UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

The Relationship Between Cerebral Blood Flow and Neuropsychological Outcomes in Veterans with History of Mild Traumatic Brain Injury

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

in

Clinical Psychology

by

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The Dissertation of Alexandra L. Clark is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2019

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To my dear friends Andrea Yoder, M.D., Randall McKnight, M.D., and Lauren Hooper—your calls, visits, and words of encouragement were essential to all of my graduate school accomplishments. Finally, to my wonderful partner, Jason L. Nienberg, J.D., you have enriched this journey in so many ways and I am always struck by how much you believe in me, my dreams, and this work. I cherish the love from you and your family and look forward to each and every moment we have together. Thank you for being on this journey with me and for constantly being a source of laughter and light in all of this. Your presence means the world to me and I know the inevitable highs and lows of the future will be easily traveled with you.

VITA

EDUCATION

2018–2019 **Internship in Clinical Psychology**
University of California, San Diego/San Diego Veterans Health Administration
Psychology Internship Training Program
Neuropsychology Track

2013–2019 **Doctor of Philosophy, Clinical Psychology**
San Diego State University/University of California San Diego
Joint Doctoral Program in Clinical Psychology
Neuropsychology Track
Dissertation: *The Relationship Between Cerebral Blood Flow and Neuropsychological Outcomes in Veterans with Mild Traumatic Brain Injury*
Dissertation Chair: Lisa Delano-Wood, Ph.D.

2014 **Master of Science, Clinical Psychology**
San Diego State University/University of California San Diego
Thesis: *Deep White Matter Hyperintensities Affect Verbal Memory Independent of PTSD Symptoms in Veterans with Mild Traumatic Brain Injury*
Thesis Chair: Lisa Delano-Wood, Ph.D.

2010 **Bachelor of Science, Psychology**
University of Florida

HONORS AND AWARDS

2018-2019 Applicant, NIH Early Independence Award (DP5)
2018-2019 Co-Chief of Internship Class, VA San Diego Healthcare System
2017–2019 Awardee, Ruth L. Kirschstein Predoctoral National Research Service Award: National Institute of Neurological Disorders and Stroke, *Cerebral Perfusion and Cognitive Outcomes in Mild TBI (1F31NS098704)*
2018 Awardee, American Psychological Association Science Directorate's Dissertation Research Award ($4,085)
2015 Honorable Mention, National Science Foundation Graduate Student Research Fellowship Program
2013–2015 Fellowship Recipient, University of California, San Diego Fellowship
2006–2010 Awardee, Florida Bright Futures Scholarship

RESEARCH EXPERIENCE

2013–2018 **Graduate Research Assistant**
Delano-Wood Laboratory, University of California, San Diego
Advisor: Lisa Delano-Wood, Ph.D.

2010–2013 **Research Coordinator**
Translational Center for TBI and PTSD (TRACTS) and Geriatric Research, Education, and Clinical Center, Boston Veterans Administration/Harvard Medical School
PI: William Milberg, Ph.D., ABPP/CN

2009–2010 **Undergraduate Lab Manager**

Cognitive Neuroscience Laboratory, University of Florida
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CLINICAL EXPERIENCE

2017–2018 **Internship in Clinical Psychology**
University of California, San Diego/San Diego Veterans Health Administration Consortium
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Supervisors: Mark W. Bondi Ph.D., ABPP-CN, Vince Filoteo, Ph.D., Lisa Delano-Wood, Ph.D, Amy Jak, Ph.D., and Benjamin Felleman, Ph.D
Rotations: Neuropsychological Assessment Unit, Primary Care Mental Health Integration

2017–2018 **Neuropsychiatry and Behavioral Medicine Service**
University of California, San Diego Medical Center
Supervisor: Marc Norman, Ph.D., ABPP-CN

2017–2018 **Neuropsychological Assessment Clinic in Oncology at the Radiation Oncology/PET Center**
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Supervisor: Carrie McDonald, Ph.D., ABPP-CN

2016–2017 **Advanced Neuropsychology Laboratory**
Department of Psychiatry, University of California, San Diego
Supervisor: Robert K. Heaton, Ph.D., ABPP-CN

2016–2017 **Neuropsychological Assessment Unit**
VA San Diego Healthcare System
Supervisors: Mark W. Bondi, Ph.D., ABPP-CN, J. Vincent Filoteo, Ph.D., and Gregory G. Brown, Ph.D., ABPP-CN

2014–2015 **ASPIRE Residential Rehabilitation Center**
Veterans Affairs San Diego Healthcare System
Supervisor: Lori Haase, Ph.D., David Call, Ph.D., Brittany Davis, Ph.D.

2014–2015 **San Diego State University Psychology Clinic**
Supervisors: Michael Taylor, Ph.D., Monica Ulibarri, Ph.D., and Mark Jacobson, Ph.D.

TEACHING EXPERIENCE

Spring 2018 **Introduction to Clinical Psychology**
Department of Psychology, University of California San Diego
Teaching Assistant for course instructor Fred Rose, Ph.D.

Spring 2017 **Introduction to Counseling and Therapy**
Department of Psychology, San Diego State University
Invited lecturer on neuropsychological assessment

Winter 2015 **Introduction to Clinical and Experimental Psychology**
Department of Psychology, University of California San Diego

Invited lecturer on clinical psychology training programs

Winter 2015 **Maximizing Access to Research Careers (MARC)**
Department of Psychology, University of California San Diego
Invited panelist member on clinical psychology training programs

Fall 2014 **Psi Chi/ Psychology Club's Pathways to Ph.D's Panel**
Department of Psychology, University of California San Diego
Invited lecturer on clinical psychology training programs

PROFESSIONAL MEMBERSHIPS

International Neuropsychological Society
APA Division 40
Association of Neuropsychology Students in Training (ANST)

SERVICE

2013-2018 Ad hoc journal reviewer for *Brain Imaging and Behavior, Neuropsychology, Journal of Clinical and Experimental Psychology, Archives of Clinical Neuropsychology, The Clinical Neuropsychologist, Frontiers in Neurology*

2014 – 2017 Representative on the University of California San Diego, Psychiatry Department, Chair's Advisory Committee on Diversity Issues

PUBLICATIONS

Peer-reviewed articles

Clark, A. L., Merritt, V. C., Bigler, E. D., Bangen, K. J., Werhane, M., Sorg, S. F., … Delano-Wood, L. (2018). Blast-exposed veterans with mild traumatic brain injury show greater frontal cortical thinning and poorer executive functioning. *Frontiers in neurology*, *9*, 873. doi:10.3389/fneur.2018.00873

Merritt, V. C., Lapira, K., **Clark, A. L**., Sorg, S. F., Werhane, M., Jak, A., Schiehser, D. M., & Delano-Wood, L. (2018). APOE-ε4 is associated with elevated post-concussive symptoms in military Veterans with post-remote mild traumatic brain injury. *Archives of Clinical Neuropsychology.* Advance online publication. doi:10.1093/arclin/acy082

Merritt, V. C., **Clark, A. L.**, Crocker, L. D., Sorg, S. F., Werhane, M. L., Bondi, M. W., ... & Delano-Wood, L. (2018). Repetitive mild traumatic brain injury in military veterans is associated with increased neuropsychological intra-individual variability. *Neuropsychologia*, *119*, 340-348.

Bangen, K. J., Werhane, M. L., Weigand, A. J., Edmonds, E. C., Delano-Wood, L., Thomas, K. Nation, D., Evangelista, N., **Clark, A.L.,** Liu, T., & Bondi, M.W. (2018). Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes. *Frontiers in aging neuroscience*, *10*.

Merritt, V. C., **Clark, A. L**., Sorg, S. F., Evangelista, N., Werhane, M., Bondi, M. W., Schiehser, D.M., & Delano-Wood, L. (2018). APOE-ε4 is associated with reduced neuropsychological performance in military Veterans with post-acute mild traumatic brain injury. *Journal of clinical and experimental neuropsychology, 40,* 1050-1061.

Werhane, M. L., Thomas, K. R., Edmonds, E. C., Bangen, K. J., Tran, M., **Clark, A. L.**, ... & Alzheimer's Disease Neuroimaging Initiative. (2018). Differential effect of APOE ε4 status and elevated pulse pressure on functional decline in cognitively normal older adults. *Journal of Alzheimers Disease*. Advance online publication.

Merritt, V. C., **Clark, A. L.,** Sorg, S. F., Evaneglista, N., Werhane, M., Bondi, M. W., Schiehser, D. M., & Delano-Wood, L. (2018). Apolipoprotein E (APOE) ε4 genotype is associated with increased psychiatric distress in Veterans with a history of mild to moderate traumatic brain injury. *Journal of Neurotrauma*, *35(9)*, 2272-2282.

Clark, A. L., Sorg, S. F., Holiday, K. A., Bigler, E. D., Bangen, K. B., Evangelista, N., Bondi, M. W., Schiehser, D. M., & Delano-Wood, L. (2017). Fatigue is associated with global and regional thalamic morphometry in veterans with a history of mild traumatic brain injury. *The Journal of head trauma rehabilitation*, *33*(6), 382-392.

Schiehser, D. M., Delano-Wood, L., Jak, A. J., Hanson, K. L., Sorg, S. F., Orff, H., & **Clark, A. L.** (2017). Predictors of cognitive and physical fatigue in post-acute mild–moderate traumatic brain injury. *Neuropsychological Rehabilitation*, *27*,1-16.

Clark, A. L., Bangen, K. J., Sorg, S. F., Schiehser, D. M., Evangelista, N. D., McKenna, B., ... & Delano-Wood, L. (2017). Dynamic association between perfusion and white matter integrity across time since injury in Veterans with history of TBI. *NeuroImage: Clinical*, *14*, 308-315.

Bangen, K. J., **Clark, A. L.**, Edmonds, E. C., Evangelista, N. D., Werhane, M. L., Thomas, K. R., ... & Delano-Wood, L. (2017). Cerebral blood flow and amyloid-β interact to affect memory performance in cognitively normal older adults. *Frontiers in Aging Neuroscience*, *9*, 181.

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Bangen, K. J., **Clark, A. L.,** Werhane, M., Edmonds, E. C., Nation, D. A., Evangelista, N., ... & Delano-Wood, L. (2016). Cortical amyloid burden differences across empirically-derived mild cognitive impairment subtypes and interaction with APOE ε4 genotype. *Journal of Alzheimer's Disease*, *52*, 849-861.

Bomyea, J., Lang, A. J. , Delano-Wood, L., Jak, A. J., Hanson, K. L., Sorg, S. F, **Clark, A. L.**, & Schiehser, D.M. (2016). Neuropsychiatric predictors of post-injury headache after mild-moderate traumatic brain injury in Veterans. *Headache: The Journal of Head and Face Pain*, 56, 699-710.

Clark, A. L., Delano-Wood, L., Sorg, S. F., Werhane, M. L., Hanson, K. L., & Schiehser, D. M. (2016). Cognitive fatigue is associated with reduced anterior internal capsule integrity in Veterans with history of mild to moderate traumatic brain injury. *Brain Imaging and Behavior*, 1-7.

Clark, A. L., Sorg, S. F., Schiehser, D. M., Luc, N., Bondi, M. W., Sanderson, M., ... & Delano-Wood, L. (2016). Deep white matter hyperintensities affect verbal memory independent of PTSD symptoms in Veterans with mild traumatic brain injury. *Brain Injury*, *30*, 864-871.

Clark, A. L., Sorg, S. F., Schiehser, D. M., Bigler, E. D., Bondi, M. W., Jacobson, M. W., ... & Delano-Wood, L. (2016). White matter associations with performance validity testing in Veterans with mild traumatic brain injury: the utility of biomarkers in complicated assessment. *The Journal of Head Trauma Rehabilitation*, *31*(5), 346-359.

Hanson, K. L., Schiehser, D. M., **Clark, A. L.,** Sorg, S. F., Kim, R. T., Jacobson, M. W., ... & Delano-Wood, L. (2016). Problem alcohol use in Veterans with mild traumatic brain injury: Associations with cognitive performance and psychiatric symptoms. *Journal of Clinical and Experimental Neuropsychology*, *38*, 1115-1130.

Schiehser, D. M., Delano-Wood, L., Jak, A. J., Hanson, K. L., Sorg, S. F., Orff, H., & **Clark, A. L.** (2016). Predictors of cognitive and physical fatigue in post-acute mild–moderate traumatic brain injury. *Neuropsychological Rehabilitation*, 1-16.

Sorg, S. F., Schiehser, D. M., Bondi, M. W., Luc, N., **Clark, A. L.,** Jacobson, M. W., ... & Delano-Wood, L. (2016). White matter microstructural compromise is associated with cognition but not posttraumatic stress disorder symptoms in military Veterans with traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *31*, 297-308.

Delano-Wood, L., Bangen, K. J., Sorg, S. F., **Clark, A. L.**, Schiehser, D. M., Luc, N., ... & Bigler, E. D. (2015). Brainstem white matter integrity is related to loss of consciousness and postconcussive symptomatology in Veterans with chronic mild to moderate traumatic brain injury. *Brain Imaging and Behavior*, *9*, 500-512.

Clark, A. L., Amick, M. M., Fortier, C., Milberg, W. P., & McGlinchey, R. E. (2014). Poor performance validity predicts clinical characteristics and cognitive test performance of OEF/OIF/OND Veterans in a research setting. *The Clinical Neuropsychologist*, *28*, 802-825.

Fortier, C. B., Amick, M. M., Grande, L., McGlynn, S., Kenna, A., Morra, L., **Clark, A.L.,** Milberg, W.P., & McGlinchey, R. E. (2014). The Boston assessment of traumatic brain injury–lifetime (BAT-L) semistructured interview: Evidence of research utility and validity. *The Journal of Head Trauma Rehabilitation*, *29*(1), 89.

Amick, M. M., **Clark, A**.**L**., Fortier, C. B., Esterman, M., Rasmusson, A. M., Kenna, A., Milberg, M.P., & McGlinchey, R. (2013). PTSD modifies performance on a task of affective executive control among deployed OEF/OIF Veterans with mild traumatic brain injury. *Journal of the International Neuropsychological Society*, *19*, 792-801.

Manuscripts in preparation

Clark, A. L & Delano-Wood. Exploring the intersection of aging and TBI in future research efforts. Brain Injury special issue.

Clark, A. L., Weigand, A., Thomas, L., Bangen, K., & Delano-Wood, L. Mild traumatic brain injury moderates the association between age and cerebral blood flood in AD vulnerable

regions.

PEER-REVIEWED PRESENTATIONS

Oral paper presentations

Clark, A. L., Merritt, V. C., Sorg, S. F., Bangen, K. B., Bondi, M. W., Schiehser, D. M., & Delano-Wood, L. *Blast exposure is associated with anterior cortical thinning in Veterans with mild traumatic brain injury.* Paper to be presented at the 46th Annual Meeting of the International Neuropsychological Society, Washington, D.C.

Merritt, V. C., **Clark, A. L**., Sorg, S. F., Evangelista, N. D., Bondi, M. W., Schiehser, D. M., Delano-Wood, L. (2017, October). *Apolipoprotein E (APOE) e4 genotype is associated with increased psychiatric distress in Veterans with a history of mild-to-moderate traumatic brain injury.* Paper presented at the 37th meeting of the National Academy of Neuropsychology in Boston, Massachusetts.

Bangen, K., **Clark, A. L.,** Edmonds, E., Werhane, M., Zalatar, Z., Nation, D., Bondi, M. W., & Delano-Wood, L. (2017, February). *Cerebral blood flow and amyloid-β interact to affect memory performance in cognitively normal older adults.* Paper presented orally at the 44th Annual Meeting of the International Neuropsychological Society, New Orleans, LA.

Clark, A. L., Bangen, K. J., Sorg, S. F., Luc, N., Schiehser, D. M., Sanderson, M., Werhane, M.L., Bondi, M.W., & Delano-Wood, L. (2016, February). *Links between perfusion, white matter integrity, and cognition in Veterans with history of mild-to-moderate tbi*. Paper presented orally at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Sorg, S. F., Luc, N., **Clark, A. L.**, Schiesher, D., Bondi, M. W., Kim, R., & Delano-Wood, L. (2015, February). *Frontothalamic structural connectivity in Veterans with mild traumatic brain injury: associations with executive functions.* Paper presented at the 43rd annual International Neuropsychological Society Meeting, Denver, Colorado.

Sheridan, M., **Clark, A. L.,** & McLaughlin, K. M. (2014, May). *Cognitive control over previously rewarded stimuli in adolescence is associated with adolescent risk behavior.* Symposium talk presented at 26th

Poster presentations

Clark, A. L., Schiehser, D., Sorg, S. F., Bangen, K., Werhane, M., Holiday, K., & Delano-Wood, L., (2019). *Mild traumatic brain injury moderates the association between age and cerebral blood flood in AD vulnerable regions.* Poster presented at the 47th annual International Neuropsychological Society Conference in New York, NY.

Clark, A. L., Schiehser, D., Sorg, S. F., Bangen, K., Werhane, M., Holiday, K., & Delano-Wood, L., (2018). *Blast exposure is associated with anterior cortical thinning in Veterans with mild traumatic brain injury* Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Clark, A. L., Schiehser, D., Sorg, S. F., Bangen, K., Werhane, M., Holiday, K., & Delano-

Wood, L., (2017). *Global and regional thalamic morphometry is associated with fatigue in Veterans with history of mTBI*. Poster presented at the 2017 American Psychological Association Annual Convention, Washington, DC.

Clark, A. L., Bangen, K. J., Sorg, S. F., Werhane, M. L, Schiehser, D., Bondi, M. W., Delano-Wood, L. (2017). *Repetitive mild traumatic brain injury moderates the association between age and cerebral blood flow of medial temporal lobe structures*. Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Evangelista, N.D., **Clark, A. L**., Bangen, K. J., Scott, S. F., Werhane, M. L., Schiehser, D.M., Delano-Wood, L. (2017). *Brain derived neurotropic factor (BDNF) val66met moderates the association between ptsd and cortical thickness in Veterans with history of traumatic brain injury.* Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Haque, S., **Clark, A. L.,** Evangelista, N. D., Werhane, M. L., Sorg, S. F., Schiehser, D. M., Delano-Wood, L. (2017). *Lower nucleus accumbens volume is associated with reduced reward-based decision making in Veterans with history of mild traumatic brain injury.* Poster presented at the 2017 UCSD Biological Sciences Annual Student Research Showcase in La Jolla, California.

Kim, R. T., Sorg, S. F., Holiday, K. A., Delano-Wood, L., Meloy, M., **Clark, A. L**., Tran, M., Locano, E., Jak, A. J., Eyler, L. T. Schiehser, D. (2017*). Brain function and task performance predict self-reported disinhibition and executive function in Veterans with mild-moderate traumatic brain injury.* Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Lapira, K. M., Werhane, M. L, **Clark, A. L**., Evangelista, N. D., Sorg, S. F., Schiehser, D. M., Bondi, M. W., Delano-Wood, L. (2017). *Apolipoproptein e-e4 genotype and pulse pressure interact to affect cortical thickness in brain regions vulnerable to Alzheimer's disease in Veterans with mild traumatic brain injury.* Poster presented at the 2017 UCSD Biological Sciences Annual Student Research Showcase in La Jolla, California.

Sorg, S.F., **Clark, A.L.,** Werhane, M.L., Kim, R.T., Schiehser, D., Bondi, M.W., Delano-Wood, L. (2017). *Elevated intra-individual variability on tests of executive functions in Veterans with mild traumatic brain injury.* Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Evangelista, N.D., **Clark, A. L**., Werhane, M. L., Sorg, S. F., Schiehser, D. M., Kim, R. T., \ Bondi, M. W., Bangen, K. J., & Delano-Wood, L. (2016). *Brain-derived neurotrophic factor (BDNF) genotype is related to executive function but not memory performance in Veterans with history of mild traumatic brain injury*. Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Kim, R. T., Sorg, S. F., Delano-Wood, L., Meloy, M. J., **Clark, A. L**., Luc, N., Evangelista, N. D., Eyler, L. T., & Schiehser, D. M. (2016). *Is subjective disinhibition associated with response inhibition performance in Veterans with mild-moderate traumatic brain injury?* Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Moore, R. C., Delano-Wood, L., Kim, R. T., Hanson, K. L., Sorg, S. F., **Clark, A. L**., Zlatar, Z. Z., Fazeli, P. L., Eyler, L.T., & Schiehser, D. M. (2016). *Engagement in an active lifestyle is associated with better neurocognitive functioning among Veterans with mild traumatic brain injury*. Poster presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA.

Clark, A. L., Schiehser, D., Sorg, S. F., Bondi, M. W., Luc, N., Kim, R., & Delano-Wood, L. (2015). *Mild traumatic brain injury (mTBI) moderates the association between white matter lesion burden and memory*. Poster presented at the 43rd annual International Neuropsychological Society Meeting, Denver, Colorado.

Kim, R., **Clark, A. L.,** Sorg, S. F., Jak., A. J., Hanson, K. L., Orff, H., Delano-Wood, L., & Schiesher, D. (2015),. *Physical fatigue and vegetative symptoms best predict quality of life (QoL) in Veterans with mild-to-moderate traumatic brain injury*. Poster presented at the 43rd annual International Neuropsychological Society Meeting, Denver, Colorado.

Sanderson-Cimino, M., **Clark, A. L.**, Delano-Wood, L., Luc, N., Eppig, J., Campbell, L., Jak, A. J., & Bondi, M. W. (2015). *Age moderates the effect of elevated pulse pressure on white matter lesion burden in older adults*. Poster presented at the 43rd annual International Neuropsychological Society Meeting, Denver, Colorado.

Clark, A.L., Sorg, S. F., Bondi, M. W., Luc, N., Schiehser, D. M., Hanson, K. L., Frank, L. R., Jak, A. J., Lohr, J. B, & Delano-Wood, L. (2014). *Relationships between performance validity, psychiatric symptom reporting, and structural brain changes in OEF/OIF Veterans with history of mild TBI.* Poster presented at the 42nd annual International Neuropsychological Society Meeting, Seattle, WA.

Hanson, K. L., Schiehser, D. M., Twamley, E., Jak, A. J., **Clark, A. L.**, Lohr, J. B, Delis, D. C., & Delano-Wood, L. (2014). *Problem alcohol use is associated with increased psychiatric symptomatology and reduced processing speed in Veterans with mild traumatic brain injury.* Poster presented at the 42nd annual International Neuropsychological Society Meeting, Seattle, Washington.

Kim, R. T., Delano-Wood, L., **Clark, A. L.**, Hanson, K. L., Matevosyan, A., Jak, A. J., Delis, D. C., Lohr, J. B., & Schiehser, D. M. (2014). *The relationship between coping style, executive function, and mood in Veterans with mild to moderate traumatic brain injury.* Poster presented at the 42nd annual International Neuropsychological Society Meeting, Seattle, Washington.

Sheridan, M., **Clark, A.L.,** & McLaughlin, K.M. (2014). *Cognitive control over previously rewarded stimuli in adolescence is associated with thickness in the medial prefrontal cortex.* Poster presented at the 21st annual Cognitive Neuroscience Society Meeting, Boston, Massachusetts.

Sorg, S. F., Bondi, M. W., Schiehser, D. M., Luc, N., Jak, A. J., **Clark, A. L.**, Hanson, K. L., Lohr, J. B, & Delano-Wood, L. (2014). *Cognitive and psychiatric dissociations between fractional anisotropy and cortical thickness in Veterans with mild TBI.* Poster presented at the 42nd annual International Neuropsychological Society Meeting, Seattle, Washington.

Bowers, D., Sapienza, C., Springer, U., Mikos, A., Nisenson, A., **Clark, A. L.,** Rodriguez, R.,

Fernandez, H., Okun, M. (2012, February). *Unmasking the face of Parkinson's patients: Results from a randomized double-blind sham-controlled behavioral intervention.* Abstract presented at the 40th annual International Neuropsychological Society Meeting, Montreal, QC, Canada.

Clark, A.L., Amick, M., Fortier, C., Milberg, W., & McGlinchey, R. (2012). *The Medical Symptom Validity Test (MSVT) in the TRACTS cohort.* Abstract presented at Boston University School of Medicine Consortium for PTSD and TBI, Boston, MA.

Jordan, L, Dietz, J., **Clark, A. L.,** McKently, H., Okun, M. S., & Bowers, D. (2012). *Muffled emotional memory in Parkinson's disease*. Poster presented at the 62nd Annual Meeting of the American Academy of Neurology, Toronto, Ontario, Canada.

ABSTRACT OF THE DISSERTATION

The Relationship Between Cerebral Blood Flow and Neuropsychological Outcomes in Veterans with History of Mild Traumatic Brain Injury

by

Alexandra L. Clark

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2019
San Diego State University, 2019

Professor Lisa Delano-Wood, Chair

Rationale. Though the short and long-term consequences of neurotrauma are only beginning to be appreciated, those with history of mild traumatic brain injury (TBI) show increased rates of psychiatric disorders, decreased quality of life, and cognitive deficits relative to those with no history of mTBI. Potentially important, though vastly understudied, is the role of the cerebrovascular system in cognitive outcomes after mild TBI. Primary injury to the cerebrovasculature (i.e., stretching and shearing of vessels) coupled with secondary pathophysiological processes (e.g., ischemia, neuroinflammation, vascular remodeling) may alter cerebral blood flow (CBF) post-injury. Such CBF changes may negatively affect the brain's process of post-traumatic repair and contribute to poor long-term outcomes. However, the contribution of CBF to cognitive dysfunction post-injury remains incompletely characterized, and no known human studies have investigated how important genetic and environmental risk factors (i.e., cumulative number of sub-concussive blasts, history of multiple TBIs, time since injury, apolipoprotein E [APOE]-ε4 genotype) may moderate CBF and cognitive associations.

Design. The current study utilized multi-phase pseudo-continuous arterial spin labeling neuroimaging methods to (1) evaluate whether resting CBF differences occur in those with history of TBI, (2) investigate the relationship between resting CBF and neuropsychological function, and (3) in exploratory analyses, examine possible moderators of resting CBF and cognition in those with history of mTBI. We recruited and enlisted 54 OEF/OIF/OND service members between the ages of 18 and 50 for this study. Study groups include those with history of mild or moderate TBI (n = 31) and military controls with no history of TBI (n = 23). Analyses of covariance controlling for age and symptoms of posttraumatic stress and depression were used to explore group differences in resting CBF of the whole brain as well as bilateral frontal and temporal regions of interest. Multiple regression analyses were performed within the TBI group to assess whether resting CBF in bilateral frontal and temporal ROIs was predictive of performance on measures of executive functioning and memory; whether regional CBF measures were associated with genetic and environmental risk factors; and whether these risk factors moderated regional CBF and cognitive associations.

Results. ANCOVAs indicated that, independent of age and symptoms of posttraumatic stress and depression, TBI Veterans demonstrated significantly higher resting CBF in several frontal and temporal regions of interest. No significant group differences in whole brain resting CBF were observed. Multiple regression analyses revealed that, independent of age, higher resting CBF in frontal regions was significantly associated with better performance on measures of executive functions within the mTBI group. However, resting CBF in temporal regions was not significantly associated with performance on memory measures. Further analyses identified number of mTBIs as the only significant risk factor associated with resting CBF of frontal regions. However, several significant risk factor x resting CBF interactions on cognition were observed. Results revealed that resting CBF and cognitive associations were generally more pronounced in those with lower versus high risk factor burden such that higher resting CBF of

frontal and temporal regions was associated with better executive functioning and memory performance in those with fewer injuries as well as in those who were closer in time to their injury; and those who were APOE-ε4 non-carriers.

Conclusions. Findings suggest that, independent of age and psychiatric symptoms, history of TBI is associated with increased resting CBF. Importantly, increased resting CBF was associated with better cognitive performance in APOE-ε4 non-carriers as well as those who were closer in time to their TBI event(s). Results suggest that elevated resting CBF may represent a critical compensatory mechanism that allows for better cognitive performance in certain Veterans with TBI. These findings align with the "compensation related utilization of neural circuit hypothesis of aging," which suggests that increases in brain activation allow for task demands to be met, though the effectiveness of these increases appear to plateau within the context of greater injury. Information gleaned from these findings has the potential to improve diagnosis and possibly provide a useful biomarker of both impairment and recovery in a vulnerable population for which persistent behavioral dysfunction remains poorly understood.

I. INTRODUCTION

Mild traumatic brain injury (mTBI) is known as the "signature wound" of military service members involved in Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND; Fischer, 2010; Hoge et al., 2008; Terrio, Nelson, Betthauser, Harwood, & Brenner, 2011). Of the nearly three million military service members that have been deployed since the beginning of these conflicts, estimates suggest that approximately 18-25% of these individuals have sustained at least one mTBI during deployment (Fortier et al., 2014; Hoge et al., 2008; Terrio et al., 2011; Warden, 2006). The vast majority are closed-head injuries (i.e., no penetration of skull) that result from either blunt-force (i.e, direct blow to the head) and/or blast-related (i.e., exposure to highly pressurized blast waves from explosive munitions) trauma. These injuries occur in or out of combat theatre, and rates of incidence are relatively comparable across the various branches of the military (DVBIC, 2018).

Although immediate or emergency medical evacuation is not frequently required at the time of injury, the clinical sequelae that emerge post-injury are by no means minor. Indeed, troubling cognitive (e.g., executive dysfunction, memory deficits; Combs et al., 2015), neurological (e.g., headaches, dizziness, fatigue; Lippa et al., 2015; Vanderploeg, Belanger, & Curtiss, 2009), and psychiatric symptoms (e.g., depression, posttraumatic stress disorder [PTSD]; Brenner, Vanderploeg, & Terrio, 2009) are commonly reported in Veterans who have sustained mild head trauma. Collectively, these negative neurobehavioral symptoms have been linked to increased rates of unemployment and disability (Lippa et al., 2015), decreased quality of life (Schiehser et al., 2015), and significant health care costs and utilization among Veterans with history of mTBI (Hoge et al., 2008; Taylor et al., 2012).

Cognitive Outcomes in mTBI

Traditionally, mTBI has largely been considered a neurological condition in which recovery was inevitable—only a "miserable minority" were demonstrated to experience

persisting cognitive deficits (Ruff, Camenzuli, & Mueller, 1996). Importantly, this recovery trajectory is somewhat distinct from that of moderate or severe TBI, where enduring neuropsychological impairment is frequently observed (Hellawell, Taylor, & Pentland, 1999; Schretlen & Shapiro, 2003). Indeed, several meta-analyses (Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005; Rohling et al., 2011) have demonstrated that while medium to large effect sizes of impairment in memory, attention, processing speed, and executive functions have been demonstrated in the acute phase of injury (i.e., within three months of injury), these impairments are negligible or non-existent in the post-acute phase (i.e., beyond three months since injury). Moreover, other studies show that cognitive dysfunction is better explain by psychiatric symptoms and ongoing litigation, as opposed to neurological factors following mTBI (Belanger, Curtiss, Demery, Lebowitz, Vanderploeg, 2005; Drag, Spencer, Walker, Pangilinan, & Bieliausakas, 2012). Nevertheless, certain inherent methodological limitations to meta-analyses (e.g., heterogeneous samples, publication bias) may obscure the detection of a "miserable minority" or any cognitive deficits that may exist on the individual level (Bigler et al., 2013; Cappa, Conger, & Conger, 2011; Pertab, James, & Bigler, 2009).

Pertab and colleagues (2009) reanalyzed two of the previously mentioned meta-analytic datasets in an effort to clarify the long-term outcomes of those with mTBI. Careful attention was paid to the inclusion/exclusion criteria of the studies, as their goal was to explore whether a lack of consideration of fundamental sample differences in mechanism of injury, diagnostic classification of injury severity, time since injury and subsequent cognitive assessment, and whether the inclusion of symptomatic or non-symptomatic patients may have obscured the detection of cognitive deficits in the post-acute phase of injury. In other words, they sought to reduce between-sample heterogeneity, which might have minimized the global detection of an effect across studies included in the meta-analyses. Interestingly, results revealed significant moderate effect sizes for impairments on measures of processing speed, working memory, and verbal memory in the post-acute phase of injury, though small or trivial effect sizes were noted

across the remaining cognitive tests. While controversial, these results suggest that there may in fact be a sizable subgroup of mTBI patients with persisting deficits that do not follow traditional, previously expected, recovery trajectories. These authors estimate the prevalence of this group may range from 11-24% in other study samples. Moreover, recent evidence suggests that as many as 50% of military service members remain symptomatic throughout the first year post-of injury (Schwab et al., 2017), and that these troublesome post-concussive symptoms (PCS) generally tend to worsen with time (MacDonald et al., 2011).

Enhancing Our Understanding of mTBI with Advanced Neuroimaging Techniques

Major efforts have been devoted to characterizing the pathophysiology, or resultant structural and functional brain changes, thought to underlie the negative health outcomes of those with history of mTBI (Bigler, 2013). Although conventional computed tomography (CT) and magnetic resonance imaging (MRI) scans largely yield normal results in the context of milder forms of head trauma (Lee et al., 2008; Yuh et al., 2013), more sophisticated and advanced neuroimaging techniques (i.e., diffusion tensor imaging [DTI], resting state functional MRI), have provided some insight into potential structural and functional brain changes of those with history of mTBI (Wilde et al., 2015). However, a reliable biomarker of mTBI has yet to be discovered. While some samples find robust structural and/or functional group differences between those with history of mTBI relative to those with without (Robinson et al., 2015; Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015), others report no such differences (Jorge et al., 2012; Levin et al., 2010), and the extent to which observed brain changes correlate with clinical outcome measures has been equally convoluted and difficult to ascertain (Brenner, 2011). While mixed results may be partially explained by sample characteristics, psychiatric status, and the heterogeneous nature of injury in mTBI (Bigler, 2013; Pertab et al., 2009; Wilde et al., 2015), there also exists the possibility that previously utilized neuroimaging techniques are in fact not sensitive to the full nature of mTBI-related brain changes.

Critically relevant in the exploration of biomarkers within the context of mTBI is the role of the cerebral blood flow (CBF). The brain is reliant on steady CBF to carry out a host of functional processes and maintain neuronal integrity. Any alterations in CBF could affect critical processes that include the brain's ability to maintain homeostasis, adequately respond to trauma, and may potentially contribute to the evolution, or maintenance of injury sequelae (i.e., cognitive deficits) in those with mTBI (Pollock et al., 2009). Moreover, across a variety of clinical populations, the notion that CBF alterations precede and contribute to negative pathological processes is gaining increased traction (Bernbaum et al., 2015; Brickman et al., 2009; Promjunyakul et al., 2016; ten Dam et al., 2007). Within the aging literature, longitudinal CBF reductions have been linked to increased amyloid deposition, suggesting that CBF is not merely a consequence, but rather a pathogenic factor in Alzheimer's disease (Mattsson et al., 2014; Sojkova et al., 2008). This concept was further highlighted by a recent mTBI study in which reduced CBF at the acute phase of injury significantly predicted negative structural alterations of cerebral gray and white matter in the chronic phase of injury (Metting, Spikman, Rodiger, & van der Naalt, 2014). In other words, CBF may not only serve as a more sensitive biomarker of impairment in mTBI but may also be point of intervention. Direct maintenance of CBF may not only inhibit the progression of negative pathological cascades, but also play a significant role in reducing or minimizing the negative cognitive and behavioral outcomes observed in those with mTBI.

Vascular Pathology as a Central Mechanism of Neurotrauma

Compelling studies have recently emerged from the animal models literature suggesting a central role of vascular pathology in both the primary (that resulting directly from the traumatic event) and secondary (protracted pathophysiological processes) phase of injury (Kenney et al., 2015). During TBI, acceleration/deceleration or linear/rotational forces may cause the brain to oscillate or glide within the cranial vault; these forces results in rapid deformation that may cause primary damage at locations where the brain makes impact with the skull (coup), or at

both the initial impact site and opposite end (i.e., coup/contercoup; Bayly, Clayton, & Genin, 2012; Viano & Pellman, 2005). Additionally, rotational forces cause shear/strain injury which is associated with a network of torn or broken vasculature throughout the brain (Kenney et al., 2015). In nearly all animal models of TBI (i.e., controlled cortical impact, fluid percussion injury, impact acceleration, blast-induced) microvascular injury is the predominant feature (Cherian, Goodman, & Robertson, 2011; Gao, Oda, Wei, & Povlishock, 2010; Park, Bell, Siddiq, & Baker, 2009). For example, decreased microvascular density has been observed around impact sites following TBI, and it has been demonstrated to persist for many weeks following initial injury (Park et al., 2009). Damage to the vessels themselves in the form of thinning of the basal lamina, and focal swelling or constriction has also been noted on histopathological exams (Sangiorgi et al., 2013). Moreover, vascular remodeling has been observed for up to three months following initial injury in a rat model of mTBI (Gama Sosa et al., 2014). One negative byproduct of this torn vasculature is the accumulation of hemosiderin deposits, which were noted to gradually increase in the three months following injury in rats (Glushakova, Johnson, & Hayes, 2014). Although human cases of mTBI rarely come to autopsy, similar findings in the arterioles and capillaries of middle and deep cortical vascular zones have been shown in autopsy investigations of fatal moderate-to-severe TBI (Rodriguez-Baeza, Reina-de la Torre, Poca, Marti, & Garnacho, 2003). Moreover, in-vivo detection of petechial hemorrhages has also been commonly noted in human neuroimaging studies of mTBI (Benson et al., 2012; Tate et al., 2017).

In addition to primary injury to the vasculature, secondary pathophysiological cascades also cause critical damage following neurotrauma. From a neurometabolic perspective, external force or mechanical stress within the brain also leads to rapid depolarization of nerve cells (Giza & Hovda, 2014). This depolarization results in an outpouring and indiscriminate release of neurotransmitters, which causes an energy crisis that alters glucose metabolism and cerebral blood flow post-injury. Other secondary sequelae for cerebrovascular dysfunction following

neurotrauma include ischemia, cerebral edema, and intracranial hypertension (Giza & Hovda, 2014). For example, decreased CBF post-injury may result in ischemia and cytotoxic edema, which negatively impacts cellular functioning and alters cellular metabolism (Donkin & Vink, 2010). Moreover, damage to blood vessels (i.e., blood brain barrier [BBB] disruption) results in vasogenic edema, which causes tissue swelling and directly increases intracranial pressure. Breakdown of the BBB has been linked to an increased neuroinflammatory response, which interferes and prevents neuronal repair (Lozano et al., 2015). While the temporal nature of the biochemical, metabolic, and cellular cascades resulting from TBI are not entirely understood, neuroinflammation has been detected up to 17 years post TBI and can persist well beyond the acute phase of injury (Giunta et al., 2012; Lozano et al., 2015).

Importantly, the combination of primary injury coupled with secondary pathological processes contributes to vascular perturbations that are thought to subsume deleterious alterations in cerebral blood flow (CBF) in the aftermath of head trauma. Indeed, recent animal studies using perfusion MRI techniques have shown sizable CBF reductions (i.e., 54-74% reductions) in TBI-injured rats relative to sham-controls (Hayward et al., 2011; Pasco et al., 2007). These changes have been observed diffusely throughout the brain (and even distally from the site of injury), and they have also been linked to behavioral deficits on vestibulomotor and working memory tasks in brain-injured rats (Hayward et al., 2011; Wei, Hamm, Baranova, & Povlishock, 2009).

Unfortunately, the translation of animal to human neuroimaging studies examining resting CBF alterations in mild neurotrauma has been both challenging and limited. First, the nature and regional specificity of resting CBF alterations post-injury remains poorly understood. For example, while some studies cite robust decreases in resting CBF (Bonne et al., 2003; Ge et al., 2009; Metting et al., 2014), others have reported increased resting CBF in those with history of mTBI relative to controls (Doshi, Ramakrishnan, & Gupta, 2015). Second, while global resting CBF alterations have been described in those with history of mTBI (Fridley, Robertson,

& Gopinath, 2015), others have noted that only regions vulnerable to impact with bony protuberances of the skull (i.e., frontal and temporal cortices) show resting CBF differences relative to controls (Metting et al., 2014; Wang et al., 2015). Moreover, the relationship between resting CBF and cognitive outcome is unclear. For example, some studies have failed to find resting CBF and cognitive associations (Meier et al., 2015), while others report robust relationships between low resting CBF and deficits on measures of memory, processing speed, and executive functions (Ge et al., 2009; Metting et al., 2014). The disparate nature of these findings may be partially explained by differing sample characteristics (e.g., inclusion of range of injury severity), use of blunt cognitive screening tools versus comprehensive neuropsychological batteries, and the heterogeneous nature of injury in mTBI. Additionally, within the context of mild neurotrauma most human neuroimaging studies have largely utilized, single photon emission computed tomography (SPECT), photon emission computed tomography (PET), and other invasive and indirect hemodynamic imaging techniques (i.e., xenon and perfusion CT) that use radioactive tracers. Other limitations to these techniques include poor prognostic utility and correlations with behavioral measures, and the inability to assess microvascular perfusion.

Arterial Spin Labeling as a Promising Tool to Detect CBF Changes

One sophisticated, advanced neuroimaging technique that may help to clarify the nature of CBF alterations in Veterans with mTBI is arterial spin labeling (ASL; Andre, 2015). ASL is a non-invasive and reliable MRI technique in which arterial water is magnetically labeled and used as an endogenous tracer to measure CBF (Detre, Leigh, Williams, & Koretsky, 1992; Shin, Ozyurt, & Liu, 2013; Williams, Detre, Leigh, & Koretsky, 1992). The magnetization of arterial blood water is altered in a region proximal to the image slice. This is followed by a delay to allow labeled blood to arrive at the capillary bed in the tissue of interest. The labeled blood diffuses into the tissue resulting in local alteration of longitudinal magnetization. Difference images are generated by subtracting images acquired with arterial spin labeling from control images that are acquired in the absence of labeling. ASL represents a powerful tool given that it provides a

quantitative measure of CBF in the capillary bed in physiological units (mL/100g of tissue per minute), without the use of an exogenous, or radioactive, contrast agent (Andre, 2015). Importantly, because ASL is not dependent on the use of an exogenous contrast agent, it does not require correction for possible leakage effects due to breakdown of the BBB and is therefore particularly useful in TBI. ASL studies examining a variety of clinical populations (e.g., stroke, Alzheimer's disease, epilepsy) have demonstrated similar patterns of regional hypoperfusion as those revealed with PET and SPECT (Alsop, Detre, & Grossman, 2000; Andre, 2015; Detre et al., 1992), but ASL has advantages of being non-invasive, cost-effective, and easily repeatable. Although ASL represents a promising tool that likely captures even the subtlest alterations in resting CBF resulting from mTBI, few ASL studies in the context of head injury currently exist, and there are no known studies to our knowledge that have investigated the association between CBF alterations and clinical outcome in Veteran mTBI samples. Therefore, given that there is sufficient evidence from the animal literature to suggest that vascular pathology is a central mechanism in mTBI, the current project utilized ASL to examine whether mTBI leads to critical alterations in resting CBF that contributes to poor cognitive outcomes.

Modeling Other Factors That May Influence CBF and Cognition

There are a variety of largely unexplored genetic and environmental risk factors (i.e., cumulative blast exposure, history of multiple TBIs, time since injury, and genetic susceptibility [Apolipoprotein-ε4 positivity]) that may influence CBF and cognitive outcomes in mTBI. Unfortunately, even studies using the most sophisticated and sensitive techniques (i.e., ASL) tend to neglect the potential influence of these factors in their explorations. As such, a more comprehensive exploration of factors that likely contribute to the heterogeneity of mTBI outcomes is important for accurately characterizing the brain changes that occur post injury and identifying those at greatest risk for negative behavioral outcomes. Importantly, these risk factors have the potential to modify CBF and cognitive associations by (1) exacerbating or contributing to brain damage and (2) reducing cognitive reserve post-TBI. As detailed in the

model below, mTBI—via primary or secondary injury—may result in CBF changes. These CBF alterations play a fundamental role in negatively influencing cognitive outcomes post-injury. However, the presence or dose of these various factors may strengthen the association

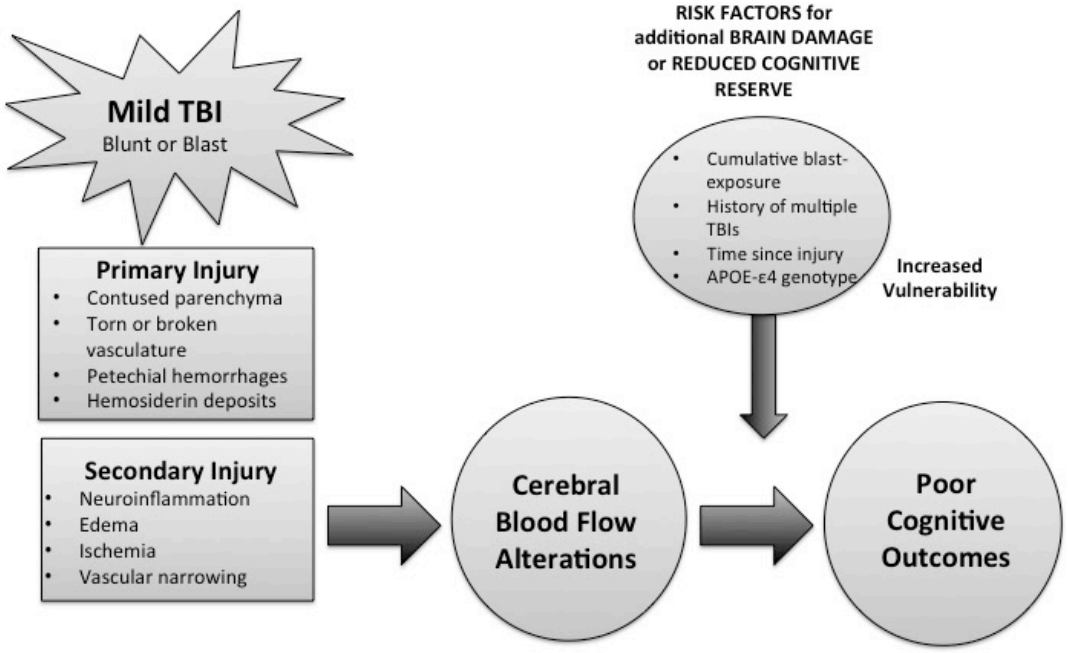

Figure 1. Theoretical Model of Resting CBF Alterations in Veterans with mTBI. Pathological brain changes sustained during or shortly after injury contributes to CBF alterations; CBF changes are related to poor cognitive outcomes and ultimately moderated by additional risk factors that increase vulnerability for brain damage and reduced cognitive reserve.

between CBF and cognition via increasing the brain's vulnerability to brain damage or limiting its ability to compensate for this damage. In other words, CBF related cognitive deficits should be more pronounced in the presence of certain risk factors. The potential role of these factors is detailed below. Evidence will focus on how these risk factors are fundamentally tied to brain changes (some of which may overlap with vascular pathology detailed above) or directly contribute to poor cognitive outcomes.

Number of TBIs. Multiple mTBIs or repeated head-injury has been linked to chronic traumatic encephalopathy and increased risk for dementia in late life (Baugh et al., 2012; McKee & Robinson, 2014). However, there is some evidence that relative to a single mTBI event, multiple mTBIs result in worse cognitive impairment, especially in the domain of executive functions even in midlife (Karr, Areshenkoff, Duggan, & Garcia-Barrera, 2014). As such, there is some evidence that sustaining mTBIs throughout one's lifetime may result in a negative "dose effect" on cognition. Indeed, a recent study of Vietnam Veterans increased rates of cognitive impairment were observed in those with history of multiple mTBI relative to those who had sustained a single mTBI event (Kaup et al., 2017). Interestingly, this study also found that those with a history of multiple mTBIs displayed cognitive impairments that were similar in both pattern and severity to those who had sustained one moderate-to-severe TBI (Kaup et al., 2017). Findings suggest that the negative effects of multiple mTBIs may result in residual cognitive deficits that mirror what might be expected in those with more severe injuries.

Multiple mTBIs has also been linked to negative brain changes in both animal and human studies (Lynch et al., 2016; (Johnson et al., 2012). In an animal model of repetitive head-injury, brain changes appear to be primarily vascular in nature. For example, in a recent mouse model of repetitive TBI, decreased vessel density and global reductions in CBF were observed at both one and six months following injury, and were also closely linked to spatial memory deficits (Lynch et al., 2016). Currently, human studies that directly examine brain changes resulting from multiple TBIs to single TBI events are limited. One known study showed that those multiple mTBIs have more severe neurometabolic abnormalities compared to both controls and those with history of a single mTBI event (Johnson et al., 2012). Another study found that examined multiple MRI metrics found that relative to controls, those with multiple mTBIs display changes in CBF, increased prevalence of microhemmorhages, and altered brain connectivity (Slobounov et al., 2017). In summary, although a single mTBI may result in

negative cognitive or brain changes, there is some evidence that these may be even more pronounced in those with history of multiple mTBIs.

Blast exposure. As noted by Fortier and colleagues (2014), blast-exposure varies considerably among OEF/OIF/OND service members, though 80% of this convenience sample reported experience at least one blast within 100 meters during deployment. Studies exploring cognitive outcomes have failed to find any categorical differences between those with single blast or blunt TBIs (Lange et al., 2012; Luethcke, Bryan, Morrow, & Isler, 2011). However, deficits in the cognitive domains of executive functioning, complex attention, and verbal learning and memory have been noted following blast TBI (Karr et al., 2014). Although TBIs resulting from blast may be detrimental, recent animal studies have shown that cumulative exposure to blast-waves (even those that do not result in an mTBI) has been linked to worse cognitive outcomes (Ahlers et al., 2012). Thus, there is some preliminary evidence to suggest that repeated exposure to blasts, even in the absence of an mTBI or concussive injury, may contribute to poor behavioral outcomes. Indeed, findings from a recent human case study revealed that a Veteran with repeated blast-exposure who never meet diagnostic criteria for a blast-related TBI, was impaired on measures of processing speed, recognition memory, working memory, and executive function (Hayes, Morey, & Tupler, 2012). Similarly, human neuroimaging studies have confirmed the negative effects of cumulative blast-exposure. For example, greater age-related reductions in white matter microstructural integrity (Trotter et al., 2015) and altered functional connectivity have been observed in those exposed to multiple blasts (Robinson et al., 2015). Moreover, recent work from our own lab has revealed anterior cortical thinning and executive dysfunction in blast-exposed Veterans with mTBI (Clark et al., 2018). Blast-injury itself has also been linked to robust vascular damage in animal studies of TBI (Gama Sosa et al., 2014; Goldstein et al., 2012; Saljo, Mayorga, Bolouri, Svensson, & Hamberger, 2011). Indeed, one of the proposed mechanisms of blast-related injury (in addition to damage from acceleration/rotation forces) to the central nervous systems involves

transmission of kinetic energy from the blast wave to the brain via large blood vessels in the chest (Chen & Huang, 2011). As a result of the blast-wave, blood surges and dramatically increases cerebral perfusion, which may disrupt the BBB and result in microvascular damage. Moreover, secondary injury responses may further alter cerebral hemodynamics following blast exposure (Cernak & Noble-Haeusslein, 2010). As such, these negative pathological consequences might be more severe with increasing levels of blast-exposure.

Time since injury. Currently, the temporal courses of the pathological processes that occur with neurotrauma are poorly understood. However, there is evidence that these secondary pathological processes may persist for minutes, days, to months following initial injury (Giza & Hovda, 2014; Loane & Faden, 2010). Understanding the evolution of damage secondary to TBI is especially critical as various neuropathological processes may influence our interpretation and characterization of neuroimaging findings. For example, with respect to DTI, fractional anisotropy—a direct marker of white matter microstructural integrity—differs depending on time between injury and neuroimaging assessment. Indeed, marked increases in FA are frequently seen when patients within two weeks of injury are compared to controls (Mayer et al., 2010; Niogi & Mukherjee, 2010). Importantly, as detailed in a recent meta-analysis, FA is significantly anti-correlated with neuropsychological measures in this sub-acute time frame (Eierud et al., 2014). Alternatively, patients who are greater than two weeks post-injury (ranging from weeks, months, to years) most often show decreased FA, which is significantly positively correlated with neuropsychological test performance. Similarly, using a different structural MRI technique, independent of PTSD, amygdala dilation was found to occur with greater time since injury and was particularly pronounced in older Veterans who are further removed from their initial injury (Tate et al., 2016). In other words, there is evidence that mTBI related brain changes are dynamic in that may continue to persist or progress many years following initial injury and that this can be captured on various neuroimaging metrics. This concept was further exemplified by our recent work that showed that reduced CBF was

significantly associated with white matter microstructural alterations in a Veteran mTBI sample, but only in those who were further removed in time from their initial injury (Clark et al., 2017). Findings suggest that CBF reductions may represent a protracted pathological process, which could serve to exacerbate trauma-induced white matter injury. Oftentimes, in Veteran TBI samples, there is considerable inter-subject variability in the time since injury and neuroimaging assessment (Delano-Wood et al., 2015; Jorge et al., 2012; Mac Donald et al., 2011; Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016). Modeling time since injury as factor in our explorations may assist in clarifying the nature and extent of mTBI related brain changes and resulting cognitive outcomes.

Apolipoprotein-ε4 positivity (APOE-ε4). There is evidence to suggest that genetic susceptibility may play a role in poor long-term outcomes following TBI. APOE is a protein that plays an important role in a number of biological processes that include synaptogenesis, neuroinflammation, and metabolism of amyloid-β (Dorey et al., 2017; Tai et al., 2015). There are three distinct isoforms of APOE (i.e., APOE2, APOE3, and APOE4) and the efficacy of APOE's functions largely differs across these isoforms. For example, while APOE3 promotes amyloid-β degradation and transport across the BBB, APOE4 facilitates amyloid-β accumulation and degradation of the BBB. In general, APOE4 has been linked to negative pro-inflammatory processes and increased vascular risk (Dorey et al., 2017; Gale et al., 2014). Within the context of TBI populations, some studies have found the possession of the APOE-ε4 genotype is associated with worse cognitive outcomes, while other have not (Merritt, Lapira, Clark, Sorg, Werhane, Jak, Schiehsher, & Delano-Wood, 2018; Merritt, Clark, Sorg, Werhane, Jak, Schiehsher, & Delano-Wood, 2018; Merritt, Clark, Sorg, Evangelista, Werhane, Bondi, , Schiehser, & Delano-Wood, 2018;Zhou et al., 2008). These mixed findings may be a product of sample heterogeneity in both phase (acute vs. post-acute) and severity of injury. Human MRI studies examining the potential role of APOE-ε4 genotype on influencing CBF are extremely limited. Nevertheless, one investigation revealed APOE-ε4 allele carriers show increased CBF

in the acute phase of injury relative to non-carriers following severe TBI (Kerr, Kamboh, Kong, Alexander, & Yonas, 2006). Importantly, these findings align well with studies in demented and non-demented older adults that show increased CBF in AD-vulnerable regions in APOE-ε4 allele carriers relative to non-carriers (Bangen et al., 2012; Wierenga et al., 2012). Possession of the APOE-ε4 genotype may be linked to an increased risk for CBF alterations or cognitive deficits relative to non-carriers following TBI. Clearly, additional research is needed to clarify the potential negative influence of APOE-ε4 genotype on both cognition and CBF following mild TBI.

Psychiatric Comorbidities in Veterans

It is important to acknowledge that recent estimates suggest that nearly 90% of Veterans with mTBI also endorse clinically significant PTSD and/or depression symptoms (Taylor et al., 2012), and that psychiatric symptoms are commonly found to be more severe in those with history of mTBI relative to those with no history of neurotrauma (Schneiderman, Braver, & Kang, 2008; Yurgil et al., 2014). Common psychiatric comorbidities (e.g., PTSD) may also explain or contribute to poor neuropsychological functioning in Veteran samples. For example, executive dysfunction, verbal memory impairments, impaired response inhibition, and deficits in sustained attention have been found in those with PTSD (DeGutis et al., 2015; Scott et al., 2015) and overlap, at least to some degree, with deficits found in mTBI (Bryant, 2011). Nevertheless, major efforts have been placed on (1) disentangling whether history of mTBI, or rather PTSD itself, explains any observed neurocognitive deficits beyond the post-acute phase of injury, and (2) determining the potential synergistic effects of co-morbid PTSD and mTBI on cognitive outcomes. In general, two approaches have been utilized in explorations of cognitive outcomes in OEF/OIF/OND Veterans. This has primarily been accomplished creating diagnostic groups and subsequently comparing cognitive test scores between controls and those with mTBI only, PTSD only, co-morbid PTSD/mTBI (Combs et al., 2015). Alternatively, another common approach is to control for PTSD symptoms when comparing neuropsychological test performance of those with and without history of head injury (Clark et al., 2016). Regardless of

the approach taken, findings have again, largely yielded mixed results; some studies demonstrate mTBI results in cognitive deficits independent of PTSD (Clark et al., 2016; Combs et al., 2015), others showing impairments are specific to PTSD (Neipert et al., 2014; Storzbach et al., 2015), and some suggest comorbid conditions results in worse neurocognitive functioning (Amick et al., 2013). Importantly, the central thesis of this proposal was to characterize *neurotrauma-related* vascular changes and the potential cognitive consequences. As such, we utilized PTSD as a covariate in an effort to determine the *independent* influence of mTBI on cognition.

Purpose of the Current Study

Considerable efforts have been placed upon examining the complex pathophysiology processes that may alter brain structure and function in the aftermath of mTBI (Bigler, 2013; McAllister, Sparling, Flashman, & Saykin, 2001). This has proven especially critical given the host of troubling neurocognitive impairments (e.g., executive dysfunction, memory deficits) that have been noted in both the acute and remote phases of injury in a sizable minority of patients with history of TBI (Bigler et al., 2013; Binder et al., 1997; Pertab et al., 2009; Rohling et al., 2011). Recent findings from the animal literature suggest that primary injury to the cerebrovasculature such as stretching and shearing of vessels coupled with secondary pathophysiological processes (e.g., ischemia) may alter cerebral blood flow (CBF) post-injury (Kenney et al., 2015; Park et al., 2009; Pasco et al., 2007; Pop & Badaut, 2011; Sangiorgi et al., 2013). However, the nature of CBF alterations in those with history of mTBI is unclear as there is a paucity of studies, and the few that exist have largely shown mixed results (Meier et al., 2015; Wang et al., 2015). Moreover, CBF's contribution to cognitive dysfunction post-injury remains incompletely characterized (Romero, Lobaugh, Black, Ehrlich, & Feinstein, 2015) and, to our knowledge, no known human studies have investigated how important risk factors (i.e., time since injury, blast exposure, apolipoprotein E (APOE)-ε4 positivity) may moderate CBF and cognitive associations.

The major goal of this study was to elucidate the long-term cognitive outcomes in Veterans with mTBI through (1) the exploration of a combination of advanced neuroimaging techniques and associations with behavioral data, and (2) precise statistical modeling of factors that may influence both brain and cognitive outcomes. Given the array of previously mentioned factors, reliable biomarkers that may assist in enhancing our ability to detect and understand the nature and extent to which mTBI is associated with long-term cognitive outcomes are very much needed. Therefore, the aims of this proposal were to (1) determine whether resting CBF changes occur within the context of mTBI; (2) explore whether resting CBF is associated with cognitive outcomes in mTBI; and (3) in exploratory analyses examine risk factor and CBF associations as well as the role of these risk factors in moderating resting CBF and cognition performance in those with history of mTBI. Strengths of the current translational, multidisciplinary proposal include the use of advanced, innovative ASL technology, comprehensive neuropsychological assessment, and a focus on a relatively homogeneous, well-characterized cohort of vulnerable Veterans with history of mild neurotrauma. Moreover, through examination of previously unconsidered factors (e.g., time since injury, APOE-ε4 genotype status, blast exposure), the current proposal sought to elucidate the underlying pathophysiology of and negative outcomes associated with history of mTBI. Findings of this proposal serve to inform the mechanistic underpinnings of poor outcome following mTBI while also informing targeted vascular-based prevention and intervention strategies that may reduce mTBI-related health consequences.

Aim 1: To investigate whether participants with history of mTBI show reduced resting CBF relative to those without history of mTBI.

Hypothesis 1a: Given that previous biomechanical and animal models suggest that vascular changes may be widespread and diffuse following mTBI, it was hypothesized that Veterans with history of mTBI will show global reductions in CBF when compared to Veterans with no history of mTBI.

Hypothesis 1b: In Veterans with mTBI, resting CBF reductions was expected to be most prominent in known predilection sites (i.e., frontal and temporal cortices) given increased risks of contusion between the brain and bony protuberances of the cranial vault in these regions.

Aim 2: To determine whether regional resting CBF predicts cognitive test performance in those with history of mTBI.

Hypothesis 2a: We expected that reduced resting CBF in frontal and anterior cingulate cortices will be associated with poorer cognitive performance, particularly on tests of executive functioning.

Hypothesis 2b: We hypothesized that reduced resting CBF in lateral and medial temporal lobe structures will be associated with poorer performance on memory measures.

Exploratory Aim 3: To explore how important risk factors (a) influence resting CBF as well as (b) the association between resting CBF and cognitive outcomes in those with history of mTBI.

Hypothesis 3a: We expected that greater blast-exposure, history of multiple TBIs, APOE-ε4 positivity, and further time from injury will be associated with reduced resting CBF.

Hypothesis 3b: We expected that reduced resting CBF and poorer cognitive performance will be more pronounced in those with greater blast-exposure, history of multiple TBIs, who are APOE-ε4 positive, and further removed from their injury.

II. METHODS

Participants

We recruited 54 Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) service members between the ages of 18 and 50 for the proposed study. Study groups include (1) those with history of mild or moderate TBI (mmTBI; n = 31) and (2) military controls (n = 21) with no history of TBI. Although we originally planned to enroll only individuals with mild TBI, seven individuals with moderate TBI were included due to sample size and power concerns after issues with scan acquisition and data collection resulted in some unusable data points. All data for this project was gathered under Dr. Lisa Delano-Wood's ongoing TBI studies. Subjects were recruited under from the VA San Diego Healthcare System (VASDHS) and University of California, San Diego (UCSD) via word-of-mouth, posted recruitment fliers, and referrals from the VASDHS TBI Clinic. All participants were carefully screened to determine study eligibility. Upon qualifying for enrollment, participants completed comprehensive cognitive testing, self-report symptom rating scales, are were interviewed for TBI and substance abuse history. Finally, after the collection of behavioral data all participants then completed MRI scanning.

Inclusion criteria. The Department of Defense (DoD)/VA TBI Task Force criteria (2009) was used for diagnosis of mild or moderate TBI. The criteria for mild TBI include loss of consciousness (LOC) < 30 minutes, or alteration of consciousness (AOC) or post traumatic amnesia (PTA) < 24 hours, while the criteria for moderate TBI was LOC >30 minutes but < 24 hours, or AOC > 24 hours or PTA >1 day but < 7 days. MCs were included in the study if they had no history of head injuries that occurred prior to, during, or immediately following discharge from the military.

Exclusion criteria. Participants were excluded from the study sample if that met criteria for severe TBI as defined by 1) LOC ≥ 24 hours, AOC > 24 hours, or PTA ≥ 7 days). Additional exclusion criteria include the following which are also applied to the entire study sample: (1)

failure to complete or pass effort testing; (2) current or past history of a significant medical condition (e.g., seizures, multiple sclerosis); (3) hearing or vision impairment that interfere with testing;(4) current substance/alcohol abuse or dependence as indicated by diagnostic clinical interview; (5) current active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; (6) any contraindications to magnetic resonance scanning (MRI) (e.g., shrapnel, ferromagnetic implants); (7) a positive toxicology screen as measured by the Rapid Response 10-drug Test Panel; (8) endorsement of a high blood pressure or cholesterol, and/or any history of diabetes, coronary heart disease, stroke, arrhythmia on the background questionnaire; (9) a calculated BMI in the overweight or obese (i.e., >25) range; and (10) listing of any antihypertensive, statins, or insulin drugs on the medication history questionnaire.

Measures

TBI History Questionnaire. TBI relevant information was obtained via open-ended questionning and prompts via a lab-based questionnaire modeled on the VA's semistructured clinical interview for TBI identification (Vanderploeg, Groer, & Belanger, 2012). This measure addressed several key aspects of traumatic events including the number of head injuries sustained, important diagnostic data for each (e.g., duration of LOC, AOC, and PTA), and the mode of injury (i.e., blast or blunt force). All participants are assessed for non-military (prior to or after discharge from the military) and military-related head injuries. Military-related injuries were assessed separately for blast and blunt mechanisms of injury. With respect to blasts, participants were also asked to estimate total number of blast exposures, distance, and the direction from which the blast was initiated (See Clark et al. 2016 for more details). Time since injury was calculated by determining how many months had passed between the date of a participant's last reported injury and the first testing session of the study.

Background Questionnaire. Employment, demographics, and health/medical history data was recorded for each subject.

Substance Interviews. Participants were administered the Mini International Neuropsychiatric Interview (MINI; van Vliet & de Beurs, 2007) which is consistent with the DSM-IV (DSM-IV., 1993), for assessment of current and past history of alcohol and/or substance use.

Self-Report Measures. Participants completed the PTSD Symptom Checklist-Military Version (PCL-M; Weathers, 1993), Beck-Depression Inventory-II (BDI-II; Beck, 1996), and Neurobehavioral Symptom Inventory (NSI; King et al., 2012).

Neuropsychological Tests. Delis-Kaplan Executive Function System (D-KEFS) Fluency and Trail Making Test subtests (Delis, 2001); California Verbal Learning Test-2nd Edition (CVLT-II; Delis, Kaplan, & Ober, 2001); Reading subtest of the Wide Range Achievement Test- 4th edition (WRAT-4; Wilkinson & Robertson, 2006); Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1981); Wechsler Memory Scale Fourth Edition (WMS-IV; Wechsler, 2009); and the Test of Memory Malingering (TOMM; Tombaugh, 1996). First, all neuropsychological variables were converted from raw scores to standardized scores (e.g., scaled scores, *T* scores, z scores) using manual-specific normative data. Next, all standardized scores were converted to z-scores, with a mean of 0 and *SD* of 1, so that all measures were on the same metric. In an effort to reduce the number of comparisons, two theory-drive neurocognitive composites were created by averaging the z-scores across these variables. The EF composite consisted of DKEFS Letter Fluency, Verbal Fluency Switching, and Number-Letter Sequencing, as well as the WCST Total Errors and Perseverative Responses scores. The memory composite consisted on CVLT-II Total score, Short and Long Delay Free Recall scores, Logical Memory I and II total recall scores.

Health variables and Genotyping. Height, weight, and blood pressure (seated and standing) were collected for every subject. Buccal swabs were collected for APOE genotyping procedures and APOE genotype was determined using two single nucleotide polymorphism assays for the APOE coding regions (APOE112 and APOE158, rs429358 and APOE158,

respectively). DNA was extracted from buccal samples and quantified using polymerase chain reaction amplification procedures described by Saunders and colleagues (1993).

Procedures

Participants were scanned on a 3.0 Tesla General Electric Medical Systems EXCITE whole body imager with an 8-channel receive-only head coil at the UCSD Center for Functional Imaging on the UCSD La Jolla campus.

Scanning Parameters. Participants were scanned on a 3.0 Tesla General Electric Medical Systems EXCITE whole body imager with an 8-channel receive-only head coil at the UCSD Center for Functional Imaging (CfMRI) on the UCSD La Jolla campus. Structural MRI: A high resolution T1-weighted Fast Spoiled Gradient Recall (3D FSPGR) scan was acquired to provide anatomic reference (172 1 mm contiguous sagittal slices, FOV = 25 cm, TR = 8 ms, TE = 3.1 ms, flip angle = 12, T1 = 600, 256 x 192 matrix, Bandwidth = 31.25 kHZ, frequency direction = S-I, NEX =1, scan time = 8 min 27 sec). Resting CBF. Whole-brain ASL data was acquired during a resting state using a multi-phase pseudo-continuous ASL (MPPCASL) sequence. Importantly, MPPCASL mitigates the adverse effects of off-resonance fields and gradient imperfections on the inversion efficiency in traditional PCASL techniques (Jung, Wong, & Liu, 2010). Blood magnetization is modulated with multiple RF phase offsets, and the resulting signal is then fit to a model function to generate a CBF estimate. Moreover, MPPCASL utilizes a new fitting procedure for flow velocity and CBF, thus provides more accurate CBF estimates. Parameters included 20 5 mm axial slices, FOV = 24, post-saturation and inversion times of TI1 = 0 ms and TI2 = 3600 ms, TR= 4200 ms, TE = 3.3 ms, volumes = 64, scan time = 5 min 28 sec. Additionally, a scan with the inversion pulses turned off was acquired to obtain an estimate of the magnetization of cerebrospinal fluid (CSF). A minimum contrast scan was also acquired to adjust for coil inhomogeneities during the CBF quantification step. A field map was acquired to correct for field inhomogeneities.

Image Processing. MRI pre-processing and post- processing was completed using

Analysis of Functional NeuroImages (Cox, 1996), Freesurfer (Dale, Fischl, & Sereno, 1999), and in-house Matlab scripts. Structural MRI. Using AFNI software, a 3-dimensional brick will be created from the structural scan slices. Regions of interest (ROIs) were created using Freesurfer, a freely available cortical and subcortical segmentation and parcellation software. Resting CBF. Processing of the resting CBF (MPPCASL) data was completed through a processing pipeline available via the Cerebral Blood Flow Biomedical Informatics Research Network (Bangen et al., 2014; Shin et al., 2013). Field map correction and motion correction (using the middle volume as reference) were also completed. A mean ASL image was formed for each participant from the average difference of control and tag images using surround subtraction (e.g., the difference between each control image and the average of the two surrounding tag images and vice versa). The mean ASL image was then converted to absolute units of CBF (mL/(100g-min). Information from the high-resolution structural image and the FSL Automated Segmentation Tool (Smith et al., 2004) was used to determine the tissue content of each gray matter voxel. The CBF data was skull-stripped using an automated program, spatially smoothed using a 4.0 mm full-width, half-maximum Gaussian filter, and thresholded to only include voxels with at least 90% probability of containing gray matter. Following the CBFBIRN pipeline procedure, the CBF data for each participant was further thresholded by removing outlier voxels (voxels with CBF values < 10 or > 150). Mean CBF values was then be extracted from the whole brain and 13 frontal and 9 temporal FreeSurfer ROIs for each hemisphere. The weighted average of lateralized FreeSurfer ROIs was calculated to obtain a total CBF value for six ROIs from the Desikan (2006) atlas in the frontal and temporal lobes that are especially vulnerable to TBI: the (1) middle frontal gyrus (MFG), (2) inferior frontal gyrus (IFG), (3) orbitofrontal cortex (OFC), (4) anterior cingulate (ACC), (5) medial temporal lobe (MTL), and (6) lateral temporal lobe (LTL).

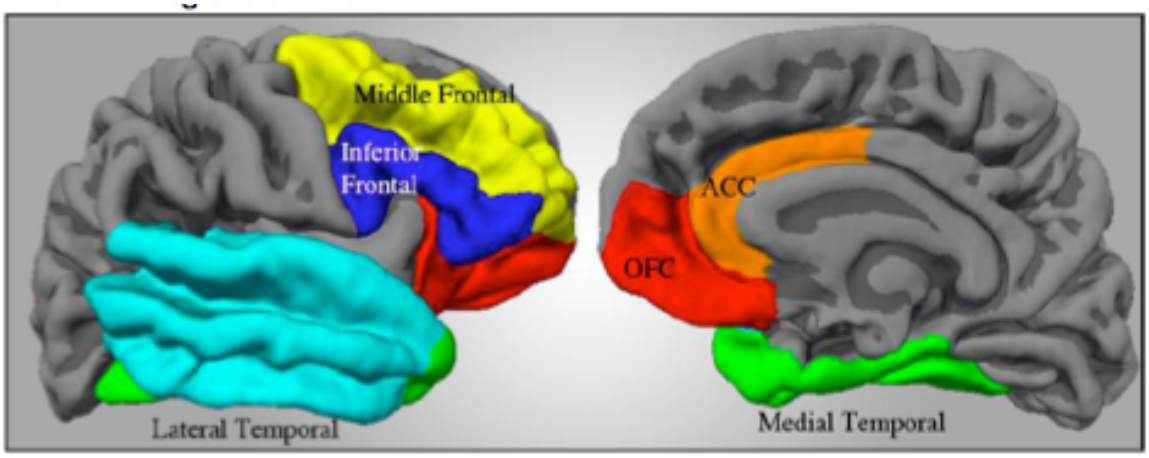

Figure 2. Cortical Regions-of-Interest Utilized in the Proposed Study. On the left is the lateral view of the right cerebral hemisphere. The middle frontal gyrus (MFG) is depicted in yellow; inferior frontal gyrus (IFG) is depicted in dark blue; lateral temporal lobe (LTL) is in teal; On the right side of the figure is a medial view of right cerebral hemisphere. The anterior cingulate cortex (ACC) is depicted in orange, orbitofrontal cortex (OFC) is in red; and medial temporal lobe (MTL) is in green.

Statistical Analyses

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 24 (SPSS IBM, New York, NY). Prior to conducting statistical analyses, all data was examined for violations of normality, heteroskedasticity, and potential outliers. The Shapiro-Wilk test and measures of skewness and kurtosis (any values below 2) were utilized to determine whether the assumption of normality was met. The Levene test was utilized to determine whether there were homogenous variances between the groups. Violations were addressed by (1) transforming variables to improve normality prior to conducting analyses, and/or (2) running additional non-parametric statistics (i.e., Kruskal-Wallis tests). There were no discrepancies between parametric and non-parametric analysis techniques, thus only results associated with parametric statistics are reported in the results section below. Finally, data was explored for

outliers (values > 3 standard deviations from mean) and individuals with extreme values were removed from analyses.

Participant Demographics. Differences between the mmTBI and MC groups on basic demographic characteristics, were explored using independent-samples *t*-tests (for continuous data). For categorical data, chi-square analyses or Fischer's exact test (when cell counts were less than 5) were employed.

Hypothesis Testing. First, two-way factorial analyses of covariance (ANCOVAs) were conducted to evaluate whether there were group differences on of (1) whole brain resting CBF and (2) resting CBF of bilateral frontal and temporal ROIs. Covariates included age, PCL-M and BDI-II total scores.

Second, a series of multiple linear regression analyses were performed to explore resting CBF and cognitive associations the mmTBI group. Cognitive composites were entered as dependent variables for each model. Independent variables entered included the age, PCL-M and BDI total scores (when relevant), and CBF of the relevant lateralized frontal ROI (i.e., right or left MFG, IFG, ACC, or OFC). Age was included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with the independent and/or dependent variable of interest. This was to ensure that any observed CBF and cognitive relationships were independent of other potential factors of influence while also making sure that the most parsimonious model was used in an effort to preserve power. Trends were interpreted when partial correlations for the predictors of interest were considered to medium (r = 0.3) or large (r = 0.5) effect sizes based on Cohen (1992) guidelines.

Third, the association between risk factors and resting CBF of frontal and temporal ROIs was explored using multiple regression models. The independent variable of interest in the models was the known risk factor. Age was included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically

significant associations with both the risk factor and CBF of the dependent variable of interest. This was to ensure that demonstrated relationships were independent of other potential factors while also making sure that the most parsimonious model was used to test the hypothesized relationships.

Finally, APOE-ε4 genotype, total number of blast-exposures and mmTBIs, and time since injury were entered into multiple regression to determine whether they were moderators of resting CBF and cognitive associations. Moderators were created by creating interaction terms with CBF ROIs and moderator variables of interest and this term was the independent model of interest in the regression. Other independent variables included CBF of relevant ROIs and the known risk factor. Age was also included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with both the risk factor and CBF of the dependent variable of interest.

III. RESULTS

Sample Characteristics

Participant demographics are presented in Table 1. Independent sample t-tests were used to explore group differences on quantitative variables of interest. Results revealed no significant differences between the mmTBI and MC groups on age $t(52) = .92$, $p = .35$, education $t(52) = -1.79$ $p = .08$, WRAT-4 Reading performance $t(59) = -1.17$, $p = .27$), height $t(51) = -1.40$, $p = .17$, weight $t(51) = 0.89$, $p = .37$, systolic $t(41) = .36$, $p = .72$ or diastolic $t(41) = .87$, $p = .39$ blood pressure. However, relative the MC group, the mmTBI group endorsed more severe posttraumatic stress $t(52) = 6.92$, $p < .001$ and depressive $t(52) = 5.35$, $p < .001$ symptoms, and also reported greater combat exposure $t(51) = 3.44$, $p = .001$.

Chi-squared or Likelihood ratio tests (when cell counts < 5) were used to explore group differences on categorical variables. Results revealed no significant differences between the groups on sex $\chi^2(54) = .68$, $p = .41$, branch of service $\chi^2(54) = .71$, $p = .87$, or $\varepsilon 4$ positivity $\chi^2(51) = .00$, $p = 1.0$. However, the groups significantly differed with respect to ethnicity $\chi^2(54) = 17.56$, $p = .007$, with the mmTBI group having fewer Caucasians and more Hispanics relative to the MCs.

Table 1. Sample Characteristics
N=54

Variable	MCs (n = 23)	mmTBI (n = 31)	Sig.
Age [*M (SD)*]	31.52 (6.07)	33.23 (7.09)	
Gender [% Male]	83	90	
Ethnicity [% Hispanic/Latino]	4	32	†
Education [*M (SD)*]	14.96 (1.85)	14.00 (1.66)	
WRAT Reading Standard Score [*M (SD)*]	104.35 (9.14)	101.39 (9.78)	
Combat Exposure Scale Total Score [*M (SD)*]	6.00 (6.43)	15.1 (12.49)	◊
Branch of Service [% Air Force]	4	7	
Height in Inches [*M (SD)*]	69.70 (3.35)	68.35 (3.5)	
Weight in Pounds [*M (SD)*]	184.26 (30.92)	193.77 (42.80)	
Systolic Blood Pressure in mmHg [*M (SD)*]	122.63 (15.61)	121.14 (11.91)	
Diastolic Blood Pressure in mmHg [*M (SD)*]	77.22 (7.63))	79.58 (9.51)	
PCL-M Total Score [*M (SD)*]	23.65 (7.69	50.35 (17.23)	◊
BDI-II Total Score [*M (SD)*]	6.87 (8.15)	22.94 (12.03)	◊
APOE-ε4 positivity [% No]	67	67	

Note. MC= Military Controls comparison group; mmTBI = mild or moderate TBI comparison group; WRAT-4: Wechsler Test of Adult Reading—4th Edition; mmHg: millimeters of mercury; PCL-M: Posttraumatic Stress Disorder Checklist ; BDI-II: Beck Depression inventory—2nd Edition; APOE-ε4 positivity: presence of at least one copy of the E4 allele; height and weight variables are missing 1 subject's data; systolic and diastolic blood pressure estimates are missing 11 subject's data; combat exposure scale is missing 1 subject's data; ◊ = MCs differs from mmTBI at $p<.001$, † = MCs differs from mmTBI at $p<.010$.

TBI Injury Characteristics

Table 2 displays injury characteristics for the mmTBI group. On average, Veterans sustained multiple TBIs (*M* = 2.82), were many months removed from their most recent injury (*M* = 44.94) and reported being exposed to multiple blast detonations (*M* = 11.45) while on deployment. With respect to the mmTBI group's most significant injury, these injuries were largely mild in severity (88%) and the majority of the subjects reported experiencing a LOC at the time of the incident (61%). Duration of LOC, AOC, and PTA were not normally distributed and thus means, median, and ranges are reported in the table to ensure adequate injury characterization.

Table 2. TBI Injury Characteristics

Variable	mmTBI
TBI Severity [% Mild]	87
Month Since Most Recent TBI [*M, Median (range)*]	44.94, 41.00 (0.8 - 78)
Number of TBIs [*M, Median (range)*]	2, 3 (1-6)
Blast Exposed [%Yes]	52
Number of Blast Exposures [*M (range)*]	11.45, 2.5 (0-100)
History of LOC with Most Significant TBI [% Yes]	61
Longest duration of LOC in minutes for Most Significant TBI [*M, Median (range)*]	19, 3 (0.05-150.00)
History of AOC with Most Significant TBI [% Yes]	39
Longest duration of AOC in minutes [*M, Median (range)*]	98.55, 13.75 (0.21-720)
History of PTA [% Yes]	65
Longest duration of PTA in minutes [*M (range)*]	864, 10 (0-10,008)
Neurobehavioral Symptom Inventory Total Score [*M (range)*]	39.61 (2 – 72)

Note. mmTBI = History of mild or moderate TBI group; TBI = traumatic brain injury; LOC = loss of consciousness; AOC = alteration of consciousness; PTA = post-traumatic amnesia.

Aim 1: Group Differences in Resting CBF of Whole Brain and Frontal and Temporal Regions of Interest

A series of ANCOVAs were performed in order to determine whether there were group differences in resting CBF of whole brain (WB) and lateralized frontal and temporal ROIs. Covariates included age and PCL-M and BDI total scores. Age was included as a covariate given its robust association with CBF. PCL-M and BDI-II total scores were included given the groups differed on these variables. Results revealed that the groups did not significantly differ in WB CBF $F(1,49) = 2.01$, $p = 0.16$, $\eta_p^2 = .04$). With respect to frontal ROIs, the mmTBI group displayed significantly higher resting CBF in the left $F(1,49) = 5.35$, $p = 0.03$, $\eta_p^2 = .10$) and right $F(1,48) = 5.92$, $p = 0.02$, $\eta_p^2 = .11$) inferior frontal gyrus (IFG); and left $F(1,49) = 6.60$, $p = 0.01$, $\eta_p^2 = 0.12$) and right $F(1,49) = 5.12$, $p = 0.03$, $\eta_p^2 = 0.09$) medial frontal gyrus (MFG). However, no significant group differences were observed for the left $F(1,49) = 0.78$, $p = 0.38$, $\eta_p^2 = 0.02$ and right $F(1,49) = 0.14$, $p = 0.70$, $\eta_p^2 = 0.003$) anterior cingulate cortex (ACC), or left $F(1,49) =$

2.45, p = 0.13, η_p^2 = 0.05) and right $F(1,49) = 0.43$, p = 0.51, η_p^2 = 0.009) orbitofrontal cortex (OFC).

With respect to temporal ROIs, results revealed the mmTBI group had significantly higher resting CBF in the right lateral temporal lobe (LTL) $F(1,49) = 4.10$, p = .04, η_p^2 = .08). However, no significant group differences were observed in the left LTL $F(1,49) = 2.45$, p = 0.12, η_p^2 = .05), or left $F(1,49) = 1.50$, p = 0.22, η_p^2 = 0.03) and right $F(1,49) = 0.43$, p = 0.51, η_p^2 = .009) medial temporal lobe (MTL).

Table 3. Estimated Marginal Means of Resting CBF Within Groups

Variable	MCs	mmTBI
Whole Brain [Mean (SE)]	59.24 (1.37)	62.09 (1.29)
Left Inferior Frontal Gyrus [Mean (SE)]	57.32 (1.36)	61.96 (1.11)*
Right Inferior Frontal Gyrus [Mean (SE)]	58.87 (1.56)	64.45 (1.29)*
Left Middle Frontal Gyrus [Mean (SE)]	57.55 (1.44)	63.05 (1.05)*
Right Middle Frontal Gyrus [Mean (SE)]	59.21 (1.59)	64.52 (1.31)*
Left Anterior Cingulate Cortex [Mean (SE)]	66.87 (2.47)	70.10 (2.03)
Right Anterior Cingulate Cortex [Mean (SE)]	56.07 (2.59)	57.55 (2.13)
Left Orbitofrontal Cortex [Mean (SE)]	51.21 (1.35)	54.30 (1.11)
Right Orbitofrontal Cortex [Mean (SE)]	53.59 (1.46)	55.09 (1.20)
Left Medial Temporal Lobe [Mean (SE)]	51.53 (1.76)	54.76 (1.45)
Right Medial Temporal Lobe [Mean (SE)]	53.47 (1.80)	55.28 (1.50)
Left Lateral Temporal Lobe [Mean (SE)]	55.07 (1.48)	58.50 (1.22)
Right Lateral Temporal Lobe [Mean (SE)]	54.98 (1.31)	58.89 (1.07)*

Note. Estimated marginal means were derived from ANCOVAs controlling for age, BDI-II and PCL-M total scores. *Denotes significant group differences at *p<.05*; SE = standard error; MCs = military controls comparison group; mmTBI = mild or moderate traumatic brain injury comparison group.

Aim 2: Resting CBF Associations with Cognition within the mmTBI Group

A set of linear regressions were performed to determine whether resting CBF was associated with cognitive performance in Veterans with mmTBI. Frontal ROIs were used in analyses exploring performance on the EF composite, whereas temporal ROIs were used in analyses exploring performance on the memory composite. Two mmTBI subjects failed to pass effort testing (CVLT-2 Forced Choice <15 or TOMM Trial 2 <45) and thus were excluded from the subsequent analyses (n = 29 for mmTBI participants included in cognitive analyses).

For the first set of regressions, performance on the EF composite was entered as the dependent variable. Independent variables entered included the age, PCL-M and BDI total scores (when relevant), and resting CBF of the relevant lateralized frontal ROI (i.e., right or left MFG, IFG, ACC, or OFC). Age was included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with the independent and/or dependent variable of interest. This was to ensure that any observed resting CBF and cognitive relationships were independent of other potential factors of influence while also making sure that the most parsimonious model was used in an effort to preserve power. Trends were interpreted when partial correlations for the predictors of interest were considered to medium (r = 0.3) or large (r = 0.5) effect sizes based on Cohen (1992) guidelines.

Results revealed that independent of age, there was a significant association between performance on the EF composite and resting CBF of the right IFG (β = 0.46, t = 2.28, p = 0.03, partial correlation = 0.41), right OFC (β = 0.51, t = 2.28, p = 0.009, partial correlation = 0.48), as well as a trend for right MFG (β = 0.30, t = 1.67, p = 0.10, partial correlation = 0.32). See Table 4 and Figures 3 and 4. However, there were no significant associations (or medium to large effect size trends) between performance on the EF composite and left IFG (β = 0.3, t = 1.5, p = 0.14), left MFG (β = 0.24, t = 0.99, p = 0.33), left (β = 0.24, t = 1.05, p = 0.31) and right (β = -

0.12, t = -0.55, p = 0.59) ACC, and left OFC (β = 0.27, t = 1.34, p = 0.19). Although Pearson's correlations revealed that there were no significant associations between PCL-M total score and/or performance on the EF composite, there was a trend with resting CBF of the right IFG (r = -.31, p = 0.10) and right OFC (r = -.34, p = 0.07). As such, another set of regressions were performed with PCL-M total score included as a covariate, and results are reported in the table below. Inclusion of the PCL-M total score attenuated the significance of the findings between performance on the EF composite and resting CBF of the right IFG and MFG, but resting CBF of the right OFC remained a significant predictor in the revised model.

Table 4. Association Between Resting CBF and Performance on the Executive Functions Composite

Performance on EF Composite	β	t	*p*-value
Model 1 Right OFC			
Age	0.15	0.82	0.42
CBF of R OFC	0.51	2.81	0.009*
Model 2 Right OFC			
Age	0.16	0.88	0.39
PCL-M Total Score	-0.17	-0.94	0.36
CBF of R OFC	0.46	2.38	0.03*
Model 1 Right IFG			
Age	0.19	.97	0.34
CBF of R IFG	0.46	2.28	0.03*
Model 2 Right IFG			
Age	0.20	1.00	0.32
PCL-M Total Score	-0.21	-1.12	0.71
CBF of R IFG	0.39	1.91	0.07

Note. EF = executive functions composite; OFC refers to orbitofrontal cortex; IFG refers to inferior frontal gyrus; PCL-M refers to Posttraumatic Stress Disorder Checklist ; BDI-II refers to Beck Depression inventory—2nd Edition; TBI Injury Severity is coded as mild versus moderate; CBF = cerebral blood flow; R OFC = right orbitofrontal cortex; β = standardized coefficient; t = t-statistic. **p<.05*

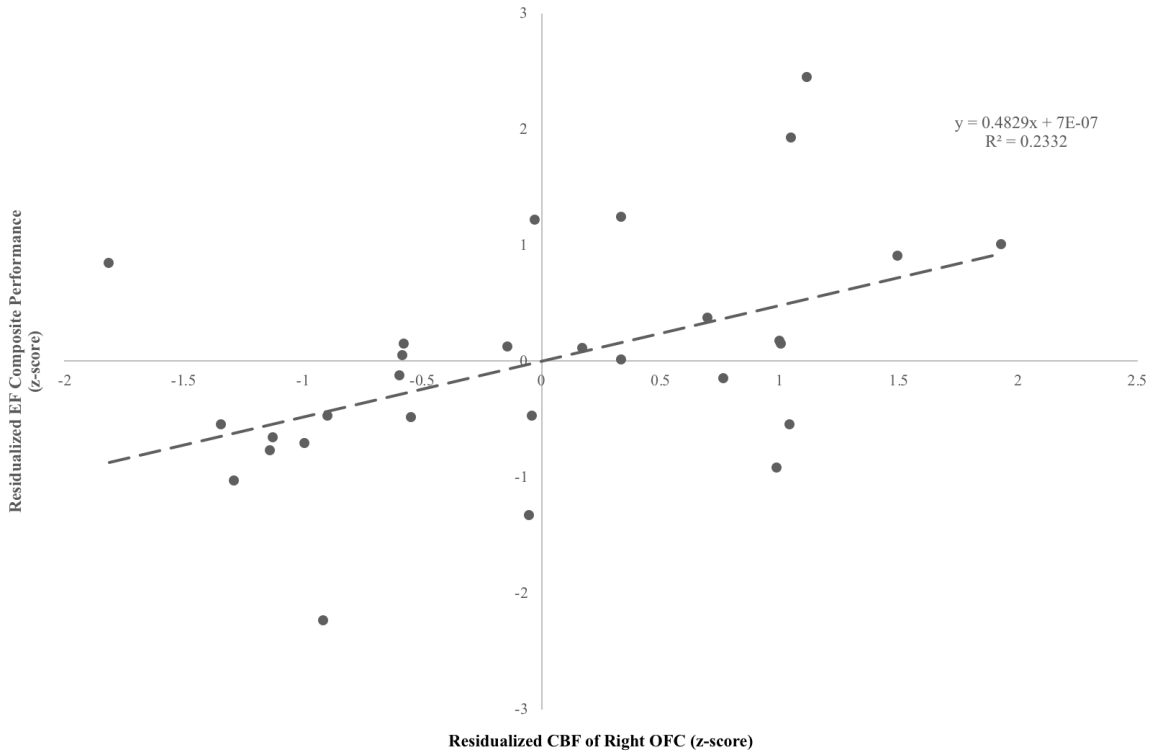

Figure 3. Relationships Between Performance on the Executive Functions Composite and Resting Cerebral Blood Flow of the Right Orbitofrontal Cortex. The Y axis represents the z-scores of the executive functions composite with age regressed out. The X axis represents the z-scores of cerebral blood flow of the right orbitofrontal cortex with age regressed out.

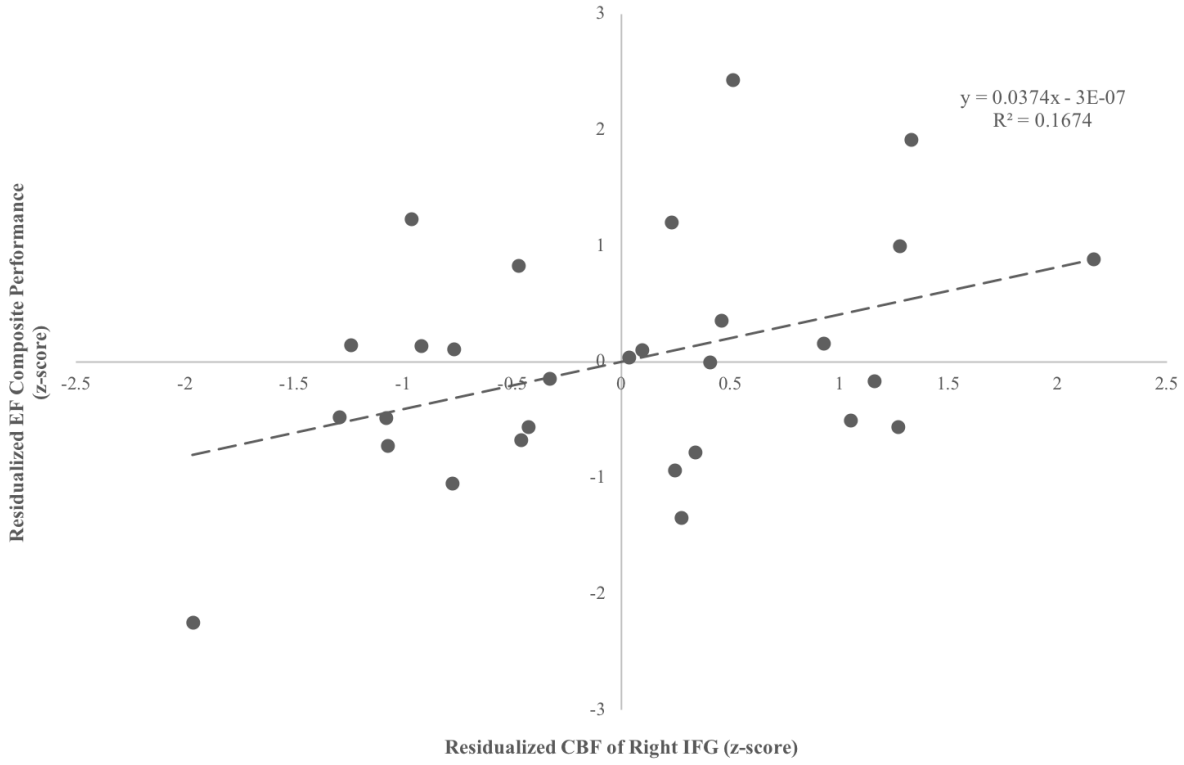

Figure 4. Relationships Between Performance on the Executive Functions Composite and Resting Cerebral Blood Flow of the Right Inferior Frontal Gyrus. The Y axis represents the z-scores of the executive functions composite with age regressed out. The X axis represents the z-scores of cerebral blood flow of the right inferior frontal gyrus with age regressed out.

Given the observed pattern of results, there was some concern that use of composite variables may have obscured the detection of any critical resting CBF and cognitive associations given averaging of multiple tests. Thus, a series of follow-up partial correlations controlling for age were conducted between each of the frontal ROIs and the 5 individual tests included in the EF composite. Significant partial correlations were observed between WCST Total Errors z-score and resting CBF of the right ACC ($r = .42$, $p = .04$); DKEFS Letter Fluency z-score and resting CBF of the right IFG ($r = 0.52$, $p = 0.009$), and left ($r = 0.48$, $p = 0.02$) and right ($r = 0.47$, $p = 0.02$) OFC. Medium to large effect size trends (r's >.3) were observed for DKEFS Letter Fluency z-score and resting CBF of the left IFG and ($r = .36$, $p = .08$) and left ACC ($r = .31$, $p = .11$; and WCST Perseverative Responses z-score and left MFG ($r = .31$, $p = .14$) and right ACC ($r = .31$, $p = .14$). Results revealed a general trend that greater resting CBF was associated with better cognitive performance. Effect sizes remained in the medium-to-large

range when both age and PCL-M total score were controlled for in the partial correlations, but significance values were somewhat attenuated.

For the second set of regressions, performance on the memory composite was entered as the dependent variable. Independent variables entered included age and resting CBF of the relevant lateralized temporal ROI (i.e., MTL or LTL). PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with the independent and/or dependent variable of interest. Results revealed that there were no significant association between performance on the memory composite and resting CBF of the left (β = 0.05, t = 0.26, p = 0.80) or right (β = 0.07, t = 0.37, p = .72) MTL, or left (β = 0.10, t = 0.48, p = 0.63) or right (β = 0.03, t = 0.13, p = 0.89) LTL. Follow-up partial correlations controlling for age were conducted between all temporal ROIs and the 5 individual tests included in the memory composite. Results revealed no significant partial correlations between resting CBF and performance on the individual tests included in the composite (p's = 0.24 - 0.86). Additionally, no notable medium to large effect size trends (r's >.3) were observed for resting CBF of temporal ROIs and individual memory tests.

Aim 3A: Resting CBF Associations with Genetic and Environmental Risk Factors

A set of linear regressions were performed to determine whether various risk factors (i.e., total number of TBIs, time since injury, total number of blast-exposures, APOE-ε4 positivity) were associated with resting CBF in Veterans with mmTBI. Dependent variables were resting CBF of WB, frontal, and temporal ROIs. The independent variable of interest in the models was the known risk factor. Age was included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with both the risk factor and resting CBF of the dependent variable of interest. This was to ensure that demonstrated relationships were independent of other potential

factors while also making sure that the most parsimonious model was used to test the hypothesized relationships.

Total Number of mmTBIs. Linear regression revealed that independent of age, total number of TBIs was significantly correlated with resting CBF of the left IFG (β = -0.38, t = -2.22, p = 0.03, partial correlation = -.34), such that a great number of TBIs was associated with reduced resting CBF. See Table 5 and Figure 5. No significant associations between total number of mmTBIs and resting CBF of the WB (β = -0.15, t = -0.89, p = 0.37), right IFG (β = -0.22, t = -1.29, p = 0.21), left (β = -0.14, t = -0.83, p = 0.41) and right (β = -0.33, t = -0.22, p = 0.74) MFG, left (β = -0.18, t = -1.12, p = 0.27) and right (β = -0.03, t = -0.71, p = 0.86) ACC, and left (β = -0.09, t = -0.45, p = 0.66) and right (β = -0.29, t = -1.47, p = 0.15) OFC were observed. With respect to temporal ROIs, no significant associations between total number of mmTBIs and resting CBF of the left (β = -0.05, t = -0.24, p = 0.81) and right (β = -0.05, = -0.24, p = 0.81) MTL, or the left (β = -0.14, t = -0.78, p = 0.44) and right (β = -0.21, t = -1.20, p = 0.22) LTL were observed. Results revealed there were no medium-to-large effect sizes when the partial correlation of the predictor variable, total number of mmTBIs, was examined in each regression model.

Table 5. Association Between Total Number of mmTBIs and Resting CBF

CBF of the L IFG Model 1	β	t	*p*-value
Age	-0.31	-1.79	0.08
Total Number of mmTBIs	-0.38	-2.22	0.03*

Note. CBF = cerebral blood flow; R OFC = right orbitofrontal cortex; β = standardized coefficient; t = t-statistic. *$p<.05$

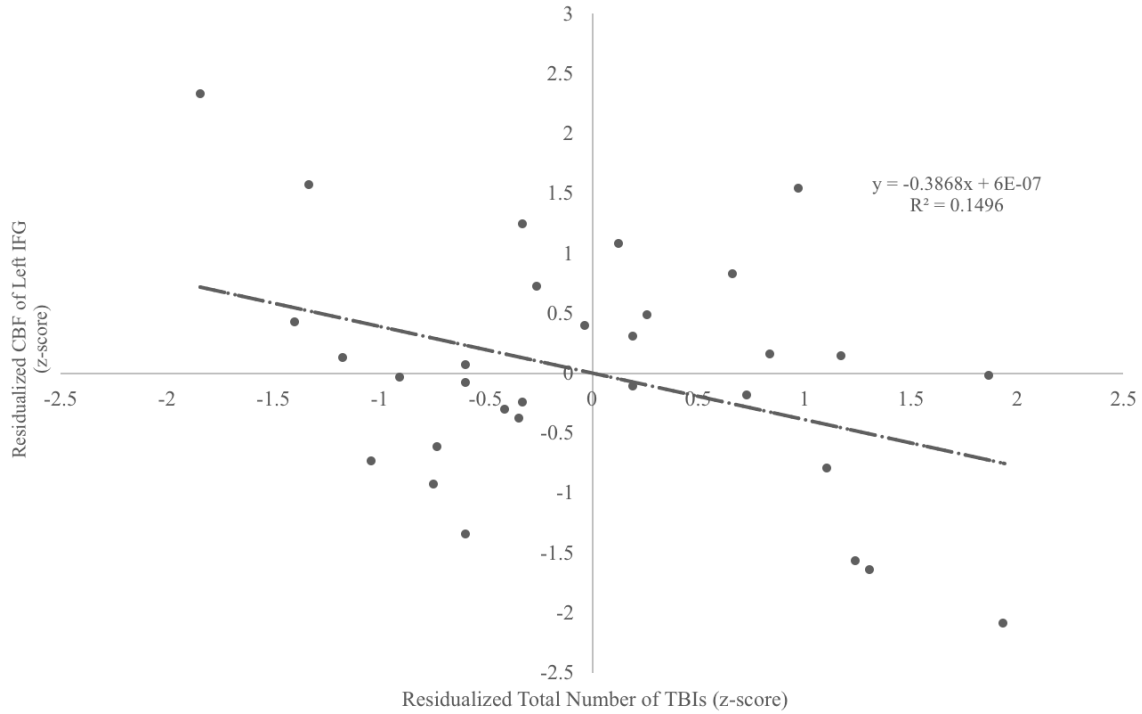

Figure 5. Relationships Between Total Number of mmTBIs and Resting Cerebral Blood Flow of the Left Inferior Frontal Gyrus. The X axis represents the z-scores of the total number of mmTBIs with age regressed out. The Y axis represents the z-scores of cerebral blood flow of the left inferior frontal gyrus with age regressed out.

Time Since Injury. Linear regression revealed that time since injury was not significantly correlated with resting CBF in the WB (β = -0.06, t = -0.39, p = 0.69), or left (β = -0.15, t = -0.90, p = 0.37) and right (β = -0.05, t = -.31, p = 0.75) IFG, left (β = -0.14, t = -.97, p = 0.34) and right (β = -0.07, t = -0.47, p = 0.64) MFG, left (β = -0.09, t = 0.59, p = 0.56) and right (β = -0.09, t = -0.55, p = 0.58) ACC, and left (β = 0.03, t = 0.16, p = 0.88) and right (β = -0.08, t = -0.47, p = 0.66) OFC. With respect to temporal ROIs, no significant associations between time since injury and resting CBF of the left (β = -0.14, t = -0.76, p = 0.45) and right (β = -0.21, t = -1.09, p = 0.28) MTL, or the left (β = 0.03, t = 0.17, p = 0.86) and right (β = -0.15, t = -0.91, p = 0.37) LTL were observed. Results revealed there were no medium-to-large effect sizes when the partial correlation of the predictor variable, time since injury, was examined in each regression model.

Exposure to blast detonations. Within the mmTBI group, 52% of the sample (n = 16) was exposed to blast detonations while on deployment. Preliminary analyses revealed that the total number of blast exposures was not normally distributed (Shapiro-Wilk= 0.43, $p < .001$) and included two outliers that were greater than 3 standard deviations from mean. Removing these outliers did not improve normality (Shapiro-Wilk = 0.86, p = .02), thus the variable underwent square root transformation to improve normality (Shapiro-Wilk= 0.91, p = .11). Results revealed no significant associations between total number of blast exposures and resting CBF of the WB (β = 0.21, t = 1.13, p = 0.27), or left (β = 0.19, t = 0.95, p = 0.35) and right (β = 0.11, t = .56, p = 0.58) IFG, left (β = 0.08, t = 0.50, p = 0.22β = 0.19, t = 1.05, p = 0.31) and right (β = -0.06, t = 0.31, p = 0.76) MFG, left (β = -0.03, t = 00.19, p = 0.85) and right (β = 0.27, t = 1.35, p = 0.19) ACC, and left (β = 0.19, t = 0.95, p = .35) and right (β = 0.005, t = -.02, p = 0.98) OFC. With respect to temporal ROIs, no significant associations between total number of blast exposures and resting CBF of the left (β = 0.18, t = 0.77, p = 0.45) and right (β = 0.05, t = 0.22, p = 0.82) MTL, or the left (β = -0.007, t = 0.03, p = 0.97) and right (β = 0.24, t = 1.17, p = 0.26) LTL were observed. Results revealed there were no medium-to-large effect sizes when the partial correlation of the predictor variable, total number of blast exposures, was examined in each regression model. Finally, a set of exploratory ANCOVAs controlling for age were used to compare resting CBF of Veterans with mmTBI who were and were not blast exposed. Results revealed that there were no significant differences in resting CBF between those with mmTBI who were and were not blast exposed across any of the WB, frontal, or temporal ROIs (p's= -0.19- 0.95).

APOE-ε4 positivity. The last factor explored was possession of the APOE-ε4 positivity. One subject's sample had degraded, and DNA could not be extracted. Veterans with mmTBI were divided into two groups (ε4-, n = 20, and ε4+, n = 10). Linear regressions revealed that APOE-ε4 positivity was not significantly associated with resting CBF of the WB (β = -0.02, t = -

.12, p = 0.90), or left (β = -0.01, t = -0.05, p = 0.96) and right (β = -0.01, t = -0.05, p = 0.86) IFG, left (β = 0.07, t = 0.46, p = 0.65) and right (β = -0.08, t = -0.51, p = 0.62) MFG, left (β = -0.02, t = -0.12, p = 0.89) and right (β = -0.09, t = -0.51, p = 0.62) ACC, and left (β = 0.15, t = 0.83, p = .41) and right (β = -0.17, t = -0.66, p = 0.51) OFC. With respect to temporal ROIs, linear regressions revealed APOE-ε4 positivity was not significantly associated with resting CBF of the left (β = 0.12, t = 0.60, p = 0.55) and right (β = 0.20, t = 1.16, p = 0.29) MTL, or the left (β = 0.08, t = 0.48, p = 0.63) and right (β = 0.21, t = 1.23, p = 0.23) LTL. Results revealed there were no medium-to-large effect sizes when the partial correlation of the predictor variable, APOE-ε4 positivity, was examined in each regression model. Given violations in homogeneity of variances, findings were replicated using the non-parametric Kruskal-Wallis *H* test, and there was no rejection of the null hypothesis across any ROI (p's =0.13-0.94).

Aim 3B: Moderators of Resting CBF and Cognitive Associations in Veterans with mmTBI

A set of linear regressions were performed to determine whether various risk factors (i.e., total number of TBIs, time since injury, total number of blast-exposures, APOE-ε4 positivity) interacted with resting CBF to predict cognitive performance within the mmTBI group. Dependent variables in the models were the EF and memory composite. The independent variable of interest in the models was interaction term between risk factor and resting CBF of relevant ROIs. Age was included as a covariate in all models, but PCL-M and BDI-II total scores were only included when Pearson's correlations revealed statistically significant associations with both the risk factor and resting CBF of the dependent variable of interest. This was to ensure that demonstrated relationships were independent of other potential factors while also making sure that the most parsimonious model was used.

Total number of mmTBIs x resting CBF on cognition. For the first set of regressions, we were interested in whether there was an interaction between total number of mmTBIs and resting CBF of frontal ROIs on performance of the EF composite. Results revealed there were

no significant interaction terms for total number of TBIs and resting CBF of the left (β = 0.07, t = 0.03, p = 0.97) and right (β = 0.19, t = 0.08, p = 0.93) IFG, left (β = -0.48, t = -0.23, p = 0.82) and right (β = -1.19, t = -0.51, p = 0.62) MFG, left (β = -0.68, t = -0.48, p = 0.63) and right (β = -0.31, t = -0.25, p = 0.80) ACC, and left (β = 1.49, t = 0.46, p = .64) and right (β = -1.12, t = -0.48, p = 0.63) OFC. Results revealed there were no medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

As above, a series of follow-up regressions were run where the five individual tests of the EF composite were entered in independent models as dependent variables of interests. Results revealed no significant interactions between total number of TBIs and resting CBF of any frontal ROI. However, medium to large effect size trends (r's >.3) were observed for interactions between total number of mmTBIs x resting CBF of the left IFG on WCST Perseverative Responses z-score (β = -3.73, t = -1.62, p = 0.11, partial correlation = -0.31); and total number of mmTBIs x resting CBF of the right ACC on WCST Perseverative Responses z-score (β = -1.85, t = -1.62, p = 0.12, partial correlation = -0.31) and WCST Total z-score (β = -1.78, t = -1.55, p = 0.13, partial correlation = -0.30). Examination of simple main effects across revealed a general trend in that there was a strong association between higher resting CBF and better cognitive performance in the mmTBI group with fewer injuries relative to those who reported multiple injuries.

For the second set of regressions, we explored whether there was a significant interaction between total number of mmTBIs x CBF of resting temporal ROIs on performance of the memory composite. Results revealed there was significant interaction for total number of TBIs and resting CBF of left LTL (β = -4.64, t = -2.11, p = 0.04, partial correlation = -0.37) and a that there was a trend for the interaction between total numbers of mmTBI and resting CBF of the right LTL on performance of the memory composite (β =-5.12, t = -1.88, p = 0.07, partial correlation = -0.35). Examination of simple main effects revealed a general trend such that there

was a strong association between higher resting CBF and better cognitive performance in the mmTBI group with fewer injuries relative to those who reported multiple injuries. See Figure 6 below. No significant interactions between total number of mmTBIs and resting CBF of the left (β = -2.78, t = -1.13, p = 0.27) or right (β = -1.59, t = -0.62, p = 0.54) MTL on performance on the memory composite were observed. Moreover, results revealed there were no other medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

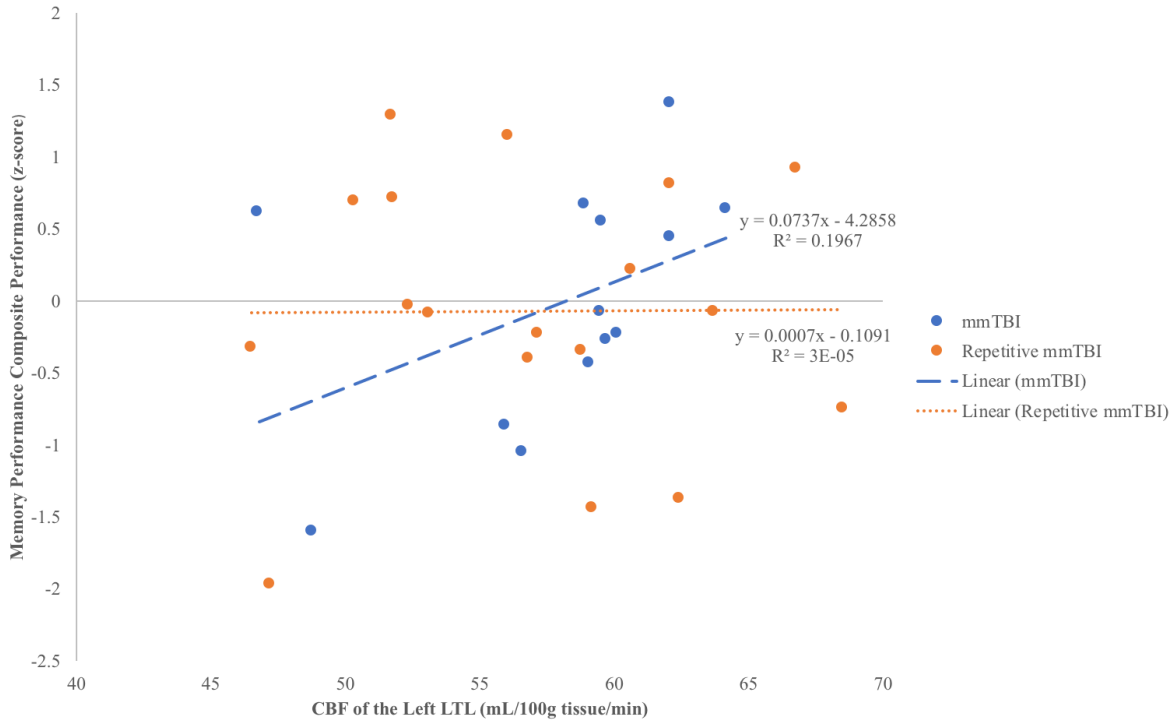

Figure 6. Relationships Between Performance on the Memory Composite and Resting CBF of the Left Lateral Temporal Lobe. The X axis represents the z-scores of performance on the memory composite. The Y axis represents the cerebral blood flow of the left inferior frontal gyrus in mL/100g tissue/min. A median split of total number of mmTBIs was used to dichotomize the groups into those with fewer (n = 12, labeled mmTBI above) versus more head injuries (n = 17, labeled repetitive mmTBI above). The blue line and dots represent those mmTBI group with fewer injuries. The orange line and dots represent the mmTBI group who reported multiple injuries.

A series of follow-up regressions were run with the five individual tests of the memory composite entered in independent models as dependent variables of interests. Results revealed

significant interactions between total number of TBIs x resting CBF of the left LTL on CVLT-II Short Delay Free Recall z-score (β = -4.87, t = -2.21, p = 0.03, partial correlation = -0.41). Moreover, medium to large effect size trends (r's >.3) were observed for interactions between total number of TBIs x resting CBF of the left LTL on CVLT-II Long Delay Free Recall z-score (β = -4.06, t = -1.78, p = 0.08, partial correlation = -0.34) and Logical Memory Trial 1 z-score (β = -3.95, t = -1.75, p = 0.09, partial correlation = -0.32); as well as total number of TBIs x resting CBF of the right LTL and on CVLT-II Short Delay Free Recall z-score (β = -5.26, t = -1.92, p = 0.06, partial correlation = -0.35), Logical Memory I Total z-score (β = -4.98, t = -1.88, p = 0.07, partial correlation = -0.34), and Logical Memory II Total z-score (β = -4.43, t = -1.59, p = 0.13, partial correlation = -0.32). Similar to results reported above, examination of simple main effects revealed a general trend in that there was a strong association between higher resting CBF and better cognitive performance in the mmTBI group with fewer injuries relative to those who reported multiple injuries. Results revealed there were no other medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

Time since injury x resting CBF on cognition. For the first set of regression we were interested in whether time since injury moderated the relationship between resting CBF of frontal ROIs and performance on the EF composite. Results revealed that there were no significant interaction terms for time since injury x resting CBF of the left (β = -1.83, t = -0.60, p = 0.55) and right (β = 0.63, t = 0.29, p = 0.77) IFG, left (β = -1.16, t = -0.44, p = 0.66) and right (β = -2.83, t = -1.07, p = 0.29) MFG, left (β = 1.21, t = 0.75, p = 0.46) and right (β = -1.25, t = -0.82, p = 0.42) ACC, and left (β = 1.28, t = 0.07, p = .95) and right (β = -1.36, t = -0.69, p = 0.49) OFC on EF performance. A series of follow-up regression analyses with the 5 individual tests included in the EF composite were conducted. Results revealed no significant interactions between total number of TBIs and resting CBF of any frontal ROI. However, medium to large effect size trends (r's >.3) were observed for interactions between time since injury x resting

CBF of the right MFG on DKEFS Verbal Fluency Switching Total z-score (β = -5.10 t = -2.05, p = 0.05, partial correlation = -0.37). Examination of simple main effects revealed a general trend showing that higher resting CBF was related to better cognitive performance in those who were closer in time to their injury relative to those whose injuries were more remote. Results revealed there were no other medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

For the second set of regressions, we explored whether time since injury moderated the relationship between resting CBF of temporal ROIs on performance of the memory composite. Results revealed there no significant interactions for time since injury x resting CBF of left (β = -1.22, t = -0.57, p = 0.57) or right (β = -.42, t = -0.21, p = 0.84) MTL, and left (β = -3.43, t = -1.45, p = 0.16) or right (β = -1.30, t = -0.61, p = 0.55) LTL on the memory composite. A series of follow-up regressions were run where the five individual tests of the memory composite were entered in independent models as dependent variables of interests. Results revealed significant interactions between time since injury x resting CBF of the left LTL on CVLT-II Short Delay Free Recall z-score (β = -5.17, t = -2.29, p = 0.03, partial correlation = -0.42). Examination of simple main effects revealed a general trend showing a strong positive association between higher resting CBF and better cognitive performance in those were closer in time to their injury relative to those whose injuries were more remote. Results revealed there were no medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

Exposure to blast detonations x CBF on cognition. For the first set of regressions, we were interested in whether there was an interaction between total number of BEs and resting CBF of frontal ROIs on performance of the EF composite. Results revealed there were no significant interaction terms for total number of BEs and resting CBF of the left (β = -2.15, t = -0.42, p = 0.68) and right (β = -1.79, t = -0.95, p = 0.36) IFG, left (β = 1.24, t = 0.37, p = 0.72) and

right (β = 0.06, t = 0.18, p = 0.99) MFG, left (β = -0.08, t = -0.04, p = 0.97) and right (β = 1.99, t = 0.69, p = 0.50) ACC, and left (β = -0.57, t = .16, p = .88) and right (β = 1.26, t = 0.39, p = 0.69) OFC. A series of follow-up regressions were run where the five individual tests of the EF composite were entered in independent models as dependent variables of interests. Results revealed no significant interactions between total number of BEs and resting CBF of any frontal ROI for the individual subtests. Results revealed there were no medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

For the second set of regressions, we explored whether total number of BEs moderated the relationship between resting CBF of temporal ROIs on performance of the memory composite. Results revealed there no significant interactions for time since injury x resting CBF of left (β = 1.17, t = 0.35, p = 0.73) or right (β = 2.54 t = 0.84, p = 0.42) MTL, and left (β = .24, t = 0.08, p = 0.94) or right (β = 2.40, t = 0.59, p = 0.56) LTL on the memory composite. A series of follow-up regressions were run where the five individual tests of the memory composite were entered in independent models as dependent variables of interests. Results revealed significant interactions between total number of BEs x resting CBF of the left MTL on Logical Memory I Total z-score (β = 4.45, t = 1.49, p = 0.15, partial correlation = 0.34); resting CBF of the right MTL on Logical Memory I Total z-score (β = 5.21, t = 1.99, p = 0.07, partial correlation = 0.43) and Logical Memory II Total z-score (β = 3.82, t = 1.37, p = 0.19, partial correlation = 0.31); and resting CBF of the right LTL on Logical Memory I Total z-score (β = 6.71, t = 1.96, p = 0.07, partial correlation = 0.39) and Logical Memory II Total z-score (β = 6.08, t = 1.60, p = 0.13, partial correlation = 0.36). Examination of simple main effects revealed a general trend in that there was a strong negative association between higher resting CBF and poorer cognitive performance in those with fewer BEs relative to those with more BEs. Results revealed there were no other medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

APOE-ε4 positivity x CBF on cognition. For the first set of regressions, we were interested in whether APOE-ε4 positivity moderated the association between resting CBF of frontal ROIs on performance on the EF composite. Results revealed there was a trend for the interaction between APOE-ε4 positivity x resting CBF of the right MFG on (β = -3.79, t = -1.97, p = 0.06, partial correlation = -.35) on performance of the EF composite. Examination of simple main effects revealed that higher resting CBF was associated with better performance on the EF composite in those who were APOE-ε4 non-carriers relative to APOE-ε4 carriers. No other significant APOE-ε4 positivity x resting CBF of left (β = -2.62, t = -0.97, p = 0.34) and right (β = -1.83, t = -0.78, p = 0.44) IFG, left (β = -2.67, t = -1.22, p = 0.623) MFG, left (β = -1.92, t = -1.17, p = 0.25) and right (β = -1.34, t = -0.94, p = 0.36) ACC, and left (β = 0.55, t = 0.18, p = .86) and right (β = -0.90, t = -0.47, p = 0.65) OFC were observed. Follow-up regression analyses exploring the individual tests included within the EF composite revealed a significant APOE-ε4 positivity x resting CBF of the right MFG on the WCST Perseverative Responses z-score (β = -3.19, t = -1.56, p = 0.13, partial correlation = -.30). Examination of simple main effects revealed that there was a strong positive ssociation between higher resting CBF and better cognitive performance in those who were APOE-ε4 non-carriers relative to APOE-ε4 carriers. Results revealed there were no other medium-to-large effect sizes when the partial correlation of the interaction term was examined in each regression model.

For the second set of regressions, we explored whether APOE-ε4 positivity moderated the association between resting CBF of temporal ROIs and performance on the memory composite. Results revealed there no significant interaction between APOE-ε4 positivity x resting CBF of left (β = 0.19, t = 0.90, p = 0.93) or right (β = -0.29, t = -0.15, p = 0.88) MTL, and left (β = -2.42, t = -0.87, p = 0.39) or right (β = -2.41, t = -0.81, p = 0.43) LTL on performance on the memory composite. Follow-up regression analyses exploring the individual memory tests also revealed no significant APOE-ε4 positivity x resting CBF interactions on memory

performance. Moreover, examination of partial correlations of the interaction term revealed no medium to large effect size trends (r's >.3).

Additional Exploratory Analyses

Group cognitive comparisons. An ANCOVA was performed in order to determine whether there were group differences in performance on the EF and memory composites. Covariates included PCL-M and BDI total scores. Results revealed there were no significant differences in performance between the groups on the EF (F (3, 52) = 0.57, p = 0.45, η_p^2 = .01) and memory composite (F(3, 48) = 0.05, p = 0.82, η_p^2 = .001) between the groups. However, when analyses were replicated without covariates using an ANOVA, results revealed the TBI group performed significantly worse than the MC group on the EF composite (F (1, 52) = 5.35, p = 0.03, η_p^2 = .09). No significant group differences were observed for the memory composite (F (1, 52) = 0.77, p = 0.38, η_p^2 = .02). See Figure 7 below for a graphical depiction of mean EF composite performance between the groups.

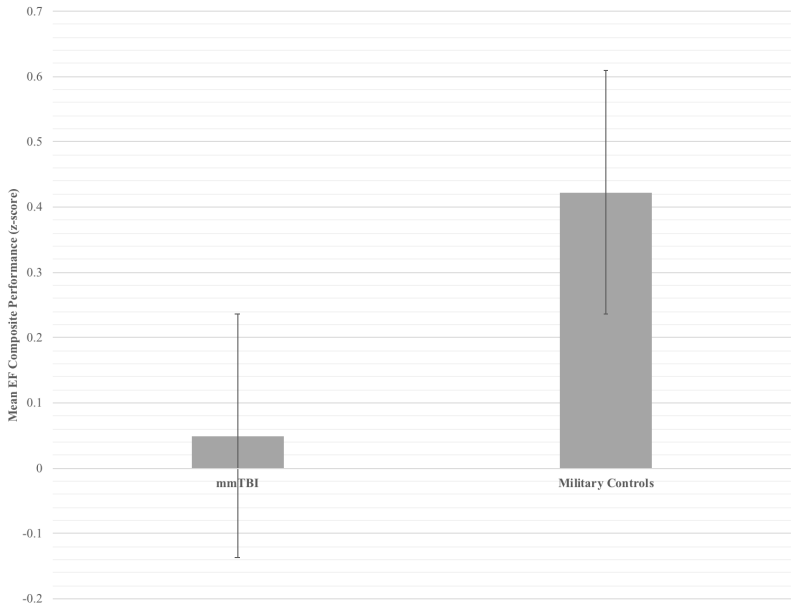

Figure 7. Average Performance Between the mmTBI and MC groups on the EF Composite. X axis presents the performance on the EF Composite in z-scores. Y axis is the depiction of average group performance for the mmTBI and MCs group with error bars that represent the standard error of the mean.

Group (mmTBI vs. MCs) x CBF on cognition explorations. A series of ANCOVAs were performed to determine whether history of mmTBI moderated associations between resting CBF and cognitive performance within our sample. Independent variables included Group (mmTBI vs. MCs), age, BDI-II and PCL-M total scores, and the Group x resting CBF interactions term for relevant frontal ROIS. Results revealed there were no significant interaction terms for time Group x resting CBF of the left (F (6, 52) = 1.70, p = 0.19, η_p^2 = .04) and right (F (6, 52) = 0.001, p = 0.97, η_p^2 <.001) IFG, left (F (6, 52) = 1.17, p = 0.28, η_p^2 = .03) and right (F (6, 52) = 0.03, p = 0.87, η_p^2 = .001) MFG, left (F (6, 52) = 0.48, p = 0.49, η_p^2 =.01) and right (F (6, 52) = 2.62, p = 0.11, η_p^2 =.05) ACC, and left (F (6, 52) = 0.67, p = 0.42, η_p^2 =.01) and right (F (6, 52) = 0.00, p = 0.98, η_p^2 <.001) OFC on EF composite performance. Follow-up ANCOVAs exploring the resting Group x CBF on performance of the five individual EF tests were performed. Results revealed no significant interactions for cognitive performance on each EF test, but there were trends for Group x resting CBF of the left IFG on DKEFS Verbal Fluency Switching Total Responses z-score (F (6, 52) = 2.52, p = 0.11, η_p^2 =.05); Group x resting CBF of the left MFG on the WCST Perseverate Errors z-score (F (6, 52) = 2.03, p = 0.16, η_p^2 =.05); Group x resting CBF of right MFG on the WCST Perseverate Errors z-score (F (6, 52) = 2.15, p = 0.15, η_p^2 =.05); Group x resting CBF of the left ACC on the DKEFS Verbal Fluency Switching Total Responses z-score (F (6, 52) = 4.08, p = 0.05, η_p^2 =.08); Group x resting CBF of the right ACC on the WCST Total Errors z-score (F (6, 52) = 2.65 p = 0.11, η_p^2 =.06); Group x resting CBF of the right ACC on DKEFS Verbal Fluency Switching Total Responses z-score (F (6, 52) = 2.87, p = 0.09, η_p^2 =.06). For interactions with the WCST variables, results revealed that higher resting CBF was associated with better performance in the TBI group, whereas there were no significant associations between resting CBF and cognitive performance within the MC group. See Figure 8 below.

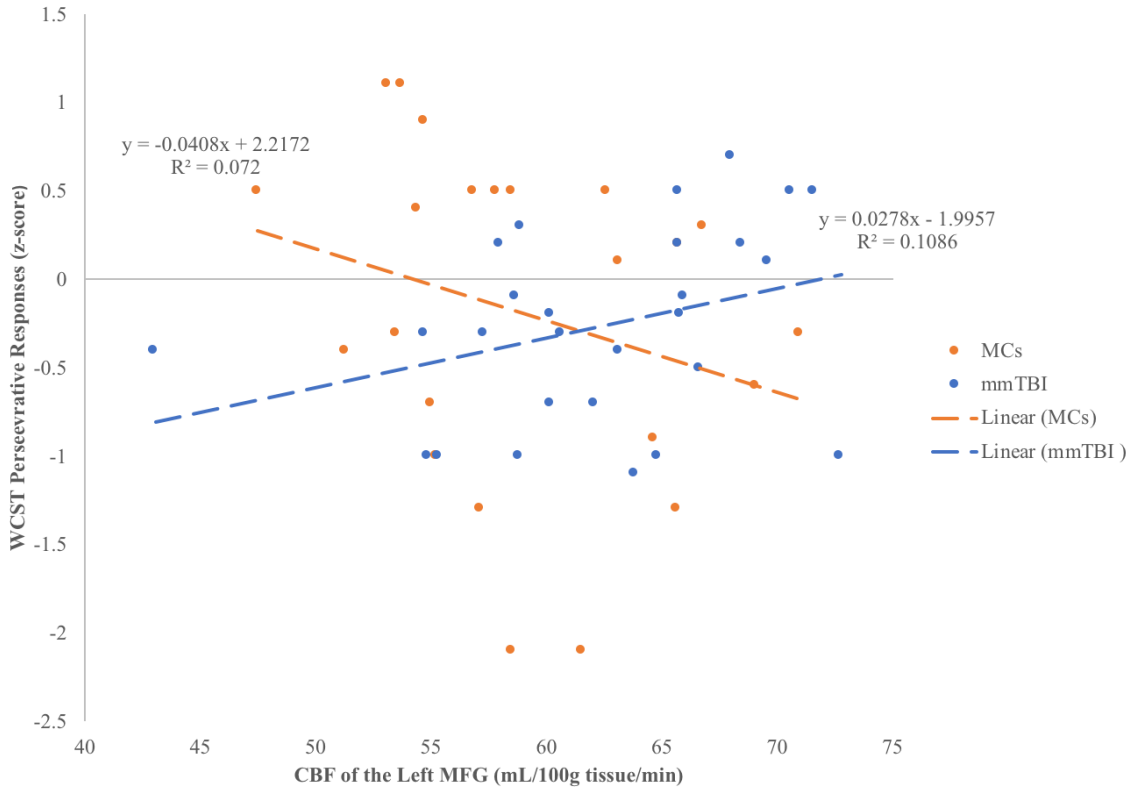

Figure 8. Depiction of Group (mmTBI vs. Military Controls) x Resting Cerebral Blood Flow of the Left Middle Frontal Gyrus for WCST Perseverative Responses Performance. Y axis represents WCST Perseverative Responses in z-scores. X axis represents cerebral blood flow of left middle frontal gyrus in mL/100g tissue/min

For interactions with the DKEFS Verbal Fluency Switching Total Responses variable, results revealed that higher resting CBF was associated with better performance in the MC group, whereas there were no significant associations between resting CBF and cognitive performance were observed within the TBI group. See Figure 9 below.

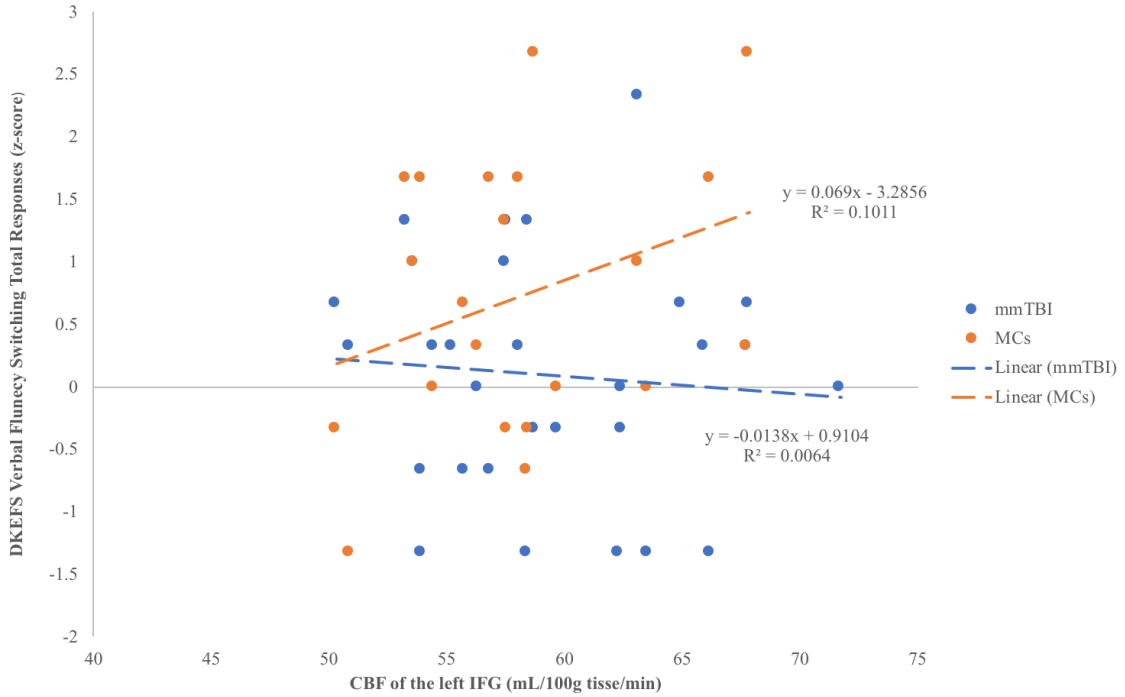

Figure 9. Depiction of Group (mmTBI vs. Military Controls) x Cerebral Blood Flow of the Left Inferior Frontal Gyrus on DKEFS Verbal Fluency Switching Total Responses Performance. Y axis represents DKEFS Verbal Fluency Total Responses in z-scores. X axis represents cerebral blood flow of left inferior frontal gyrus in mL/100g tissue/min

A second series of ANCOVAs were performed to determine whether history of mmTBI moderated associations between resting CBF and performance on the memory composite within our sample. Independent variables included group (mmTBI vs. MCs), BDI-II and PCL-M total scores, and the Group x resting CBF interactions term for relevant temporal ROIS. Results revealed there were no significant interaction terms for Group x resting CBF of the left (F (6, 52) = 0.002, p = 0.96, η_p^2 < .001) and right (F (6, 52) = 0.05, p = 0.83, η_p^2 <.001) MTL, and left F (6, 52) = 0.01, p = 0.92, η_p^2 < .001) and right (F (6, 52) = 0.21, p = 0.65, η_p^2 = .005). Follow-up ANCOVAs exploring the Group x resting CBF on performance of the five individual tests included within the memory composite were performed. Results revealed no significant Group x resting CBF interactions of temporal ROIs interactions for each cognitive test.

IV. DISCUSSION

We explored whether there were group differences in resting CBF between those with and without history of mmTBI; resting CBF associations with cognition and important genetic and environmental risk factors (i.e., total number of TBIs, time since injury, total number of blast-exposures, APOE-ε4 positivity) within the mmTBI group; and the extent to which risk factors moderate the association between resting CBF and cognition in those with mmTBI. Results showed that, relative to MCs with no history of head-trauma, mmTBI Veterans demonstrated significantly higher resting CBF in several frontal and temporal ROIs. Within the mmTBI group, higher resting CBF in frontal regions was associated with better performance on measures of executive functions, although no such associations between resting CBF and measures of memory were observed. Finally, several significant risk factor x resting CBF associations with cognition were demonstrated, such that higher resting CBF was associated with better memory and executive functions performance in those with lower risk. These findings suggest that increased resting CBF may represent a critical compensatory mechanism that allows for better cognitive performance in Veterans with mmTBI. However, this compensatory mechanism seems to be reduced within the context of multiple mmTBIs, greater time since injury, and APOE-ε4 positivity.

Group Resting CBF Differences

The current study is the first to our knowledge to use ASL MRI in order to quantify resting CBF within the context of a military mmTBI sample. While ASL has been widely utilized in civilian moderate to severe TBI samples, it has only recently been applied to sports concussion and civilian TBI samples of milder severity. As summarized by Stephens (2018) and colleagues, only 11 known mTBI studies using ASL have been published and results have largely been mixed. While some studies find that relative to controls, history of mTBI is associated with global and/or regionally specific increases in CBF (Doshi et al., 2015; Mutch,

et al., 2016; Stephens, Liu, Lu, & Suskauer, 2018), others find robust decreases (Churchill, Hutchinson, Graham, & Schweizer, 2018; Peng et al., 2016; Wang et al. 2016). The current study found significantly increased resting CBF in several frontal and temporal ROIs, but no global resting CBF differences between Veterans with and without history of mmTBI. Despite inconsistences in directionality within the existing literature, our findings overlap with regions commonly implicated in other ASL studies of mTBI (Doshi et al., 2015; Wang et al., 2015). Notably, most of the existing ASL studies have leveraged samples that are largely in the acute or post-acute phase of injury. Thus, the current study provides some clarification into the nature of resting CBF within the *chronic* phase of injury. Moreover, these increases in resting CBF were determined to be independent of common psychiatric comorbidities that have frequently not been considered in existing studies.

Our findings of increased regional resting CBF in Veterans with mmTBI were in direct contrast to our original hypotheses, as we expected that damage to the cerebrovasculature coupled with neuroinflammatory cascades would result in chronically decreased resting CBF post-injury. The precise mechanisms underlying increased resting CBF remains unclear but could represent vascular dysfunction in the form of neurovascular uncoupling. The neurovascular unit (NVU) is comprised of blood vessels (e.g., arteries, capillaries), endothelial cells, abutting neurons, and support cells (e.g., astrocytes, microglia), and it is responsible for many important functions (i.e., establishing homeostasis, ensuring neuronal functioning, regulating inflammatory and reparative processes). During TBI, primary injury (i.e., twisting, shearing) disrupts the integrity of the NVU. This structural damage has negative *functional consequences* that may persist and worsen with time, as it alters the dynamic signaling cascades that occur between components of the NVU. As a result, there may be a mismatch between the NVU's ability to modulate CBF in accordance with local metabolic demands of neuronal tissue. One well documented consequence of damage to the NVU is functional *hyperemia*—that is, the NVU commonly overshoots delivery of CBF with respect to relative

oxygen demands of the tissue to ensure the proper delivery of fuel as well as the removal of detrimental waste (Armstead, 2016; Ellis et al., 2016). Cerebrovascular reactivity (CVR) provides a measurement of this mismatched response and several recent studies have demonstrate altered and variable CVR responses in those with mTBI relative to controls (Amyot et al., 2018; Kenney, Haber, Amyot, Davis, Pronger, Moore & Diaz-Arrastia, 2016; Ellis et al., 2016; Haber et al., 2018). However, less clear is what drives a hyperemic versus ischemic response within the context of *mild* neurotrauma. While purely speculative, we suspect that hyperemia may occur within the context of less vascular pathology and that ischemia may be more likely to occur with profound damage to multiple elements of the NVU and may therefore explain why reduced CBF seems to be a more consistent finding in moderate to severe TBI samples.

It is important to acknowledge that variability in ASL sequences and precisely how resting CBF values are reported in the literature may also play a pivotal role in the discrepancies across studies. For example, both pulse and pseudo-continuous ASL sequenced have been used to characterize group differences between those with and without history of TBI. Arterial blood is magnetically labeled in a spatially selected manner with pulsed ASL sequences, whereas pseudo-continuous ASL sequences use a radiofrequency pulse train to continuously label blood feeding into arteries. Thus, distinct differences in signal intensity, image contrast, and reproducibility across these sequences warrant consideration when comparing across or within study samples (Nezamzedah, Matson, Younhg, Weiner, & Schuff, 2010; Stephens et al., 2018). Moreover, it appears that both relative and absolute resting CBF values are reported in the existing literature. Relative resting CBF provides a metric of perfusion of an ROI relative to the rest of the brain, whereas absolute resting CBF quantifies regional CBF independent of other regions. The current study reported absolute resting CBF values, which has increased susceptibility to physiological factors (e.g., caffeine, breathing rate), transit time delay, and partial volume effects (Borogovac & Asllani, 2012; Stephens et al., 2018). However, this method

has increased sensitivity to detect small effects, relative to resting rCBF, which is essential given the lower power in the current study.

CBF and Cognitive Outcomes

We found that higher resting CBF of the right IFG and OFC was associated with better cognitive performance on the EF composite within the mmTBI group. Moreover, similar results were observed between resting CBF of other frontal ROIs and performance on the individual subtests of the larger EF composite. Results suggest that higher resting CBF may represent a compensatory mechanism within the context of mmTBI. On average, the mmTBI group performed largely within normative limits and follow-up exploratory analyses revealed the independent of psychiatric factors, there were no group differences in cognitive performance between the mmTBI and MCs group. The current findings align with existing fMRI blood oxygenation level-dependent (BOLD) studies showing increases in frontal activation during working memory tasks in those with mild TBI relative to controls, even in the in the absence of group differences in behavioral performance (McDonald, Saykin, & McAllister, 2014). Moreover, resting state fMRI (rs-fMRI) studies have also revealed that the default mode network (DN) is more active at rest in mTBI subjects relative to controls (Han et al., 2014; Sours, Zhuo, Roys, Shanmuganathan, & Gullapalli, 2015). Nevertheless, when ASL, BOLD, and rs-FMRI studies delineate mmTBI subjects into those who do and do not recover based on PCS reporting, patterns of increased activation, network activity, or CBF of frontal regions have been linked to poorer recovery, or increased PCS reporting (Barlow, Marcil, Dewey, Carlson, MacMaster, Brooks, & Lebel, 2017; Han et al., 2014; Lin, Tseng, Hsu, Chen, Chen, Yan, & Chiu, 2016; Wylie, Freeman, Thomas, Shpaner, O'Keefe, Watts, & Naylor, 2015). Ancillary analyses revealed that, independent of age and PCL-M total scores, higher CBF was associated with worse PCS symptom reporting. Results suggest that while higher CBF may be compensatory for neurocognitive performance, it may be detrimental for subjective experiences of PCS. Future work will explore discrepancies between resting CBF, subjective cognitive complaints, and

objective neuropsychological performance. Notably, there were no associations between resting CBF in temporal regions and performance on memory composite, individual memory tests, or PCS symptoms. Thus, there may be some regional specificity in that frontal regions may be more vulnerable to vascular injury and therefore more likely to demonstrate altered patterns of resting CBF.

We conducted a series of exploratory analyses to determine whether group (mmTBI versus MCs) moderated the association between resting CBF and cognitive performance. We expected that greater vascular pathology in the mTBI group would alter resting CBF and cognitive associations. Results revealed a trend toward differential associations with individual EF tests, but not the EF composite, across the two groups. Higher resting CBF was associated with fewer errors on a measure of abstract problem solving in the mmTBI group, whereas there were no significant associations between resting CBF and cognitive performance on this measure within the MCs group. In contrast, higher resting CBF was associated with better performance on a measure of cognitive set-shifting in the MCs group, but there no such association between resting CBF and cognitive performance in the mmTBI group. Results suggest that increased resting CBF may allow for greater self-monitoring and/or compensation on untimed (WCST) versus timed tasks (DKEFS Verbal Fluency Switching) in the mmTBI group. The lack of an association between resting CBF and cognitive performance on the timed task may suggest that those with mmTBI may be overloaded by task demands and unable to compensate with increased resting CBF. Additional research with a larger sample size and greater variability on cognitive performance is needed to better tease apart any differential associations between resting CBF and cognitive performance between the groups.

Resting CBF and Risk Factors

We also explored associations between risk factors (i.e., cumulative blast exposure, history of multiple TBIs, time since injury, and genetic susceptibility [APOE-ε4 positivity]) and resting CBF in those with mmTBI. Results revealed that a greater total number of TBIs was

significantly associated with reduced resting CBF of the left IFG. Human studies directly exploring repetitive TBI and CBF are relatively limited and while repetitive TBI may be common in military samples (Fortier et al., 2013), many published studies do not comprehensively characterize lifetime history of TBIs of their samples and it is difficult to tease apart to what extent repetitive TBI may be a relevant factor in observed brain findings within the literature. Nevertheless, research from sports concussion or athlete samples have provided some insight into the nature of brain changes within repetitive TBI samples. For example, Slobounov and colleagues (2017) recently showed pre- to post-season increases in both global and regional resting CBF in collegiate football players presumed to have repetitive subconcussive blows. In contrast, decreased resting CBF was observed in the inferior temporal lobe of active professional fighters with repeated head trauma (Mishra, Sreenivasan, Banks, Zhuang, Yang, Cordes, & Bernick, 2018). Although our mmTBI group showed higher regional CBF relative to MCs, there may be a point at which this compensatory response is altered in the presence of repetitive injuries. We failed to find any robust associations between resting CBF and other critical risk factors, though our resting CBF x risk factor on cognitive performance interactions provided insight into the nature of these null findings and will be discussed below.

Resting CBF x Risk Factors on Cognitive Outcomes

Our final goal was to explore the extent to which risk factors may influence resting CBF and cognitive outcomes in mTBI. We hypothesized that resting CBF-related cognitive deficits would be more pronounced in mmTBI Veterans with greater blast-exposure, history of multiple TBIs, APOE-ε4 positivity, and who are further removed from their injury. We suspected that the presence of these risk factors would modify resting CBF and cognitive associations by either (1) exacerbating or contributing to vascular-related brain damage and/or (2) reducing cognitive reserve post-TBI. The current study found results that largely contradicted our original hypotheses, as resting CBF and cognitive associations were generally *more* pronounced in those with lower versus higher risk factor burden. For example, there was a strong association

between higher resting CBF and better cognitive performance in the mmTBI group with fewer injuries relative to those who reported multiple injuries; those who were closer in time to their injury relative to those whose injuries were more remote; and those who were APOE-ε4 non-carriers relative to APOE-ε4 carriers. Results suggest that there may be a threshold in which increased resting CBF is no longer compensatory within the context of greater risk factor burden. That is, individuals with milder pathology and injury can maintain cognitive performance through increased resting CBF, though there is a point at which this compensatory mechanism is no longer effective. These findings align with the compensation related utilization of neural circuit hypothesis of aging in which increases in brain activation allow for task demands to be met, though the effectiveness of these increases plateau much earlier in older versus younger adults (Lustig & Sarter, 2015; Rueter-Lorenz & Lustig, 2005; Rueter-Lorenz & Cappell, 2008).

Unexpectedly, we found a strong negative association between higher resting CBF and poorer memory performance in those with fewer blast exposures. These findings are in direct contrast to the other CBF and risk factors associations observed and also contradict most of the existing literature demonstrating greater BE is associated with poorer brain and behavioral outcomes (Clark et al., 2018; Grande et al., 2018; Robinson et al., 2017). We suspect that these findings may be spurious and additional research with a larger sample size is needed. Notably, only 52% of the original mmTBI sample was blast exposed, which was futher delineated into those with low (n = 8) versus high (n = 8) levels of BE for interpretation. While our analyses revealed there was no association between BE and resting CBF within the sample, Pearson's correlations revealed largely negative associations between BE and cognitive test performance within the sample. BE is generally quite difficult to characterize in human studies and we currently have no understanding what level of intensity illicits detrimental effects in the human brain. Moreover, many of the current BE studies fail to take into other known risk factors such as combat exposure or repetitive TBI in their analyses. Our work in exploring the potential

detrimental effects of BE is is in its infancy, but increased efforts should first be made towards characterizing BE in humans by focusing on quantifying distance or intensity as a marker of potential severity.

Limitations

It is important to note that the current study has several limitations that warrant discussion. The cross-sectional design of this study does not speak to any preexisting differences in CBF that may have existed between our groups and also does not allow us to make causal inferences about our imaging findings. Second, as is common in most military TBI studies, our diagnosis of TBI was based on retrospective self-report of injuries that occurred many years prior and is therefore subject to recall bias. However, we worked to mitigate these effects by also conducting comprehensive chart reviews of injuries and administering a semi-structured TBI clinical interview that reduces risk of leading questions and ensures more adequate characterization and confidence in diagnosis of these injuries. Third, our sample size was considerably smaller than our proposed recruitment target and we likely did not have the power to detect differences in some of our analyses. However, we examined and reported medium to large effect sizes which speaks to the nature of our findings within the context of a larger sample. We did not correct for multiple comparisons, but examined a-priori ROIs commonly implicated in the TBI literature and created larger composite ROIs in an effort to reduce our comparisons. However, in doing so, we may have reduced our sensitivity and cannot speak to distinct differences in regional specificity of resting CBF changes. Finally, our sample consisted of mixed injury severity due to issues of power, but sensitivity analyses generally showed that our findings did not drastically differ due to the inclusion of those with moderate TBI in the sample.

Conclusions, Strengths, and Future Directions

In summary, to our knowledge, this is the first investigation to utilize ASL in order to explore CBF differences in a military sample of Veterans with and without mmTBI. Our results

provide preliminary evidence that increased resting CBF is observed within the context of mmTBI and likely represents a compensatory mechanism that allows for better cognitive performance following injury. However, interestingly, increased resting CBF as a compensatory mechanism for better cognitive performance appears to only be present in Veterans with lower risk factor burden. Strengths of this study include comprehensive characterization and statistical modeling of known risk factors that have largely not been considered in brain-behavior explorations within the existing TBI literature. This study also employed novel MRI technology and comprehensive behavioral and biomarker assessment in a way that directly translated critical developments shown in the animal literature to explorations in humans.

Although the exact timeline of resting CBF alterations post-TBI is unclear, our study provides evidence that TBI causes persisting functional changes. Currently, there is an ever-pressing need to consider precisely how resting CBF changes may differ with time and to what extent these resting CBF changes may represent endothelial dysfunction that worsens within the context of common age-related pathological processes (e.g., vascular risk, dementia). These findings enhance our understanding of the pathophysiological mechanisms underlying negative outcomes in Veterans with head trauma histories. Future prospective studies are needed to identify (1) consistent and reliable biomarkers of PCS, cognitive dysfunction, and poor functional outcomes across different phases of mTBI; (2) individuals at greatest risk for poor outcomes; (3) the utility of novel MRI indices in monitoring outcomes; and (4) neurobiological targets for intervention that improve quality of life and lower health-related costs.

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