .108$, $t = .946$, $p = .347$, $R^2 = .012$.

Table 5. Neural activation in mTBI and VC in the ACC during correct-incorrect trials and individual trial types

ACC activation	Correct	Incorrect	Correct-Incorrect
mTBI	-.0071 (.0091)	.0033 (.0091)	-.0104 (.0104)
VC	-.0049 (.0108)	-.0030 (.0138)	-.0020 (.0137)

Values reflect mean (SD).

3.8.4.1 Correct-Incorrect ACC Activation & d'

Due to the significant group differences in ACC activation during the contrast between correct-incorrect trials, the relationship between ACC activation and d' was then compared within each group. Within the mTBI group, ACC correct-incorrect activation ($\beta = -.128$, $t = -.881$, $p = .384$) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 40) = 2.706$, $p = .058$, $R^2 = .169$, after controlling for years of education ($\beta = .307$, $t = 2.056$, $p = .046$) and depressive symptoms ($\beta = -.171$, $t = -1.150$, $p = .257$). When PTSD

symptoms were included instead of depressive symptoms, results were similar, $F(3, 40) = 2.327$, $p = .089$, $R^2 = .149$. Exploratory analyses revealed that ACC correct-incorrect activation ($r = -.106$; $p = .492$) was not significantly associated with mPASAT performance (d') in mTBI.

Within the VC group, ACC activation during correct-incorrect trials ($\beta = -.287$, $t = -1.773$, $p = .086$) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 30) = 3.503$, $p = .027$, $R^2 = .259$, after controlling for years of education ($\beta = .198$, $t = 1.178$, $p = .248$) and depressive symptoms ($\beta = -.243$, $t = -1.458$, $p = .155$). When PTSD symptoms were included in lieu of depressive symptoms, ACC correct-incorrect activation ($\beta = -.228$, $t = -1.418$, $p = .167$) also did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 30) = 4.468$, $p = .010$, $R^2 = .309$, after controlling for years of education ($\beta = .138$, $t = .825$, $p = .416$) and PTSD symptoms ($\beta = -.362$, $t = -2.103$, $p = .044$) in VC. In contrast, exploratory analyses revealed that ACC correct-incorrect activation ($r = -.373$; $p = .030$) was significantly associated with mPASAT performance (d') in VC when covariates are not included, such that greater ACC activation (less deactivation) was associated with lower hit rates in VC (see Figure 16).

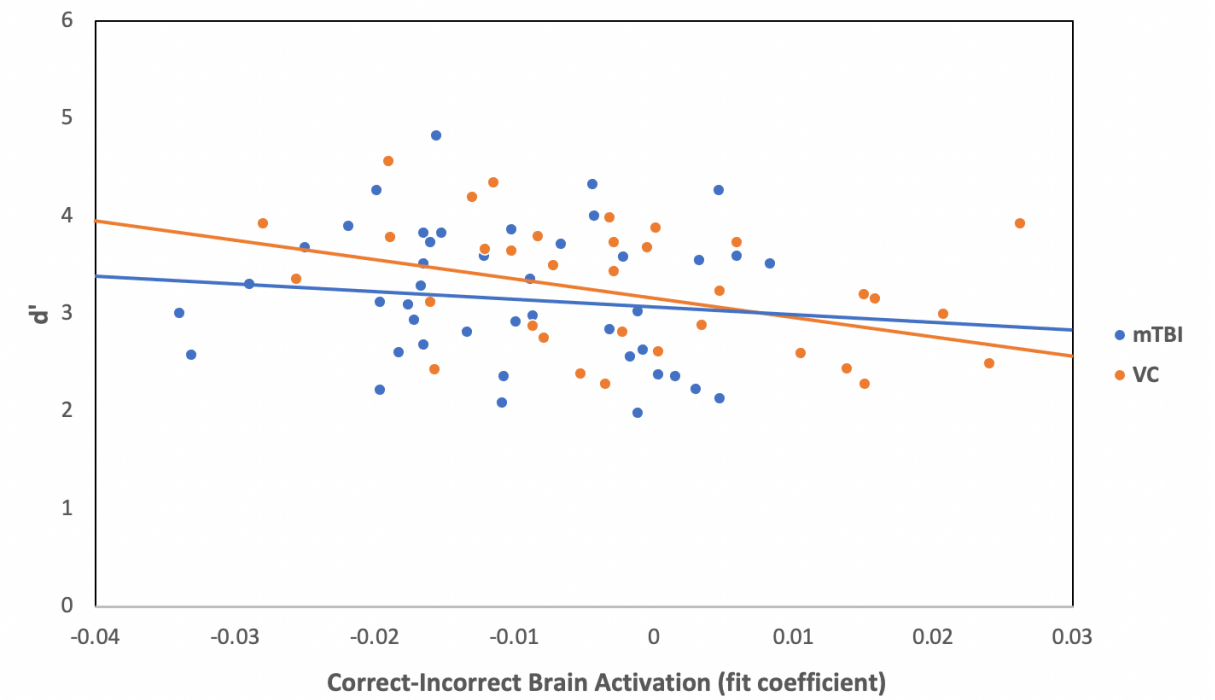


Figure 16. Scatterplot depicting the relationship between ACC activation during Correct-Incorrect trials and mPASAT performance as measured by d' in VC and mTBI.

Given that there was a strong relationship between PTSD and mPASAT performance in VC, such that higher PTSD symptoms were associated with poorer WM performance as measured by d' (r = -.709, p < .001), and that there was a positive, but non-significant, relationship between PTSD symptoms and ACC activation during correct vs. incorrect trials (r = .319, p = .066), we examined whether PTSD might mediate the relationship of ACC correct-incorrect activation to d' in VC. As shown above, the association of ACC correct-incorrect activation and mPASAT performance (d') was not significant when PTSD was included in the model. However, in a model without PTSD, ACC activation during correct vs. incorrect trials (β = -.373, t = -2.272, p = .030) did account for a significant proportion of variance in mPASAT performance (d'), $F(1, 30) = 5.160$, p = .030, R^2 = .139, such that higher ACC activation was associated with worse performance. PTSD symptoms (Cohen's f^2 = .218) exhibited a medium effect size in the brain-behavior relationship model; therefore, symptoms of PTSD appear to

partially mediate the relationship between ACC correct-incorrect activation and mPASAT performance (d') in VC.

3.8.4.2 Correct-Incorrect ACC Activation & Hit Rate

Given that correct-incorrect ACC activation did not significantly predict d' in mTBI, components of d' (i.e., hit rate, false alarm rate) were explored as alternative outcome measures for brain-behavior relationships. Within mTBI, ACC correct-incorrect activation (β < .001, t = -.001, p = .999) did not account for a significant proportion of variance in mPASAT hit rate, $F(3, 40) = 1.759$, $p = .171$, $R^2 = .117$, after controlling for years of education (β = .200, t = 1.303, p = .200) and depressive symptoms (β = -.236, t = -1.542, p = .131). Results did not significantly change when PTSD was included instead of depression, $F(3, 40) = 1.068$, $p = .374$, $R^2 = .074$. Exploratory analyses revealed that ACC correct-incorrect activation (r = -.106; p = .495) was not significantly associated with hit rate in mTBI (Figure 17).

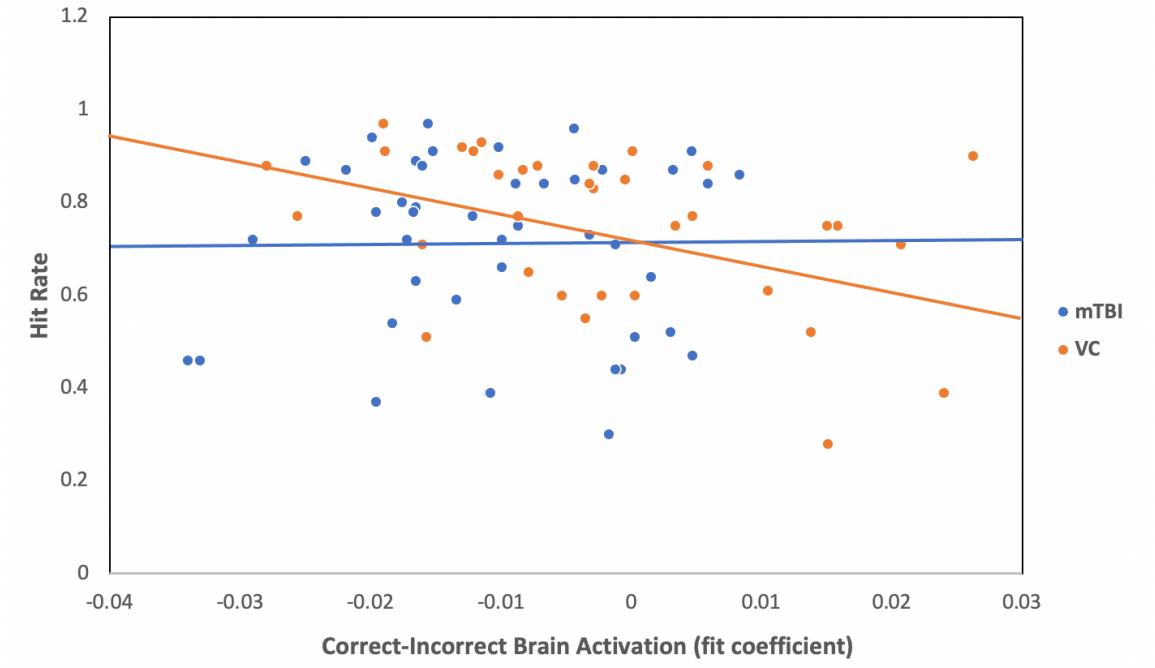


Figure 17. Scatterplot depicting the relationship between ACC activation during Correct-Incorrect trials and mPASAT performance as measured by hit rate.

Within the VC group, ACC activation during correct-incorrect trials (β = -.295, t = -2.022, p = .052) did not account for a significant proportion of variance in hit rate, $F(3, 30)$ = 6.621, p = .001, R^2 = .398, after controlling for years of education (β = .247, t = 1.634, p = .113) and depressive symptoms (β = -.356, t = -2.372, p = .024). When PTSD symptoms were included in lieu of depressive symptoms, ACC activation (β = -.194, t = -1.505, p = .143) also did not account for a significant proportion of variance in hit rate, $F(3, 30)$ = 12.582, p < .001, R^2 = .557, after controlling for years of education (β = .138, t = 1.031, p = .311) and PTSD symptoms (β = -.591, t = -4.290, p < .001) in VC.

Since higher PTSD symptoms were associated with poorer WM performance as measured by hit rate (r = -.491, p = .003), and, as mentioned above, there was a small, positive association of PTSD with ACC correct-incorrect trial activation, we examined whether PTSD might mediate the relationship of ACC correct-incorrect trial activation with hit rate in VC. Given that years of education were not significantly associated with brain activation in these regression models, we conducted exploratory analyses to examine whether models differed without the inclusion of education. A model without either depression or PTSD included showed that ACC activation (β = -.411, t = -2.554, p = .016) significantly predicted hit rate, $F(1, 32)$ = 6.522, p = .016, R^2 = .169, in VC (Figure 17). PTSD symptoms (Cohen's f^2 = .810) exhibited a large effect size in the brain-behavior relationship model, suggesting that PTSD is a partial mediator of the relationship of correct-incorrect ACC activation and hit rate. Therefore, PTSD appears to, at least partially, mediate the relationship between ACC correct-incorrect activation and mPASAT performance as measured by both d' and hit rate in VC.

3.8.4.3 Correct-Incorrect ACC Activation & False Alarm Rate

Within the VC group, ACC activation during correct-incorrect trials (β = .117, t = .672, p = .507) did not account for a significant proportion of variance in false alarm rate, $F(3, 30)$ = 1.640, p = .201, R^2 = .141, after controlling for years of education (β = -.241, t = -1.334, p = .192) and depressive symptoms (β = .162, t = .900, p = .375). When PTSD symptoms were included in lieu of depressive symptoms, results were similar, $F(3, 30)$ = 1.598, p = .210, R^2 = .138. Exploratory analyses revealed that ACC correct-incorrect activation (r = .197; p = .263) was not significantly associated with false alarm rates in VC (Figure 18).

In mTBI, ACC activation (β = .315, t = 2.167, p = .036) did account for a significant proportion of variance in mPASAT false alarm rate, $F(3, 40)$ = 2.788, p = .053, R^2 = .173, after controlling for years of education (β = -.285, t = -1.921, p = .062) and depressive symptoms (β = .050, t = .341 p = .735). When PTSD was included in lieu of depression, results were similar, $F(3, 40)$ = 2.743, p = .056, R^2 = .171. However, these overall models were not significant, likely due to the presence of mood symptoms that did not significantly contribute to the outcome variable. Exploratory analyses revealed that ACC correct-incorrect activation (r = .289; p = .057) was not significantly associated with false alarm rates in mTBI. However, some might consider this relationship a trend such that greater ACC correct-incorrect activation is associated with higher false alarm rates, or worse WM performance, in mTBI (Figure 18).

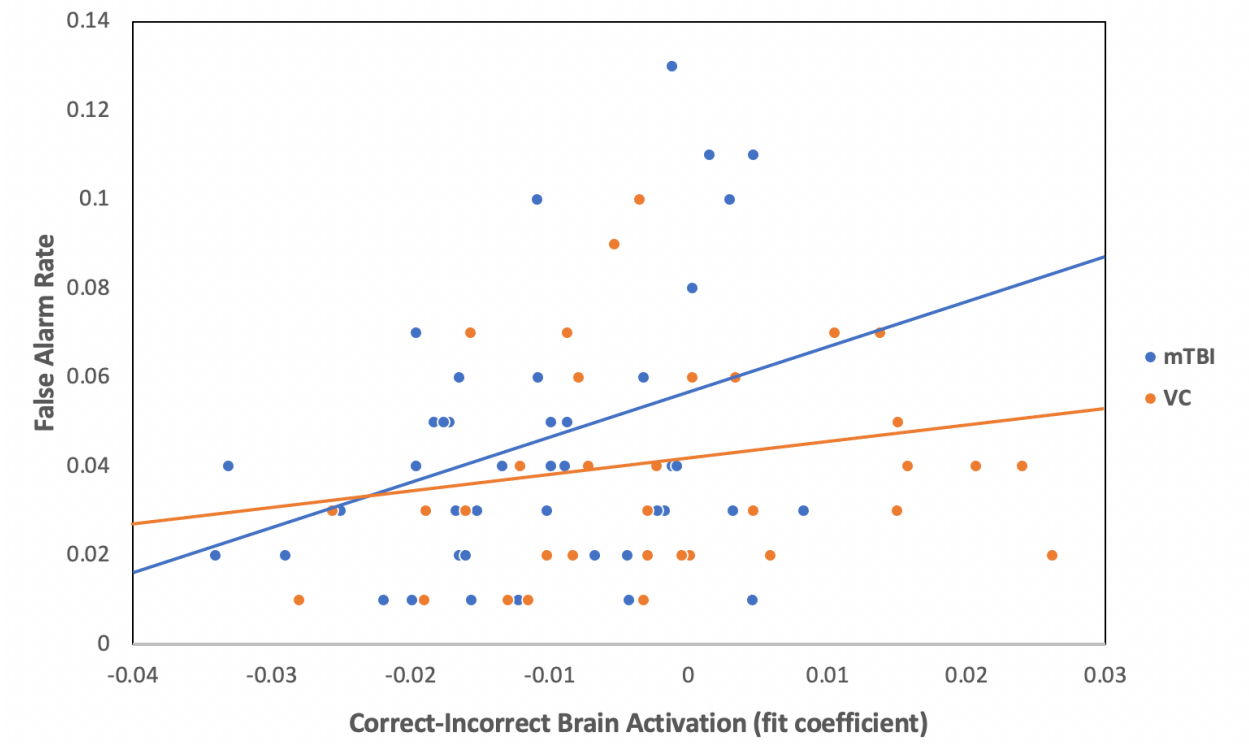


Figure 18. Scatterplot depicting the relationship between ACC activation during Correct-Incorrect trials and mPASAT performance as measured by false alarm rate.

3.8.4.4 Incorrect-only ACC Activation

In order to more fully understand the nature of this brain-behavior relationship in mTBI, incorrect-only trials were explored. Results revealed that groups (mTBI vs. VC; β = -.149, t = -1.129, p = .263) did not significantly differ in ACC activation during incorrect-only trials, $F(2, 75) = .263$, $p = .769$, $R^2 = .007$ (Figure 11, 12, 13), after adjusting for depressive symptoms (β = .211, t = 1.598, p = .061). When PTSD was included in lieu of depression, results were similar, $F(2, 75) = 2.895$, $p = .735$, $R^2 = .072$. An exploratory t-test revealed that groups significantly differed in ACC incorrect-only activation, $t(76) = 2.415$, $p = .018$, $\eta_p^2 = .071$, such that VC evidenced ACC *deactivation* during incorrect trials while the mTBI veterans evidenced *increased* ACC activation during incorrect trials (Table 5).

In mTBI, ACC activation during incorrect-only trials (β = .221, t = 1.472, p = .149) did not significantly predict mPASAT performance (d'), $F(3, 40) = 3.253$, $p = .032$, $R^2 = .196$, after

controlling for years of education (β = .342, t = 2.325, p = .025) and depressive symptoms (β = -.239, t = -1.590 p = .120). In mTBI, ACC activation during incorrect-only trials (β = .044, t = -.280, p = .781) did not significantly predict hit rate, $F(3, 40) = 1.759$, p = .171, R^2 = .117, after controlling for years of education (β = .207, t = 1.342, p = .187) and depressive symptoms (β = -.247, t = -1.570, p = .124). In contrast, ACC activation during incorrect-only trials (β = -.364, t = -2.425, p = .020) significantly predicted mPASAT false alarm rate, $F(3, 40) = 3.215$, p = .033, R^2 = .194 (Figure 19), after controlling for years of education (β = -.305, t = -2.066, p = .045) and depressive symptoms (β = .173, t = 1.147 p = .258) in mTBI. Exploratory analyses revealed that ACC incorrect-only activation was not significantly associated with false alarm rate (r = -.248; p = .104), hit rate (r = -.072; p = .641), or d' (r = .078; p = .616) in mTBI.

In VC, ACC activation during incorrect-only trials (β = .039, t = .230, p = .820) did not significantly predict mPASAT performance (d'), $F(3, 40) = 2.244$, p = .104, R^2 = .183, after controlling for years of education (β = .241, t = 1.374, p = .180) and depressive symptoms (β = -.284, t = -1.622 p = .115). Moreover, ACC activation during incorrect-only trials (β = -.364, t = .341, p = .736) did not significantly predict mPASAT false alarm rate, $F(3, 40) = .059$, p = .232, R^2 = .131, after controlling for years of education (β = -.271, t = -1.494, p = .146) and depressive symptoms (β = .168, t = .934 p = .358). In VC, ACC activation during incorrect-only trials (β = .064, t = .420, p = .678) did not significantly predict hit rate, $F(3, 30) = 4.714$, p = .008, R^2 = .320, after controlling for years of education (β = .288, t = 1.799, p = .082) and depressive symptoms (β = -.401, t = -2.515 p = .018). However, ACC incorrect-only activation was not significantly associated with false alarm rate (r = .041; p = .817), hit rate (r = .065; p = .716), or d' rate (r = .043; p = .808) in VC.

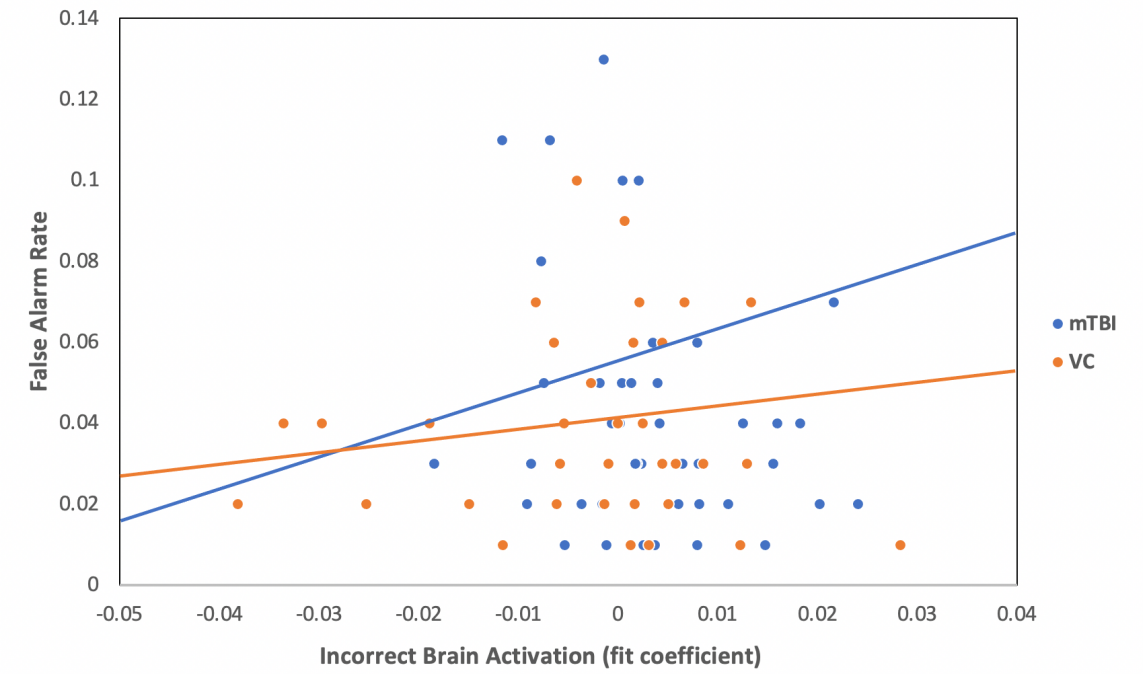


Figure 19. Scatterplot depicting the relationship between ACC activation during Incorrect-only trials and mPASAT performance as measured by false alarm rate.

3.8.4.6 Correct-Incorrect DLPFC Activation

A hierarchical regression analysis revealed group (mTBI vs. VC; β = .016, t = .117, p = .907) did not account for a significant proportion of variance in bilateral DLPFC activation during the contrast between correct-incorrect trials, $F(2, 75) = .263$, $p = .769$, $R^2 = .007$ after adjusting for depressive symptoms (β = -.073, t = -.528, p = .599). When PTSD was included in lieu of depression, results were similar, $F(2, 75) = .309$, $p = .735$, $R^2 = .008$. Because of the lack of group differences in DLPFC activation in correct-incorrect trials, we did not explore any brain-behavior relationships in this ROI for this contrast.

3.8.5 Self-reported Cognitive Complaints

We also explored the bifurcation of the mTBI group into subgroups delineated by the presence of self-reported cognitive complaints of executive function (as measured by the FrSBe), which encompass complaints of working memory. Based on FrSBe manual defined cutoffs (Grace & Malloy, 2001) the "mTBI-NoSubjDis" group consisted of mTBI Veterans with few

self-reported complaints of disinhibition (FrSBe t-score < 60; n = 16). The "mTBI-SubjDis" group (FrSBe t-score ≥ 60; n = 24) consisted of mTBI Veterans with borderline (FrSBe t-score = 60–64; n = 2) and clinically significant levels of disinhibition (FrSBe t-score ≥ 65; n = 22). Previous research (Holiday et al., 2020) has revealed the mTBI borderline disinhibition group (FrSBe t-score = 60-64) significantly differed on an executive function task from the mTBI-NoSubjDis group (FrSBe t-score < 60) and non-mTBI Veterans, but did not significantly differ from the mTBI clinical disinhibition group (FrSBe t-score ≥ 65); thus, the mTBI borderline and clinical disinhibition were collapsed across groups to form the mTBI-SubjDis group. Within the mTBI group, the presence of self-reported cognitive complaints of executive function (β = .183, t = 1.000, p = .324) did not account for a significant proportion of variance in mPASAT performance (d'), $F(3, 36) = 2.831$, p = .324, R^2 = .191, after controlling for years of education (β = .318, t = 2.046, p = .048) and depressive symptoms (β = -.277, t = -1.467, p = .151). Within the mTBI group, the presence of self-reported cognitive complaints of executive function (β = -.070, t = -.361, p = .720) did not account for a significant proportion of variance in ACC activation during correct+null trials, $F(2, 37) = 1.362$, p = .269, R^2 = .069, after controlling for depressive symptoms (β = .295, t = 1.531, p = .134). Similarly, the presence of self-reported cognitive complaints of executive function (β = .259, t = 1.360, p = .182) did not account for a significant proportion of variance in bilateral DLPFC activation during correct+null trials, $F(2, 37) = 1.852$, p = .171, R^2 = .091, after controlling for depressive symptoms (β = .067, t = .350, p = .728). Imaging results remained the same with the inclusion of PTSD instead of depression and without the inclusion of mood as a covariate. Furthermore, results did not change when alternative contrasts were examined as exploratory analyses (i.e., run3-run1, correct+null, mPASAT runs minus visual monitoring, correct-incorrect).

3.8.6 Relationship between mPASAT and Alternative Neuropsychological Measures

Given that the mPASAT was a novel task for this study, correlations were examined between the mPASAT performance (d', hit rate, false alarm rate) and traditional neuropsychological measures that tap similar domains of WM, sustained attention, and processing speed including WAIS-III/IV Digit Span, WAIS-III/IV Digit Symbol Coding, WAIS-III/IV Symbol Search, and D-KEFS TMT (see Table 6). (Of note, versions of the WAIS-III were updated to the WAIS-IV during the study, so five participants received only WAIS-III, while the rest received only WAIS-IV. Of the participants who received the WAIS-III, three participants were in the mTBI group, and two participants were in the veteran control group. Performance between both versions (i.e., WAIS-III vs. WAIS-IV) Digit Span and Digit Symbol Coding scaled scores were directly compared using independent sample t-tests. There were no significant differences between performance on WAIS-III vs. WAIS-IV Digit Span (t = 1.952, p = .055) and Digit Symbol Coding (t = .043, p = .966). Therefore, performance was collapsed across both versions of the WAIS. Though comparison of performance on two different versions of the same test is not optimal, scaled scores of WAIS subtests were extracted from either WAIS-III or WAIS-IV depending on the data available.) As displayed in Table 6, WAIS-III/IV Digit Span, WAIS-III/IV Digit Symbol Coding, WAIS-III/IV Symbol Search, D-KEFS TMT: Letter Sequencing, and D-KEFS TMT: Letter-Number Sequencing were significantly positively correlated with d' and hit-rate and negatively correlated with false alarm rate. Group differences on traditional neuropsychological measures was examined using independent sample t-tests, and no significant differences were detected between mTBI veterans and VC.

Table 6. Group differences in performance and Pearson correlations between mPASAT performance (d', hit rate, false alarm rate) and traditional neuropsychological measure in the whole sample.

Neuropsychological Measures	mTBI: mean (SD)	VC: mean (SD)	p-value	Correlation with mPASAT		
				d'	Hit Rate	False Alarm Rate
WAIS-III/IV Digit Span	9.58 (3.30)	9.97 (2.48)	.569	**.457*** **	**.440*** **	**-.324** **
WAIS-III/IV Digit Symbol Coding	10.33 (2.40)	10.85 (1.99)	.305	.174	.170	-.136
WAIS-III/IV Symbol Search	10.14 (2.93)	10.00 (2.64)	.826	**.417*** **	**.441*** **	**-.230***
D-KEFS Trail Making: Number Sequencing	11.14 (2.35)	11.35 (2.56)	.704	.119	.102	-.069
D-KEFS Trail Making: Letter Sequencing	11.00 (2.30)	11.06 (2.79)	.919	**.247***	**.225***	-.178
D-KEFS Trail Making: Number-Letter Sequencing	9.65 (3.00)	9.97 (2.54)	.621	**.338** **	**.405*** **	**-.279***

Abbreviations: mTBI, mild traumatic brain injury; VC, veteran controls; *r*, correlation. p-value (* < .05; ** < .01, *** < .001).

3.8.7 Neural Activation During Alternative Neuropsychological Measures

Correlations were examined between the neural activation in the ACC and bilateral DLPFC during the mPASAT and other neuropsychological measures in the entire sample. Previously discussed contrasts (i.e., correct+null, correct-incorrect, correct+null run3-run1, correct+null mPASAT minus visual monitoring task) were correlated with other neuropsychological measures. No neuropsychological measures were significantly correlated with imaging contrasts in the entire sample.

Within mTBI, correlations between neural activation in the ACC and bilateral DLPFC during the mPASAT and other neuropsychological measures were examined (Table 7). ACC was not correlated with any neuropsychological measures during any contrast, except for correlations between ACC activation during correct+null run3-run1 trials and TMT: Number Sequencing.

Within the mTBI group, bilateral DLPFC activation was not significantly correlated with other neuropsychological measures during any contrast. For the neuropsychological test that demonstrated a significant relationship with ACC activation in mTBI (i.e., DKEFS TMT Number Sequencing scaled score), we explored brain activation in the ACC as mediators of the relationship between group (i.e., mTBI v. VC) and performance on the TMT. As demographic (i.e., age, years of education, sex, ethnicity) and mood symptom variables were not significantly correlated with DKEFS TMT Number Sequencing scaled score in the entire sample, no covariates were included in this model. ACC activation during correct+null trials run3-run1 (β = -.178, t = -1.554, p = .124) and group (mTBI vs. VC; β = .042, t = .364, p = .717) did not account for a significant proportion of variance in DKEFS TMT Number Sequencing scaled score, $F(2,74) = 1.281$, $p = .284$, $R^2 = .033$, in mTBI, and thus, did not mediate the relationship between group and performance.

Table 7. Pearson correlations between imaging contrasts in the anterior cingulate cortex (ACC) and traditional neuropsychological measures.

ACC Imaging Contrasts in mTBI	Digit Span	Coding	Symbol Search	Trails: Number	Trails: Letter	Trails: Number -Letter
Correct+Null	-.011	-.048	.091	-.047	.111	-.058
Correct-Incorrect	.056	-.036	-.074	-.276	-.151	.031
Correct+Null: Run3-run1	-.061	-.170	.105	**-.341***	-.055	.083
Correct+Null minus Visual Monitoring	.051	-.102	.187	.027	.036	-.081

Within the VC group, DKEFS TMT Number Sequencing scaled score was significantly correlated with DLPFC activation during correct+null minus visual monitoring trials (r = .359, p = .037). There were no other significant correlations within the VC group. For the neuropsychological tests that demonstrated a significant relationship with brain activation in VC

(i.e., DKEFS TMT Number Sequencing scaled score), we explored brain activation in the DLPFC as mediators of the relationship between group and performance. As noted above, demographic and mood symptom variables were not significantly correlated with DKEFS TMT Number Sequencing scaled score in the entire sample and thus were not included as covariates in these models. Bilateral DLPFC activation during correct+null trials minus visual monitoring trials (β = .182, t = 1.569, p = .121) and group (mTBI vs. VC; β = .022, t = .193, p = .847) did not account for a significant proportion of variance in DKEFS TMT Number Sequencing scaled score, $F(2,74) = 1.283$, $p = .283$, $R^2 = .034$. Taken together, these results reveal that brain activation does not mediate the relationship between group and performance in other WM domains.

3.8.8 Psychiatric Measures and Neural Activation

The relationship between the neural activation and psychiatric measures (i.e., PTSD, depression) was also examined to explore the independent influences of mTBI and psychiatric symptoms. Surprisingly, PTSD and depressive symptoms were not significantly correlated with ACC activation or DLPFC activation for any combination of contrasts explored above (i.e., run3-run1, correct+null minus visual monitoring, correct-incorrect) in the entire sample. Within the mTBI group, PTSD and depressive symptoms were not significantly correlated with ACC activation or DLPFC activation for any combination of contrasts explored above (i.e., run3-run1, correct+null, minus visual monitoring, correct-incorrect). In the VC group, PTSD symptoms were significantly correlated with correct+null run3-run1 (r = .416, p = .014). Similarly, depressive symptoms were also significantly correlated with correct+null run3-run1 (r = .433, p = .011) in the VC group.

RESULTS ACKNOWLEDGEMENTS

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4. DISCUSSION

The overarching aim of this project was to examine WM performance and the underlying neural mechanisms of WM performance using a cognitively demanding task in mTBI veterans via fMRI. Contrary to our hypothesis, results revealed no significant group (mTBI veterans vs. VC) differences in WM performance as measured by d', hit rate, or false alarms. This was the case regardless of whether or not education, depression or PTSD was included in the model. The only significant predictor of WM performance in this sample was years of education; this was true in both groups with no differential relationship in mTBI vs. VC. Despite not finding significantly different brain activation in ROI-based or whole brain analyses during our primary fMRI contrast (correct+null), a secondary, arguably more precise contrast (correct-incorrect), revealed that mTBI participants had lower ACC response during correct compared to incorrect trials, while the ACC response among VC was equivalently low (deactivated) during both correct and incorrect trials. Thus, the group differences were primarily during the incorrect trials, which drove the finding for the contrast. This finding held when controlling for education, and either depressive symptoms or PTSD symptoms. The finding appeared to be specific to the ACC, as DLPFC activation to the correct vs. incorrect contrast was not different between groups. In mTBI, greater ACC activation during the contrast of correct and incorrect trials was associated with higher false alarm rates, or worse WM performance. Consistent with this pattern in mTBI, in VC, higher ACC activation was also associated with poorer performance; response during the contrast of correct and incorrect trials was associated with worse d' and lower hit rates. In VC, but not mTBI, PTSD symptoms appear to mediate these relationships such that these associations are not significant and have lower effect sizes in models that account for PTSD symptoms. Contrary to our hypothesis, DLPFC activation was not associated with any measure of WM

performance in mTBI or VC. Several alternative analyses were pursued, including whole brain voxel-based comparisons, which confirmed strong cortex-wide response to the tasks, including in the *a priori* regions of interest, but did not reveal strong group differences in brain activation. Taken together, results revealed that, despite no differences in WM performance, veterans with mTBI demonstrated more negative ACC activation during the contrast of correct vs. incorrect trials, driven by heightened response during incorrect trials compared to VC. In mTBI, this pattern of ACC activation to incorrect compared to correct trials was associated with more false alarms in models accounting for depression or PTSD; comparable relationships of ACC activation during this contrast with d' and hit rate in VC were mediated by associations of PTSD symptoms to both brain and behavior.

4.1 WM Performance in mTBI

Contrary to civilian study findings that mTBI was associated with WM impairments (Bohnen et al., 1992; Dean & Sterr, 2013; Helmich et al., 2015; Kumar et al., 2013; McAllister et al., 2004; Smits et al., 2008), results revealed that a history of mTBI was not significantly associated with WM performance after accounting for years of education and mood symptoms. One of the main aims of this study examined mPASAT performance using d', which was calculated as the z-score of the hit rate minus the z-score of the false alarm rate. This metric of performance was selected because d' is a comprehensive measure of WM, encompassing both task accuracy (hit rate) and response inhibition (false alarm rate). When significant relationships were detected using d' as the overarching measure of WM performance, the individual components of d' were explored to determine whether task accuracy (hit rate) or response inhibition (false alarm rate) was contributing to the findings. As an exploratory analysis, we examined whether veterans with and without a history of mTBI differed on hit rate or false alarm

rate and found that the groups did not differ. Therefore, regardless of the WM metric used to examine performance (i.e., d', hit rate, false alarm rate), veterans with and without a history of mTBI did not significantly differ in WM.

Previous studies in chronic mTBI have demonstrated that WM deficits were only detected using highly demanding tasks (Bryer et al., 2013; Dean & Sterr, 2013). One possible explanation for the lack of differences in behavioral performance between mTBI veterans and VC in the current study is that the task may not have been challenging enough. Although the visually presented PASAT demonstrated comparable results to the traditional auditory PASAT in regards to detecting individuals with mTBI, Fos et al. (2000) found the visual version of the PASAT to be less difficult than the traditional auditory version. Thus, it is possible that the mPASAT might not have been challenging or specific enough to detect persisting working memory deficits that veterans with subjective executive function/working memory complaints in the chronic phase of mTBI are experiencing in their daily lives. In order to examine whether low task difficulty was prohibiting the detection of group differences, we explored whether the mPASAT task demonstrated a ceiling effect, which is defined as a relatively easy task with such that substantial proportions of individuals obtain either maximum or near-maximum scores (Wang, Zhang, McArdle, & Salthouse, 2008). We examined the hit rate (i.e., percentage correct) of the mPASAT performance for each group, and the average (mean) hit-rate in the VC group was 75% (SD = 17%) and the average hit-rate mTBI group was 71% (SD = 19%). Results revealed that no participants received a perfect score, and only sixteen percent of mTBI veterans (7/44) and eighteen percent of VC (6/34) scored above the 90th percentile. These results suggest that a ceiling effect due to low task difficulty is not likely to be entirely responsible for the lack of group differences.

In addition to task accuracy (hit rate), we also explored whether groups differed in response inhibition, as measured by false alarm rate. Response inhibition has been found to be diminished in TBI (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011; Dockree & Robertson, 2011), and we suspected that veterans with a history of mTBI might exhibit more false alarms during the WM task as a result of poor response inhibition. However, current study results revealed that veterans with and without a history of mTBI did not significantly differ in false alarm rate. Thus, veterans with or without a history of mTBI did not differ in accuracy or response inhibition on the WM task. These findings are consistent with several studies that did not detect differences in WM performance between civilians with and without a history of mTBI (Chen et al., 2012; Chen et al., 2004; Dean et al., 2015; van der Horn et al., 2016; Wylie et al., 2015).

Given the high incidence of comorbidity of mTBI with psychiatric disorders such as post-traumatic stress disorder (PTSD; Lew et al., 2008) and depression (Hoge et al., 2008; Spencer et al., 2010), we also explored whether a relationship between mood symptoms (i.e., PTSD or depression) and WM performance was masking a significant relationship between mTBI status and WM performance. Consistent with these previous studies (Hoge et al., 2008; Lew et al., 2008; Spencer et al., 2010), examination of mood symptoms and combat exposure revealed that veterans with a history of mTBI endorsed greater levels of PTSD symptoms, depressive symptoms, and combat exposure than veterans without a history of mTBI. In contrast to previous studies that found that discrepancies in WM task performance between mTBI veterans and veteran controls was due to psychiatric comorbidity (Dolan et al., 2012; Simmons & Matthews, 2012), the current study revealed that years of education was a significant predictor of WM performance, while depressive or PTSD symptoms were not. Furthermore, exploratory analyses

revealed that even when mood symptoms were excluded from the model, mTBI status was not associated with WM performance. Thus, psychiatric comorbidity does not appear to be influencing the relationship between mTBI status and WM performance in this sample.

In addition to mood symptoms, another important factor to consider is task load over time. Bryer et al. (2013) hypothesized that continuous tasks with a high task load over time require greater executive control and recruit compensatory neural recruitment to facilitate task performance in comparison to shorter, discrete tasks. Thus, another potential explanation for the lack of group influence on behavior during the entire task is that initial task performance might be similar between groups, but veterans with mTBI might encounter difficulty sustaining performance on the task overtime. It is also plausible that veterans with mTBI might start out with stronger performance, but they might burn out or fatigue earlier than veterans without a history of mTBI. Therefore, we examined whether performance differed between groups during the final run compared to the first run of the task. Results revealed that whether a veteran had a history of mTBI did not influence the difference between the performance on the final and first run of the task; both groups improved over time. This increased task performance over time is likely due to practice effects, which is consistent with the results of a comprehensive review of the PASAT (Tombaugh, 2006). Thus, high task load over time does not appear to play a key role in differentiating behavioral performance in between veterans with and without a history of mTBI in this sample. Despite finding similar behavioral performance between groups, current study results contrast with previous findings that individuals with mTBI recruit additional cognitive resources to facilitate performance at higher in comparison to lower levels of task demands (Bryer et al., 2013; McAllister et al., 2006; McAllister et al., 2001). Unfortunately, the task in the current study did not systematically vary task load over time, so we were unable to

directly compare brain activation and performance between levels of high and low task load. Future studies could benefit from the inclusion of multiple levels of task difficulty.

One of the most consistent findings revealed across the models in the current study was the relationship between education and performance on the mPASAT. In both veterans with and without a history of mTBI, greater years of education was associated with better mPASAT performance. Veterans with and without a history of mTBI did not significantly differ in average (mean) levels of education, and the median and range of education levels was similar between veterans with mTBI (median = 14; range = 12 – 18) and veterans without a history of mTBI (median = 15; range = 12 - 18). Therefore, it does not appear that the range or distribution of education levels is driving these findings. Cognitive reserve, or higher levels of education known as premorbid functioning prior to injury, has been proposed as a protective factor for cognition following mTBI (Kesler, Adams, Blasey, & Bigler, 2003; Stenberg et al., 2020). In fact, a longitudinal study in mTBI found that cognitive reserve moderates cognitive outcomes after mTBI (Stenberg et al., 2020). Given the consistent relationship between education and performance in this study, we examined whether years of education moderated the relationship between group and mPASAT performance. Contrary to previous findings (Stenberg et al., 2020), years of education did not moderate the relationship between group and WM performance. Similarly, the relationship between brain activation in the ACC or DLPFC and WM performance did not differ based on years of education in either mTBI or veteran controls. While it is possible that individuals with higher premorbid functioning or cognitive reserve are less vulnerable to deleterious outcomes following mTBI, the association between premorbid functioning and WM performance does not appear to be specific to mTBI in the current study. Thus, it is more likely that the individuals with higher levels of education perform better at this cognitively demanding

WM task regardless of their mTBI status. In addition to cognitive demand, this task incorporates specific cognitive abilities, such as serial addition, that may be highly sensitive to education and may not tap into everyday WM problems.

The relationship between years of education and WM performance is not unexpected as education has demonstrated a consistent relationship with cognition (Rosselli & Ardila, 2003) and was specifically included as a covariate to account for these effects. Another demographic variable that has shown an association with cognition following mTBI is age (Almeida, Hankey, Yeap, Golledge, & Flicker, 2015), which was surprisingly unrelated to WM performance or brain activation during the WM task. One possible explanation for the lack of relationship between age and cognitive performance in the current study is the restricted range of the current sample. Veterans recruited for this study were on average 31.28 years old with a maximum possible age of 50 years old. While a history of mTBI has been identified as a significant risk factor for cognitive decline (Almeida et al., 2015), one study identified the average age of onset for this decline to be approximately 68 years old (Li, Risacher, McAllister, & Saykin, 2016). Another study found that mTBI was associated with the increased risk of dementia when the injury occurred over the age of 65, but mTBIs were not significantly predictive of dementia in individuals younger than 65 years old (Gardner et al., 2014). Additionally, Gardner et al. (2014) suggested that adults under the age of 65 are more resilient to the cognitive effects of mTBI than older adults. Thus, the young age of injury as well as testing age of the veterans in this cohort may have reduced our ability to detect age-related cognitive effects in the current study.

Given that the mPASAT was a novel task implemented in this study, performance on the mPASAT (d', hit rate, false alarm rate) was compared to traditional neuropsychological measures (Table 6). The significant associations between mPASAT performance and these

traditional neuropsychological measures support that the mPASAT is indeed reflecting WM performance. Similar to the mPASAT behavioral results, no significant differences in traditional neuropsychological measures were detected between veterans with and without a history of mTBI. Taken together, these results reveal that group differences in WM performance were not detected using the cognitively demanding mPASAT or more traditional neuropsychological tests. One explanation for the dearth of differences detected between veterans with and without a history of mTBI across numerous WM tasks of varying cognitive load is that veterans with a remote history of mTBI actually may not differ in WM from veterans without a history of mTBI. Thus, results of the current study are consistent with literature suggesting that the clinical course of mTBI may fully resolve within days to months following the injury (Bigler, 2008). Furthermore, the current study suggests that other factors, such as education level, may be stronger predictors of WM performance than remote history of mTBI.

4.2 Brain Activation in mTBI

As demonstrated in previous studies, it is not uncommon for individuals with a history of mTBI to be able to maintain a similar level of performance to those without a history of TBI (Chen et al., 2012; McAllister et al., 1999; McAllister et al., 2001). Therefore, fMRI was used to explore whether veterans with and without a history of mTBI employ different neural mechanisms during the task to support this performance. Previous studies have found increased activation in mTBI compared to controls, which is hypothesized to serve as a compensatory mechanism to facilitate adequate WM performance (Chen et al., 2012; McAllister et al., 1999; McAllister et al., 2001). Results of the current study revealed different findings based on the contrasts selected. In contrast to our original hypothesis, results revealed similar brain activation in veterans with and without a history of head injury during correct trials (i.e., correct+null

contrast in which participants correctly respond or withhold response; referred to as "correct trials" hence forth) on the mPASAT. When only correct trials are examined, results reveal that veterans with and without mTBI both exhibit deactivation of the ACC and increased activation in the bilateral DLPFC, as well as numerous other cortical and subcortical regions as seen in our exploratory whole-brain analyses. This finding is inconsistent with previous findings that individuals with mTBI activate the DLPFC *and* ACC during WM tasks (Chai et al., 2018). Activation of the bilateral DLPFC in mTBI veterans at similar magnitudes to veteran controls implies that the mTBI veterans in the current study did not evidence the chronic DLPFC injuries that McAllister et al. (2001) suggested diminishes the central executive's capacity to appropriately allocate resources to cognitively demanding WM tasks.

In addition to correct trials, we examined brain activation in the ACC and bilateral DLPFC during the contrast of correct and incorrect trials as we believed that this contrast may encapsulate the entirety of the WM task. This contrast subtracted brain activation on inaccurate trials from brain activation during accurate trials and enabled isolation of WM performance unique to accurate trials. The contrast of correct vs. incorrect trials may be considered a closer proxy to d' given that it incorporates the brain activation during accurate and inaccurate responses. On this correct vs. incorrect contrast, veterans with and without a history of mTBI *significantly differed* in ACC activation above and beyond the influence of mood symptoms. Specifically, veterans with a history of mTBI exhibited a *more negative contrast of activation in* the ACC than veterans without a history of mTBI. The individual trial types (i.e., correct, incorrect) were explored to understand how these trial types are contributing to these group differences in the contrast. We found that both groups demonstrated deactivation of the ACC during correct trials, but the veteran controls also evidenced ACC *deactivation* during incorrect

trials while the mTBI veterans evidenced *increased* ACC activation during incorrect trials. We will discuss this finding further in the context to brain-behavior relationships below. Veterans with and without a history of mTBI did not differ on the incorrect-only contrast when controlling for mood symptoms. Therefore, the within-subject pattern of higher activation to incorrect than correct trials might be more important than group differences on incorrect-only trials. Thus, the detection of group differences in ACC activation during correct vs. incorrect trials highlights the importance of selecting appropriate contrasts for imaging analyses. There were no differences detected between veterans with and without mTBI in bilateral DLPFC activation on the contrast of correct and incorrect trials.

Alternative contrasts designed to isolate WM processes from visual and motor system involvement were also explored. In order to better distinguish the processes unique to WM from more general task demands (e.g., processing speed, sustained attention), we contrasted brain activation during the mPASAT to activation during a visual monitoring control task. It was proposed that the contrast of the mPASAT to the visual monitoring task could facilitate detection of subtle differences in brain activation specific to WM. Results of the current study revealed that brain activation on this contrast did not differ between veterans with and without a history of mTBI. Thus, after accounting for more general task demands such as visual and motor system involvement, processing speed and sustained attention, differences in brain activation of isolated WM components between veterans with and without a history of mTBI were not detected.

In addition to the investigation of group differences in *a priori* selected ROIs, we also explored a whole-brain voxel-wise approach to examine BOLD responses. This whole-brain approach enabled us to examine potential activation differences outside of the *a priori* defined ROIs proposed above. We observed widespread significant clusters of cortical activations for all

contrasts examined, including in regions within and outside our *a priori* ROIs, in each group (Figure 6, Table 4) after accounting for multiple comparisons (Cox et al., 2017). However, whole-brain voxel-wise comparisons of the two groups revealed that there were no clusters of activation that evidenced a significant difference between veterans with and without a history of mTBI. The lack of detection of significant differences using the whole-brain approach is not surprising given the added technical challenges of the whole-brain approach in comparison to *a priori* techniques. Specifically, the number of brain regions compared between groups is often large in comparison to the number of observations (i.e., trials, participants; Ryali, Supekar, Abrams, & Menon, 2010). Thus, one must correct for the multiple comparisons between all of the voxels between groups to avoid spurious detection of brain regions that differ between groups and an inflated false positive rate (Cox et al., 2017). Unfortunately, after employing the appropriate techniques to correct for these multiple comparisons (Cox et al., 2017), there were no regions of significant group difference between veterans with and without a history of mTBI for any of the proposed contrasts. Detecting whole brain differences, especially after appropriate statistical controls, may require more statistical power than finding ROI-based differences, which may be why we did not see significant clusters of group difference in the ACC in the whole brain group comparison analysis using the correct-incorrect contrast.

4.3 Brain-Behavior Relationships

In order to fully understand the role of the DLPFC activation and ACC deactivation that was found in both groups during correct trials, we first examined the relationship between brain activation during correct trials and behavioral performance in each group. Within veterans with a history of mTBI, neither DLPFC activation nor ACC activation during correct trials (i.e., Correct+Null contrast) was associated with WM performance as measured by d', hit rate, or false

alarm rate. Similarly, DLPFC activation during correct trials was not related to WM performance as measured by d', hit rate, or false alarm rate in veteran controls. However, ACC activation during correct trials was significantly related to WM performance (d') and false alarm rate, but not hit rate in veteran controls. Specifically, there was a negative relationship between ACC activation during correct trials and WM performance, such that stronger deactivation of the ACC was associated with better WM performance (d') and fewer false alarms in VC.

The finding that ACC deactivation was associated with *better* WM performance in the VC group may be explained by the role of the ACC in the default mode network. The default mode network is a group of brain regions that are generally *more* active during rest and *less* active during tasks, such as those that tap into WM (Greicius, Krasnow, Reiss, & Menon, 2003). It is possible that the region of the ACC examined in the current study is actually involved in the default mode network rather than the working memory network as initially proposed. Greicius et al. (2003) found that healthy individuals actually demonstrate deactivation of regions within the default mode network, including the ventral ACC, to facilitate performance of cognitively demanding WM tasks. It appears that VC who were better able to turn off the ACC node of the default mode network during correct trials had a better d' and fewer false alarms. It is not clear why this brain-behavior relationship was not also seen in the mTBI group except that, as discussed below, WM performance may be more driven by the relative response of the ACC to correct versus incorrect trials in the mTBI group.

Given the group differences in ACC activation during the contrast of correct and incorrect trials described above, we explored the relationship between correct-incorrect trials and WM performance. Surprisingly, depressive and PTSD symptoms were not significantly associated with false alarm rate when examining the contrast of correct-incorrect trials in the

mTBI group; thus, mood was excluded for these analyses. In veterans with mTBI, ACC activation was not associated with WM performance as measured by d' or hit rate; however, ACC activation to correct vs. incorrect trials *was* significantly associated with false alarm rate after accounting for education, but not mood, in mTBI. The nature of this relationship is such that greater ACC activation, particularly during incorrect in comparison to correct trials, is associated with higher false alarm rates, or worse WM performance, in mTBI. Previous studies have highlighted the role of the ACC in attentional control and conflict monitoring (Chai et al., 2018; Hillary, 2008), and making errors often leads to engagement of the ACC, an phenomenon affectionately called the "Oh S*!#" effect. It appears that this effect was more common in the mTBI group than the VC group despite similar performance on the task. Furthermore, those mTBI with the highest number of false alarms showed this ACC activation on incorrect relative to correct trials to the greatest extent. Interestingly, the VC do not show a relationship of ACC correct-incorrect response to false alarms, but do show a relationship to d' and hit rates, such that those VC who have relatively less deactivation during incorrect compared to correct trials have poorer d' and hit rates. However, we found that these associations in the VC group were attenuated and non-significant when accounting for PTSD symptoms. As we did not observe similar PTSD or depression mediation effects in the mTBI group, the link between overall false alarm rate and relative ACC response during incorrect trials in mTBI is unlikely to be driven by PTSD symptoms.

Correlations between the neural activation during the mPASAT and other neuropsychological measures that tap similar domains were examined. Specifically, the relationship of brain activation during the mPASAT with alternative neuropsychological measures of WM, sustained attention, and processing speed including WAIS-IV Digit Span,

WAIS-IV Digit Symbol Coding, and D-KEFS Trail Making Test (TMT; Tombaugh, 2006) was examined. Only D-KEFS TMT Number Sequencing test demonstrated a significant relationship with bilateral DLPFC activation during mPASAT minus visual monitoring trials, and we explored brain activation in the DLPFC as a mediator of the relationship between group and performance. However, these results reveal that brain activation does not mediate the relationship between group and performance on other WM measures.

4.4 WM Performance in mTBI subgroups

Results of the current study are consistent with literature suggesting that the clinical course of mTBI may fully resolve within days to months following the injury (Bigler, 2008). The heterogeneity of clinical injury characteristics (e.g., mechanism of injury) and potential psychiatric comorbidities (e.g., depression, PTSD) of veteran mTBI might confound the detection of genuine cognitive deficits in chronic mTBI as a whole. It has been proposed that 10-20% (i.e., "miserable minority") of individuals (Ruff, Camenzuli, & Mueller, 1996) for whom injuries have been linked to chronic (> three months post injury) cognitive, psychiatric symptoms, and physical PCS (Schwab et al., 2017). One possible mechanism for identifying individuals who may be experiencing chronic WM deficits is to examine the presence of self-reported cognitive complaints of executive function. One measure that has been used to identify complaints of executive dysfunctions, which include complaints reflecting working memory difficulties (e.g., pay attention, concentrate even when there are distractions), is the FrSBe. Prior studies have found that civilians and veterans with mTBI with subjective complaints of persistent difficulties performed significantly worse on WM tasks than mTBI civilians and veterans without these complaints, who performed similarly to controls without a history of head injury (Chamelian & Feinstein, 2006; Holiday et al., 2020; Smits et al., 2009; Sterr et al., 2006). Given

this information, we explored whether veterans with mTBI who endorsed symptoms of executive dysfunction on the FrSBe differed in WM performance or brain activation during the mPASAT. In contrast to these findings, the current study found that the presence of self-reported cognitive complaints of executive function in mTBI was not associated with WM performance or brain activation in the ACC or DLPFC. Thus, veterans with a history of mTBI who endorsed persistent executive function deficits did not perform worse or exhibit different activation than veterans with a history of mTBI who did not endorse persistent executive function deficits. It is possible that the FrSBe, the measure used in this study, was not effective at detecting the veterans in this miserable minority with persisting deficits. However, the executive function scale of this measure was used to successfully isolate veterans with persisting deficits on a response inhibition task (Go-NoGo) in a previous study by this group (Holiday et al., 2020). It is entirely possible that the FrSBe is better suited to tasks of disinhibition and another measure with more targeted self-report WM complaints might be more appropriate for the PASAT. Finally, it must be considered that mTBI veterans with subjective complaints of WM do not perform significantly worse in their daily lives than veterans without these complaints.

Given that some previous studies have found WM deficits in veterans with blast-related mTBI in comparison to those with blunt-only injuries (Karr et al., 2014; Mendez et al., 2013), we also explored whether mTBI veterans with blast injuries performed significantly worse or exhibited differential brain activation to mTBI veterans with blunt injuries. However, current study results indicated that veterans with blast-related mTBI did not exhibit differences in WM performance or brain activation in the ACC or DLPFC in comparison to veterans with blunt-mTBIs. These findings are consistent with a systematic review of the blast-related mTBI

literature that found the clinical and functional outcomes to be comparable between blast and non-blast-related mTBI (Greer et al., 2018).

4.5 Limitations

There are several limitations of the study worth noting. First, the cross-sectional study design and retrospective self-reporting of mTBI history and injury characteristics, though common and frequently unavoidable in many mTBI veteran studies, are major limitations. Specifically, accurate measures of injury severity including the presence/duration of AOC, LOC, and PTA and blast exposure were impossible to verify. Despite these intrinsic limitations, this is an acceptable method of conducting mTBI research due to limited ability to obtain objective TBI metrics in Veterans (Davenport, 2016). Additionally, results of the current study rely on accurate retrospective self-report of veteran controls that they have never experienced a mTBI. Given the mild nature of these injuries, it is possible that veterans in our control group may have experienced, but inadvertently neglected to report, mild head injuries that they did not consider to be TBIs. Longitudinal studies with pre/post injury testing that record TBI injury characteristics at the time of injury would likely increase the precision of this information and reduce the potential confounding influence of premorbid factors (e.g., education, previous head injuries).

Assuming that the self-reported clinical injury characteristics in this study accurately reflect the veterans' injuries, the mTBIs experienced by the veterans in this study were on the "milder" end of the spectrum. As described above, the criteria for mTBI used in this study included (1) LOC ≤ 30 minutes; (2) AOC ≤ 24 hours; and/or (3) PTA ≤ 24 hours. The modal duration of LOC, AOC, and PTA was 5 minutes, 2.5 minutes, and 1 minute, respectively. Additionally, the modal number of mTBIs that veterans in the mTBI group reported was two mTBIs. It is possible that veterans who experienced mTBIs with longer duration of LOC, AOC,

or PTA and/or higher number of mTBIs might evidence worse WM than we detected on the current task. However, there were few individuals at the more severe side of the mTBI spectrum, which limited subgroup analyses of these veterans. Therefore, it is important to note that the findings of this study might not generalize to veterans with more severe mTBIs, as well as moderate or severe TBIs. Additionally, our study examined *veterans* with mTBI, and the results may not generalize to civilian populations.

Although consistent with the demographics of U.S. military veterans in Iraq and Afghanistan (Lindquist et al., 2017), the mTBI group evidenced higher levels of combat exposure and psychiatric symptoms (i.e., PTSD, depression) than veterans without a history of head injury. Additionally, significantly fewer females reported experiencing mTBIs than males. This distribution of gender and psychiatric symptoms is likely tied to the common factor of combat exposure. Women were banned from serving in combat roles in the U.S. military until the January 24, 2013, when Secretary of Defense, Leon Panetta, formally rescinded the law that prohibited women from serving in combat units (Burrelli, 2013). Given that many of the mTBI veterans in this study received their mTBIs during combat, it is not surprising that the mTBI group contains higher levels of combat exposure and fewer females than the veteran control group. Similarly, it is not unexpected that the mTBI group with a higher number of combat veterans also evidences higher levels of PTSD and depressive symptoms than the veteran control group. As U.S. military demographics change, such as an increased prevalence of women in combat, it is important to consider the limitations of generalizing the findings from the current study to other demographic samples,

It is entirely possible that factors outside the purview of this investigation could account for the lack of behavioral differences between veterans with and without a history of mTBI. One

factor that was not directly screened for in this study was overall health. In the US military, intensive health screenings are administered prior to deployment to a combat zone. It is entirely possible that the VC group had more premorbid health problems that prohibited them from getting deployed to combat zones than the mTBI group. Alternatively, personality factors such as risk taking (e.g., mTBI group might have a higher proportion of risk takers who volunteered for combat) could play a key role. Future studies should examine other factors outside of the scope of this investigation such as overall health and personality.

Although the task was designed to be cognitively demanding, and participants did not evidence a ceiling effect, it is possible that the mPASAT in the current study does not fully capture the challenges encountered by engaging in complex WM and executive function tasks in their everyday lives (such as driving). In addition to cognitive demand, this task incorporates specific cognitive abilities, such as serial addition, that may be highly sensitive to education and may not tap into everyday WM problems. Future studies examining the ecological validity of the mPASAT used in the current study could provide valuable information regarding the similarities between the demands of the current task and everyday challenges that veterans encounter. Alternatively, the use of a more challenging WM or executive function task that has demonstrated solid ecological validity in veterans might be able to tap into deficits that were not detected in mTBI veterans in the current study.

The methodology of the current study was designed to examine possible differences in hyperactivation and hypoactivation in specific *a priori* defined brain regions between veterans with and without a history of mTBI. Although outside of the scope of the current study, it is possible that group differences do not lie within specific brain regions but rather in the

connectivity *between* these brain regions. Future studies should examine the functional connectivity of the ACC and DLPFC with other brain regions during WM tasks.

4.6 Conclusions, Strengths, and Future Directions

The overarching aim of this project was to examine WM performance and the underlying neural mechanisms of WM performance using a cognitively demanding task in mTBI veterans via fMRI. Contrary to our hypothesis, we did not find significant group (mTBI veterans vs. VC) differences in WM performance. Imaging results revealed that mTBI participants had lower ACC response during correct compared to incorrect trials, while the ACC response among VC was equivalently low during both correct and incorrect trials. This finding held when controlling for education, and either depressive or PTSD symptoms. In mTBI, greater ACC activation during the contrast of correct and incorrect trials was associated with higher false alarm rates, or worse WM performance. In VC, higher ACC activation during the contrast of correct and incorrect trials was associated with poorer performance and lower hit rates, but not after accounting for PTSD symptoms, which were associated strongly with performance in the VC group. Given that the elevated ACC activation was evident *only* in the contrast that emphasizes brain activation during incorrect trials, and that this brain response correlated with overall false alarm errors, it is possible that the ACC was acting as a salience detector that signals increased activation in response to errors in the mTBI group.

One strength of the study, compared to previous investigations in civilian samples, is its generalizability to the veteran population given heterogeneity of clinical injury characteristics (e.g., mechanism of injury) and psychiatric comorbidities (e.g., PTSD, depression) of the sample. Future studies should expand upon the current findings by examining the functional connectivity of brain regions implicated in WM and mTBI. Studying the impact of chronic mTBI directly in

a veteran sample is crucial to provide targets for intervention strategies to improve cognitive function and reduce disability in veterans following mTBI. Findings from this study contribute to our understanding of chronic sequelae following mTBI and identify methodology for exploration in future studies, which could ultimately be utilized in intervention studies to decrease distress and disability following mTBI in this vulnerable population. Future studies with more ecologically relevant tasks or symptom measurement, such as ecological momentary assessment, could possibly identify poor WM that is reported, but often not objectively found.

DISCUSSION ACKNOWLEDGEMENTS

The Discussion chapter contains unpublished research co-authored by Holiday, Kelsey A.; Eyler, Lisa T; Sorg, Scott F.; and Schiehser, Dawn M. The dissertation author was the primary author of this work.

5. APPENDIX

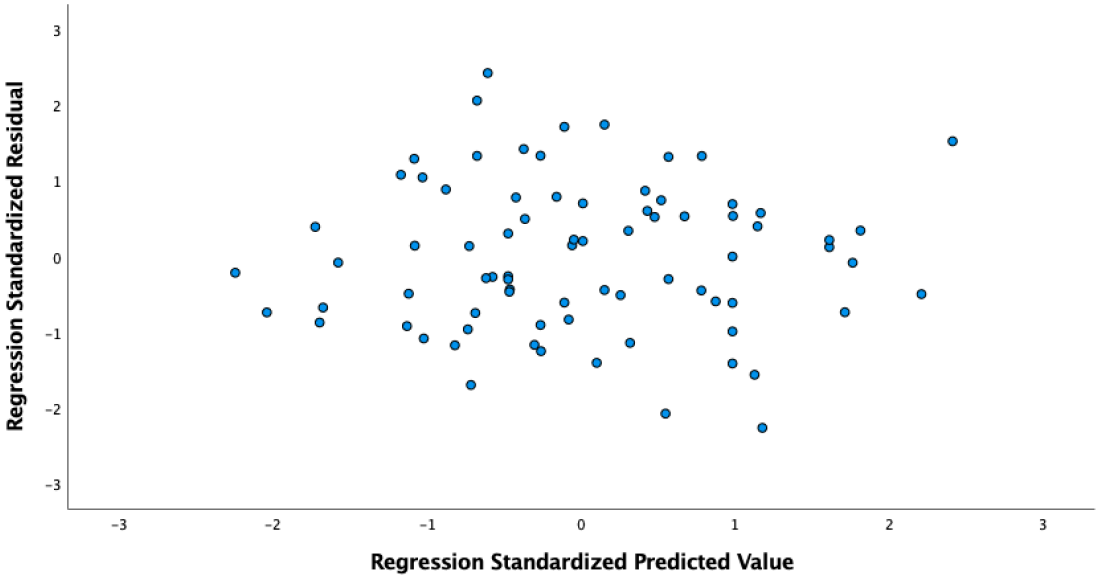

Figure 20. Residual plot of the relationship between group (mTBI vs. VC) and mPASAT performance (d') after accounting for years of education and depression.

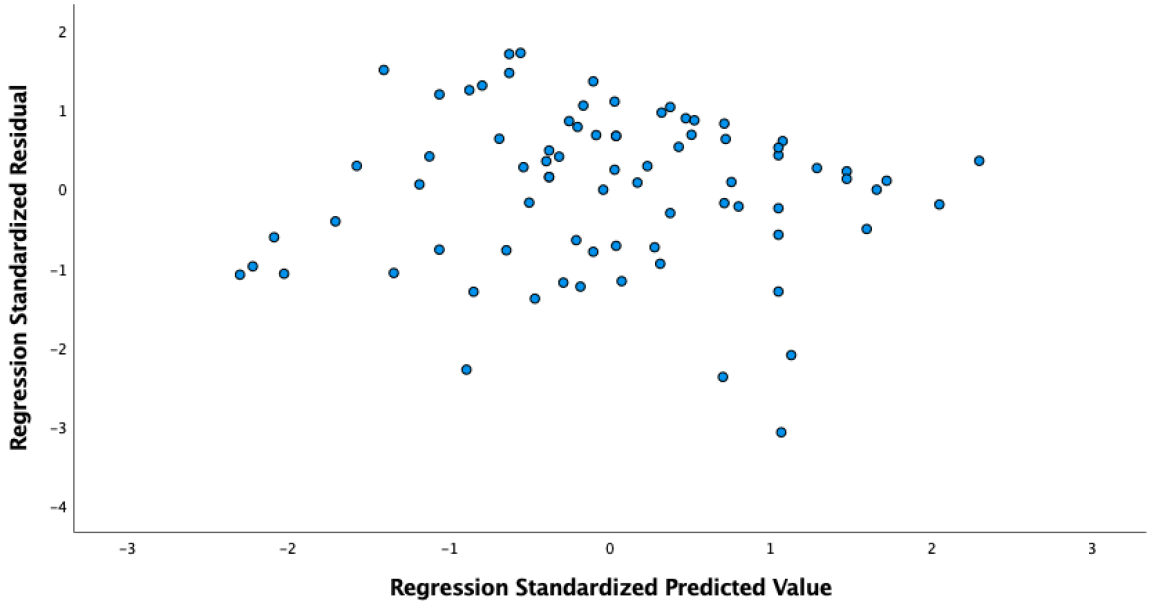

Figure 21. Residual plot of the relationship between group (mTBI vs. VC) and hit rate after accounting for years of education and depression.

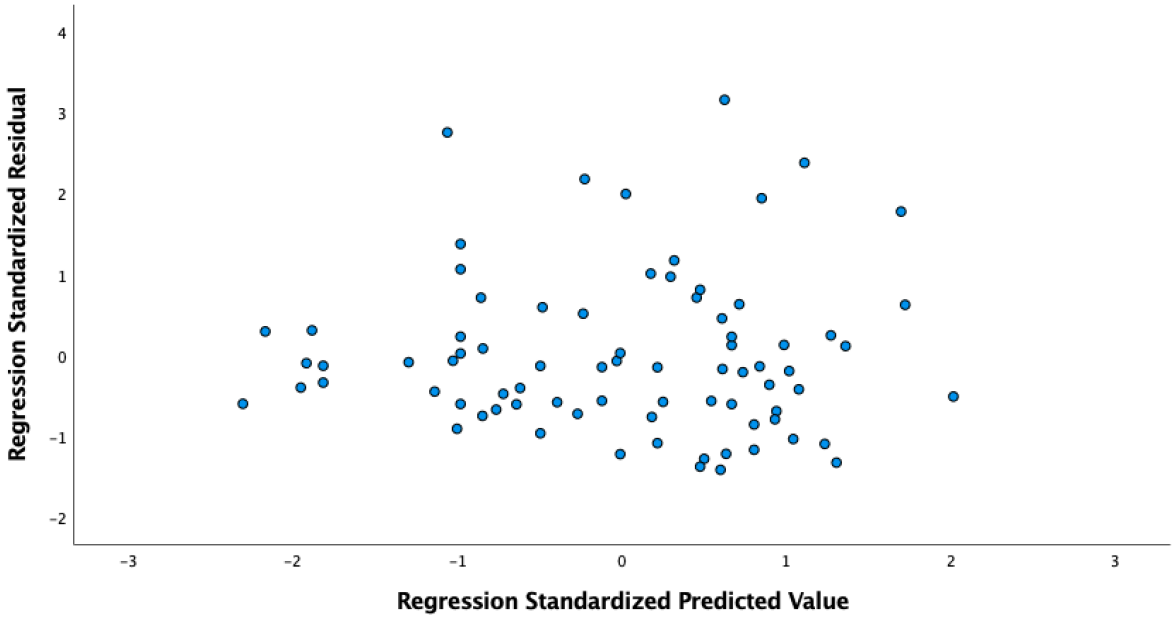

Figure 22. Residual plot of the relationship between group (mTBI vs. VC) and false alarm rate after accounting for years of education and depression.

Figure 23. Residual plot of the relationship between group (mTBI vs. VC) and ACC activation during correct+null trials after accounting for depressive symptoms.

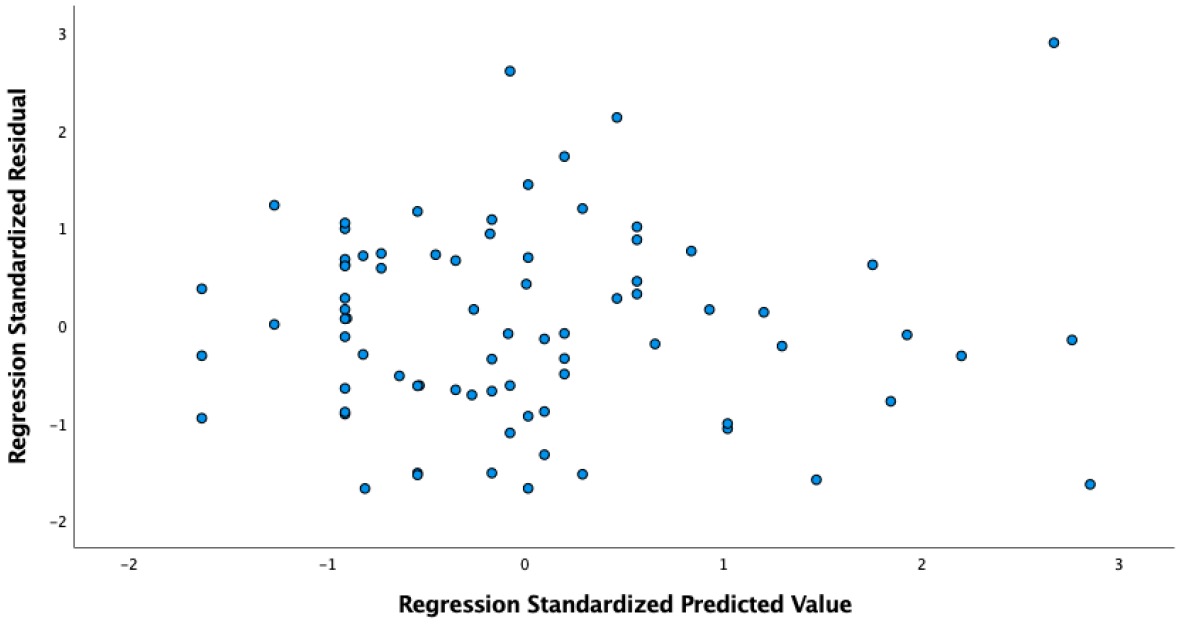

Figure 24. Residual plot of the relationship between group (mTBI vs. VC) and bilateral DLPFC activation during correct+null trials after accounting for depressive symptoms.

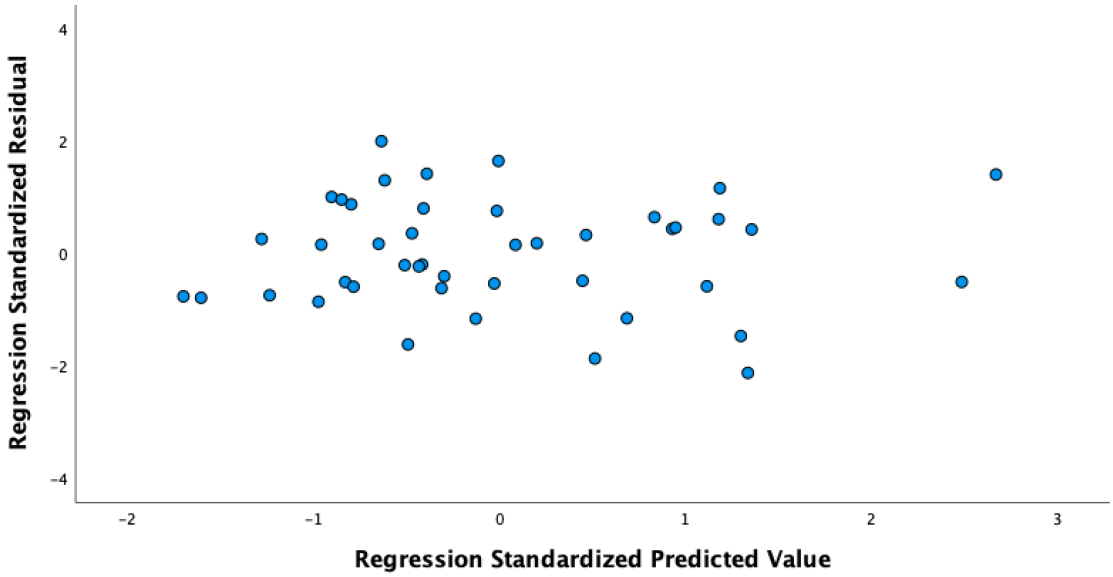

Figure 25. Residual plot of the relationship between correct+null ACC activation and d' after accounting for education and depressive symptoms in mTBI.

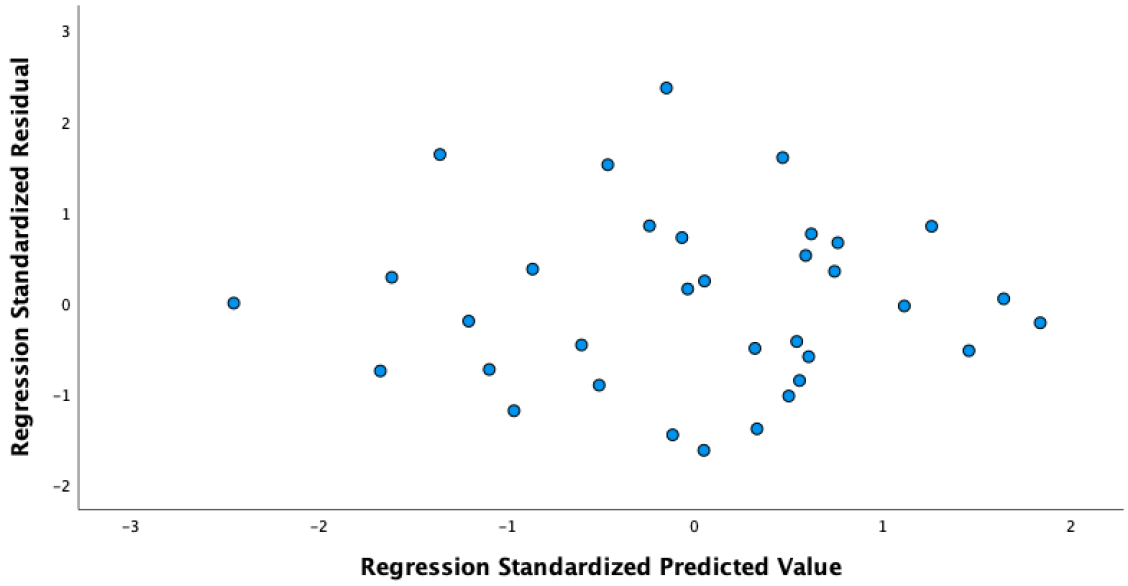

Figure 26. Residual plot of the relationship between correct+null ACC activation and d' after accounting for education and depressive symptoms in VC.

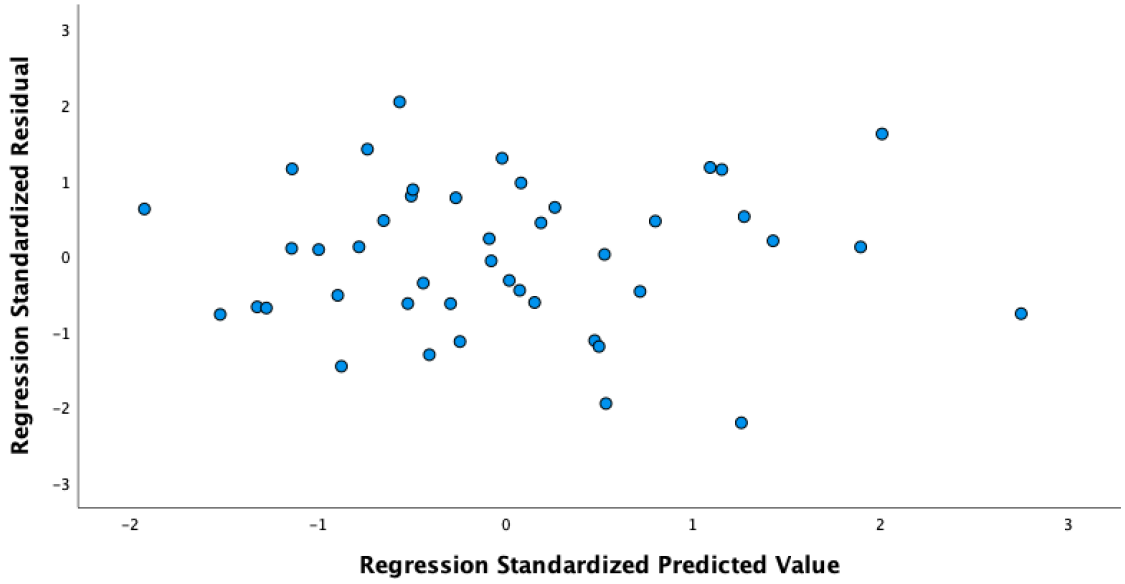

Figure 27. Residual plot of the relationship between correct+null bilateral DLPFC activation and d' after accounting for education and depressive symptoms in mTBI.

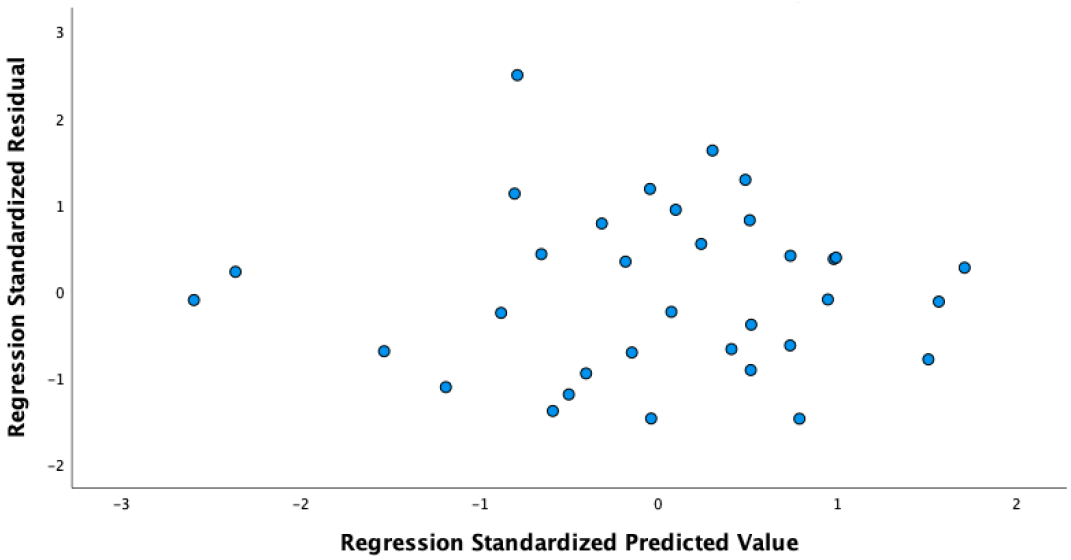

Figure 28. Residual plot of the relationship between correct+null bilateral DLPFC activation and d' after accounting for education and depressive symptoms in VC.

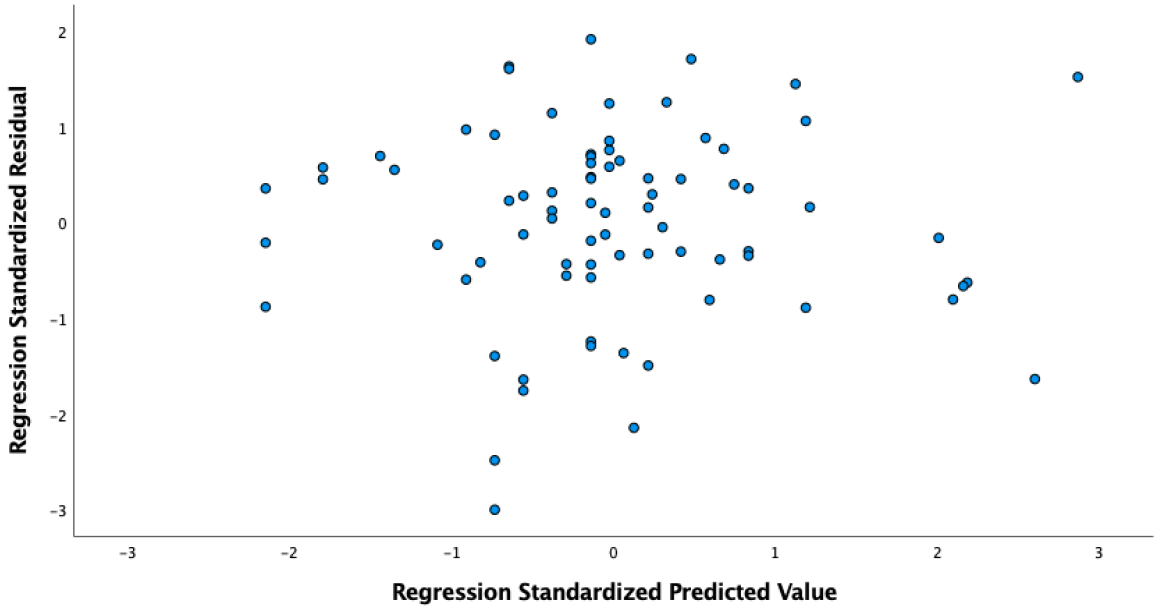

Figure 29. Residual plot of the group differences in correct-incorrect ACC activation after accounting for education and depressive symptoms.

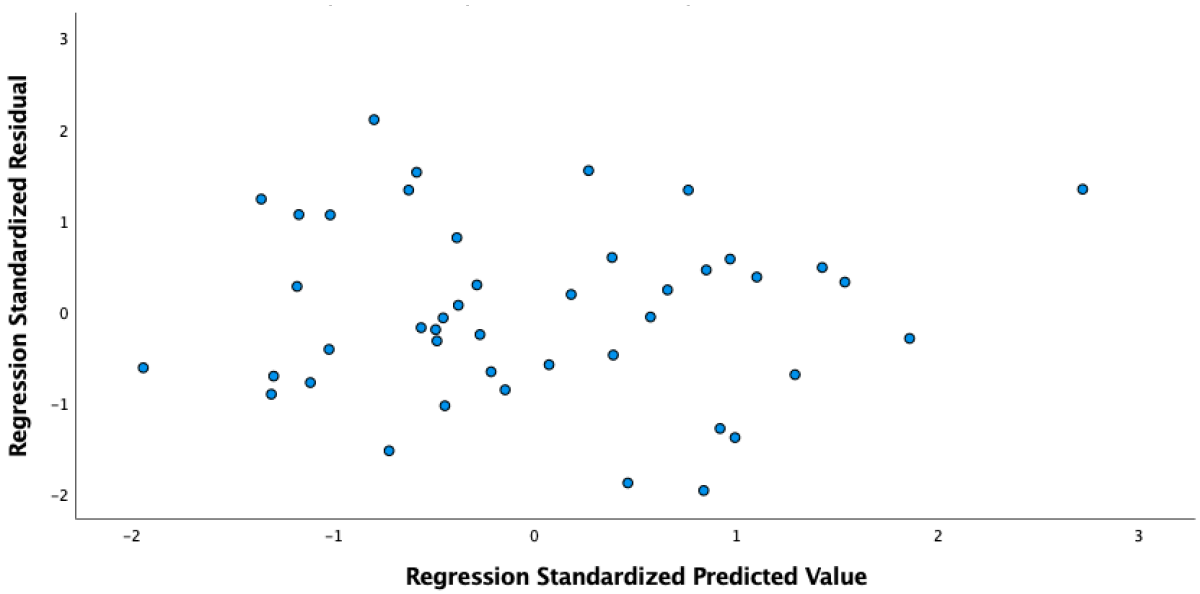

Figure 30. Residual plot of the relationship between correct-incorrect ACC activation and d' after accounting for education and depressive symptoms in mTBI.

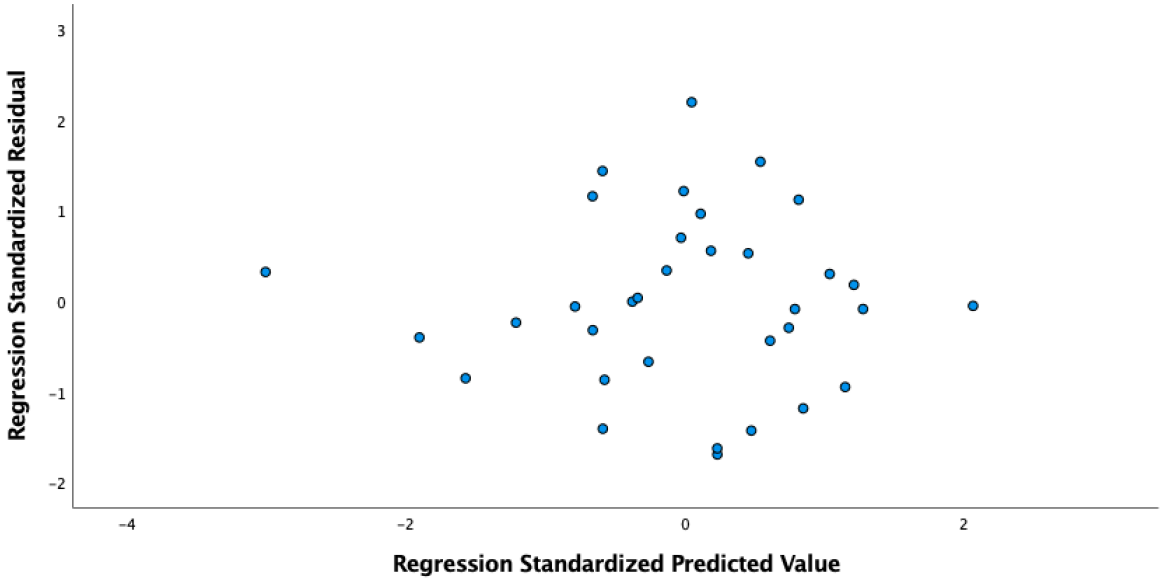

Figure 31. Residual plot of the relationship between correct-incorrect ACC activation and d' after accounting for education and depressive symptoms in VC.

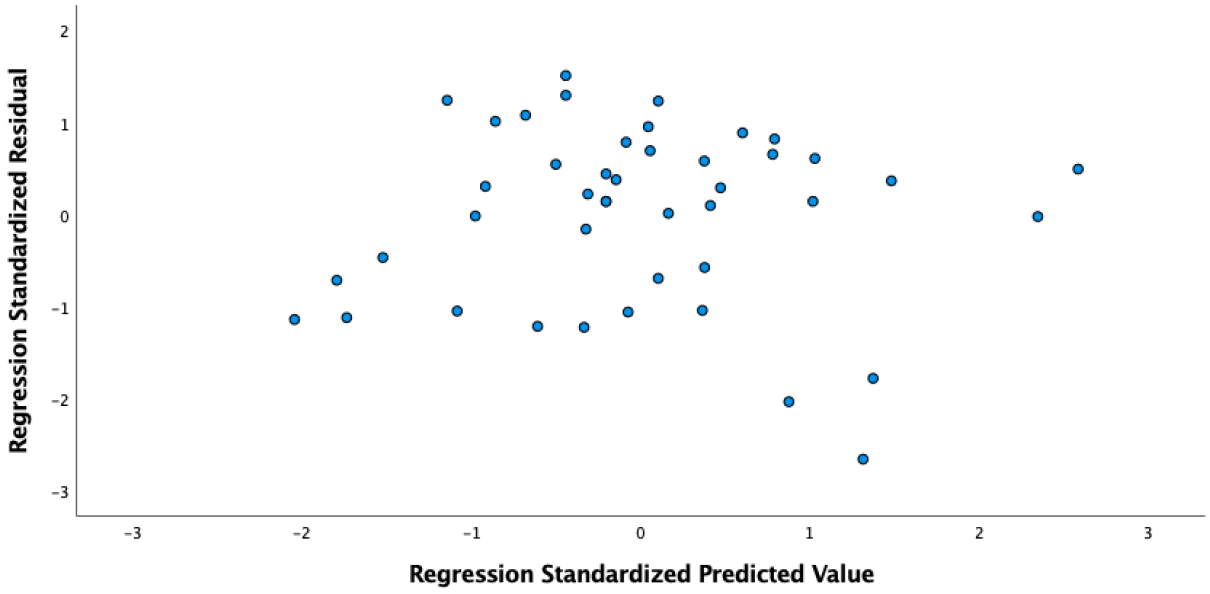

Figure 32. Residual plot of the relationship between correct-incorrect ACC activation and hit rate after accounting for education and depressive symptoms in mTBI.

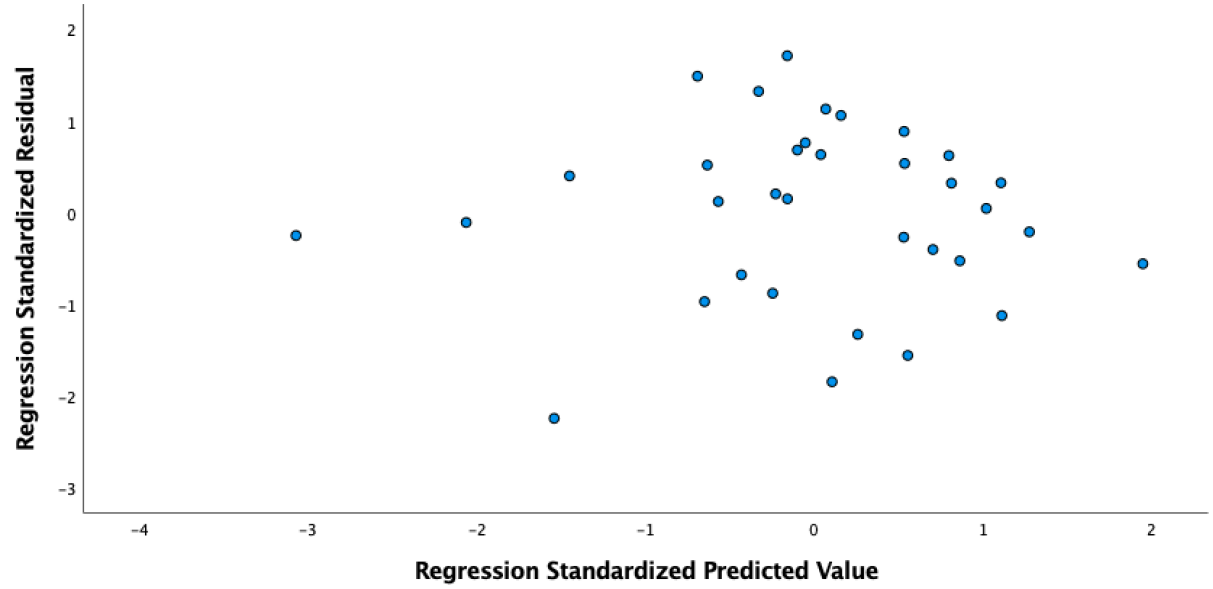

Figure 33. Residual plot of the relationship between correct-incorrect ACC activation and hit rate after accounting for education and depressive symptoms in VC.

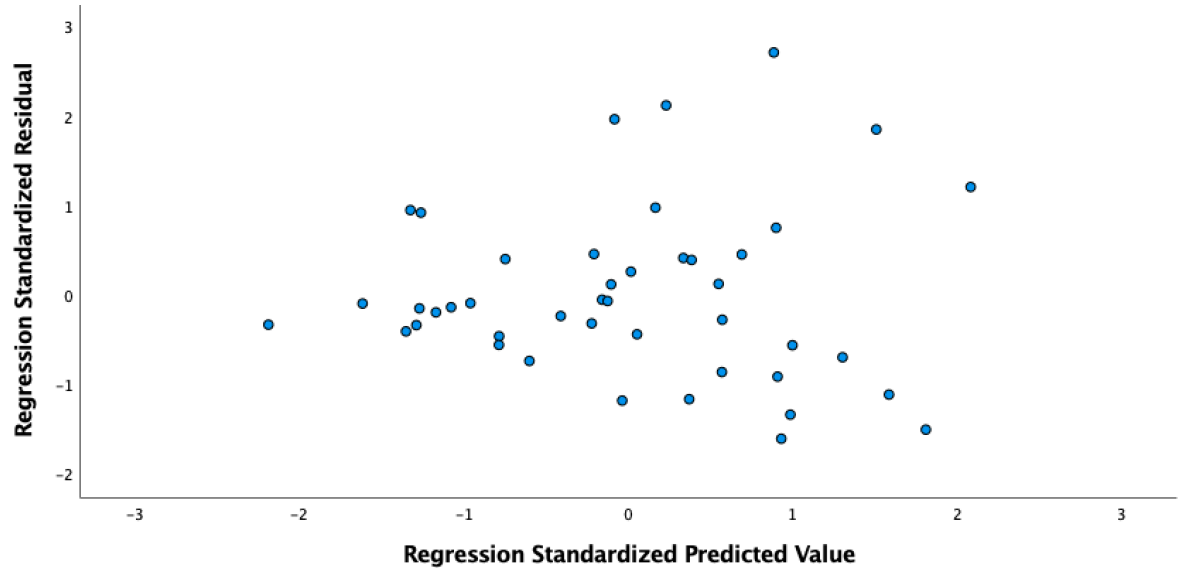

Figure 34. Residual plot of the relationship between correct-incorrect ACC activation and false alarm rate after accounting for education and depressive symptoms in mTBI.

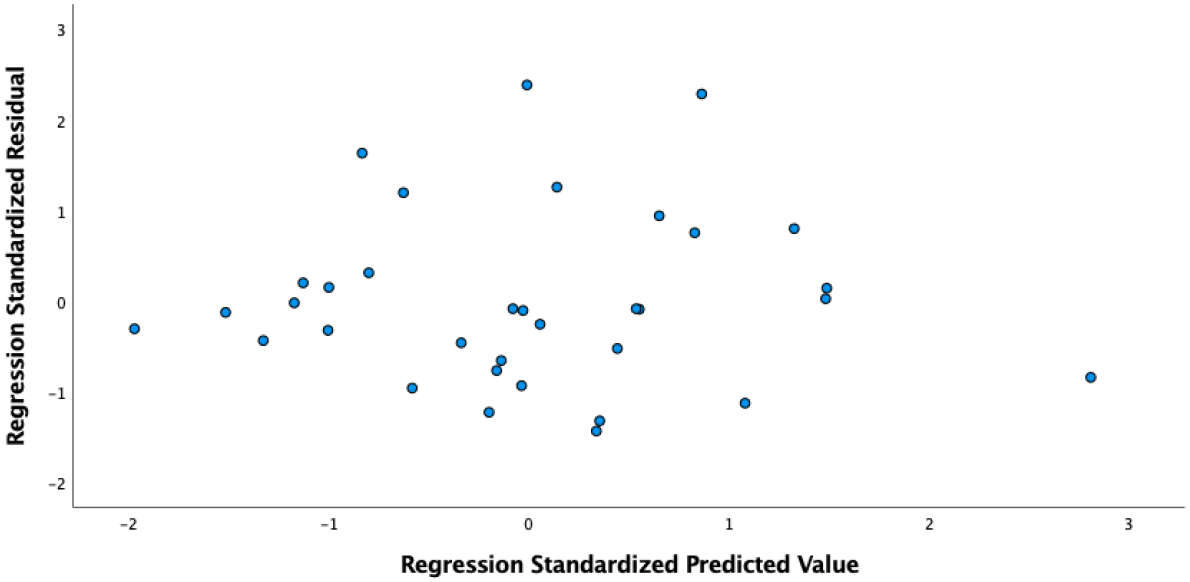

Figure 35. Residual plot of the relationship between correct-incorrect ACC activation and false alarm rate after accounting for education and depressive symptoms in VC.

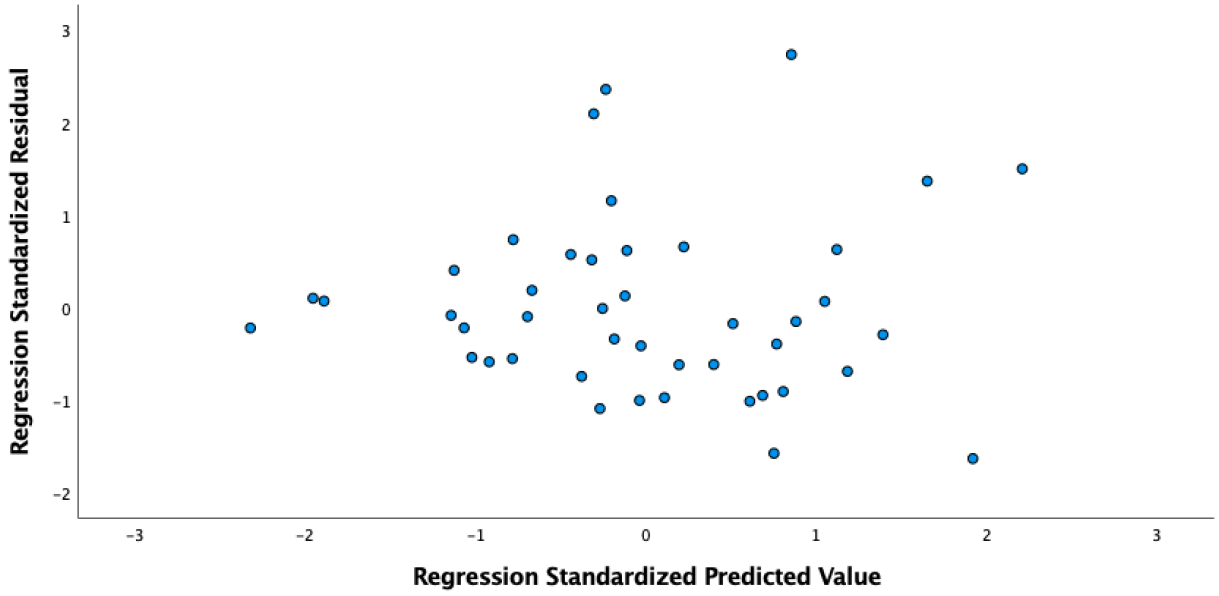

Figure 36. Residual plot of the relationship between incorrect-only ACC activation and false alarm rate after accounting for education and depressive symptoms in mTBI.

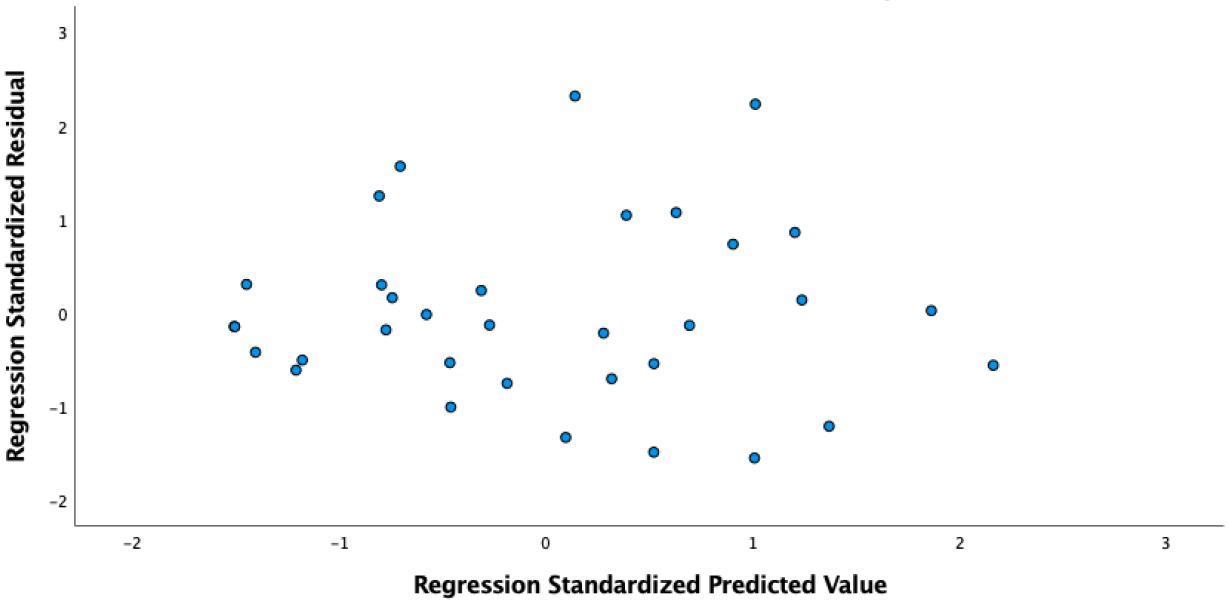

Figure 37. Residual plot of the relationship between incorrect-only ACC activation and false alarm rate after accounting for education and depressive symptoms in VC.

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