

NEURAL GAIN MODULATION IN CHRONIC MILD TRAUMATIC BRAIN INJURY

by

Jamie Nicole Hershaw

Dissertation submitted to the Faculty of the
Medical Psychology Graduate Program
Uniformed Services University of the Health Sciences
In fulfillment of the requirements for the degree of
Doctor of Philosophy

Distribution Statement

Distribution A: Public Release.

The views presented here are those of the author and are not to be construed as official or reflecting the views of the Uniformed Services University of the Health Sciences, the Department of Defense or the U.S. Government.



UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES

SCHOOL OF MEDICINE GRADUATE PROGRAMS

Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814



FINAL EXAMINATION/PRIVATE DEFENSE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Name of Student: Jamie N. Hershaw

Date of Examination: November 28, 2018

Time: 2:00 PM

Place: Room B4004

DECISION OF EXAMINATION COMMITTEE MEMBERS:

PASS

FAIL

[Redacted Signature]

✓

Dr. Andrew Waters

DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY

Committee Chairperson

[Redacted Signature]

✓

Dr. Mark L. Ettenhofer

DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY

Dissertation Advisor

[Redacted Signature]

✓

Dr. Connie C. Duncan

DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY

Committee Member

[Redacted Signature]

✓

Dr. Joscelyn Fisher

DEPARTMENT OF PSYCHIATRY

Committee Member



UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES

SCHOOL OF MEDICINE GRADUATE PROGRAMS

Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814



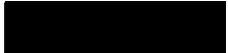
APPROVAL OF THE DOCTORAL DISSERTATION IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Title of Dissertation: "Neural Gain Modulation in Chronic Mild Traumatic Brain Injury"

Name of Candidate: Jamie N. Hershaw
Doctor of Philosophy Degree
November 28, 2018

DISSERTATION AND ABSTRACT APPROVED:

DATE:


Dr. Andrew Waters
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Chairperson

12/3/18


Dr. Mark L. Ettenhofer
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Dissertation Advisor

12/03/18


Dr. Connie C. Duncan
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Member

12/3/18


Dr. Joscelyn Fisher
DEPARTMENT OF PSYCHIATRY
Committee Member

12/23/18

[Dissertation approval form inserted here]

ACKNOWLEDGMENTS

I wish to acknowledge my committee members for their consistent and thoughtful guidance as I completed this dissertation. I am also appreciative of the Center for Neuroscience and Regenerative Medicine for their financial support of my dissertation.

I am eternally grateful for the mentorship I have received over the course of my education. Although he will never take the credit I give him, I would have never realized my own potential as a scientist without the nurturance and support of Dr. Paul D. Kieffaber. I am also grateful to Dr. Mark L. Ettenhofer for giving me the tools necessary to conduct this research and the encouragement and empathy he provided at every turn. Finally, Dr. Connie C. Duncan has been a constant source of knowledge, praise, and inspiration. I am so lucky to call Dr. Duncan my mentor.

Finally, I wish to acknowledge the support of my family and friends during this process. My family—my father, sister, brother-in-law, nieces, aunt, and grandmothers—have provided much needed love and support throughout this journey. I am grateful to my partner, Dr. Brian Guise, and our own little family (Sneaker, Peepers, and Aspen) for their unconditional love and reminding me that there is more to life than a dissertation. I am also thankful to my friends for their friendship and support during this time.

DEDICATION

I dedicate this dissertation to the cheerleaders I've had along the way, including (but not limited to) KH, KV et al., BG, BH, CCD, PK, ME, GG, JG, RM, LS, LC

This dissertation is also dedicated to all the little girls with big dreams. Be unapologetically ambitious and fearless in your journey. **Set the world on fire.**

COPYRIGHT STATEMENT

The author hereby certifies that the use of any copyrighted material in the dissertation manuscript entitled: Neural Gain Modulation in Chronic Mild Traumatic Brain Injury is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.



Jamie N. Hershaw

February 5, 2019

DISCLAIMER

The views presented here are those of the author and are not to be construed as official or reflecting the views of the Uniformed Services University of the Health Sciences, the Department of Defense or the U.S. Government.

ABSTRACT

Neural gain modulation in chronic mild traumatic brain injury:

Jamie N. Hershaw, MS

Thesis directed by: Mark L. Ettenhofer, PhD, Assistant Professor, Department of
Medical and Clinical Psychology

Persistent symptoms of mild traumatic brain injury (TBI) after the typical recovery period are a public health concern with high personal and economic costs. The etiology of symptomatic chronic mild TBI is the subject of much debate; some research suggests psychogenic factors such as pre-morbid psychiatric problems and financial incentive are the basis of self-report symptoms, while other research shows evidence of subtle neuropathological deficits in this population, including impaired resource allocation. To further complicate the understanding of symptomatic chronic mild TBI, many patients with subjective complaints perform within normal ranges on neuropsychological assessments and the constellation of symptoms in this population is non-specific. Research on the neurological basis of persistent symptoms in chronic mild TBI suggests that under low levels of cognitive load, patients may experience more resource allocation through enhanced neural gain, but behavioral manifestation of increased resource allocation are not apparent until higher levels of cognitive load. Thus, the ability to modulate neural gain in response to increases in cognitive load may be

dysfunctional in chronic mild TBI and explain the discrepancy between subjective complaints of cognitive difficulty and behavioral outcomes. The current program of research investigated effects of cognitive load manipulations on measures of neural gain in chronic mild TBI and controls. It was proposed that patients with chronic mild TBI would have impaired modulation of neural gain and this neurological impairment would underlie subjective effort and cognitive performance. The first study confirmed group differences in modulating neural gain in response to varied attentional demands, although it was not affected by cognitive load. In the second study, group differences in global and attentional neural gain were demonstrated using pupillary responses and event-related potentials; the relationship between neural gain, cognitive performance, and neurobehavioral symptoms also indicated that neural gain differences may underlie cognitive sequelae of chronic mild TBI. Finally, the third study methodologically identified optimal measures of global neural gain using pupillary data. Together, this program of research demonstrates that 1) individuals with chronic mild TBI have difficulty modulating neural gain in response to changing task demands; 2) impaired neural gain modulation may explain the discrepancy between subjective cognitive complaints and normal behavioral performance in chronic mild TBI; and 3) pupillary and electrophysiological measures of neural gain can be used to augment behavioral measures of cognitive performance to better assess long-term cognitive sequelae of mild TBI.

TABLE OF CONTENTS

LIST OF TABLES	xi
LIST OF FIGURES	xii
Chapter 1: Introduction	1
Chronic Mild Traumatic Brain Injury	1
Neural Basis of Chronic mTBI	1
Resource Allocation in Mild TBI	3
Neural Gain	5
Current Program of Research	7
Study One	8
Study Two	9
Study Three	10
Chapter Two: Effects of Cognitive Load and Varied Attentional Demands on Spectral Power in Chronic Mild Traumatic Brain Injury	23
Introduction	23
Cognitive Load and Neural Gain	23
Neural Gain in Mild TBI	25
Event Related Spectral Perturbations	27
Event Related Spectral Perturbations in Mild TBI	28
Hypothesis	29
Methods	30
Participants	30
Procedure	31
Cued Attention Task	31
ERSP Pre-Processing and Measurement	33
Statistical Analyses	35
Results	35
Participant Characteristics	35
Task Performance	36
Load-Based Metrics	37
Mid-Latency Beta	37
Long-Latency Beta	38
Cue-Based Metrics	38
Short-Latency Gamma	38
Short-Latency Beta	38
Mid-Latency Theta	39
Long-Latency Beta	39
Discussion	40
Effects of Attentional Demands	41

Effects of Cognitive Load	42
Conclusion	44
CHAPTER 3: Attentional Gain Modulation in Chronic Mild Traumatic Brain Injury	56
Introduction.....	57
Attentional Gain.....	57
Global Neural Gain	60
Current Study	62
Methods.....	63
Participants.....	63
Procedure	64
Cued Attention Task	64
Self-Reported Symptoms and Neuropsychological Performance.....	66
Psychophysiological Data Collection and Processing	66
Apparatus	66
Pupil Diameter	67
ERPs.....	68
Statistical Analyses	68
Sample Characteristics.....	68
Task Performance	69
Global Neural Gain	69
Attentional Gain.....	70
Correlational Analyses.....	70
General Statistical Considerations	71
Results.....	71
Sample Characteristics.....	71
Task Performance	72
Baseline Pupil Diameter	73
P1 Amplitude	73
N1 Amplitude.....	74
Correlations.....	74
Discussion	76
Limitations and Future Directions	81
Conclusions.....	82
Chapter 4: Insights into Cognitive Pupillometry: Evaluation of the Utility of Pupillary Metrics for Assessing Cognitive Load in Normative and Clinical Samples	102
Introduction.....	103
Applications of Cognitive Pupillometry	103
Pupillary Metrics.....	105
Study Aims.....	107
Methods.....	108
Participants.....	108
Apparatus	110
Procedure and Task Design	110
Pupillometry Acquisition and Processing	112

Analytic Strategy	113
Internal Consistency.....	113
Empirical Data Analyses.....	113
Replicability Analyses	114
Results.....	116
Participants.....	116
Manual Response Time.....	116
Presentation of Results.....	117
Internal Consistency.....	117
Group Effects	118
Load Effects	118
Group*Load Interaction.....	120
Discussion	120
Limitations	128
Conclusion	130
Appendices.....	151
Chapter 5: Conclusion.....	162
Proposed Theory	163
Study One.....	163
Study Two	164
General Theoretical Conclusions.....	165
Study Three.....	167
Applications	168
Future Directions	169
Appendix.....	176

LIST OF TABLES

Table 2.1. Participant Demographics and Injury Characteristics	50
Table 2.2. Descriptive Data for Significant Main Effects	51
Table 3.1. Participant Characteristics, Symptoms, and Neuropsychological Performance	97
Table 3.2. Correlation Coefficients.....	98
Table 4.1. Pupillary Metrics.....	145
Table 4.2. Bootstrapped and Empirical Results.....	146
Table 4.A. Internal Consistency.....	151
Table 4.B. Group Effects	152
Table 4.C. Cognitive Load Effects	154
Table 4.D. Cognitive Load Effects within Controls	156
Table 4.E. Cognitive Load Effects within mild TBI.....	158
Table 4.F. Group*Cognitive Load Interaction Effects	160

LIST OF FIGURES

Figure 2.1: Task Schematic.....	52
Figure 2.2: ERSPs	53
Figure 2.3: Probability Maps	54
Figure 2.4: Topographical Plots.....	55
Figure 2.5: Group * Cue Interactions	56
Figure 3.1. Task Schematic.....	99
Figure 3.2. Response Time	100
Figure 3.3. Baseline Pupil Diameter	101
Figure 3.4. ERP Results	102
Figure 4.1. Task Schematic.....	146
Figure 4.2. Prototypical Pupillary Waveform.....	149
Figure 4.3. Cue-Locked Pupillary Waveforms	150

Chapter 1: Introduction

CHRONIC MILD TRAUMATIC BRAIN INJURY

The incidence of traumatic brain injuries (TBI) is roughly 1.5 million per year and approximately 80% are considered “mild” in severity (Bazarian et al., 2005; Cassidy et al., 2004; Sosin, Snieszek, & Thurman, 1996), although this number is likely underestimated as many mild TBIs are undocumented (Powell, Ferraro, Dikmen, Temkin, & Bell, 2008). Mild TBIs are commonly defined as any head injury that results in loss of consciousness (LOC) fewer than 30 minutes, post-traumatic amnesia (PTA) fewer than 24 hours and/or alterations of consciousness (AOC) following the injury (Head, 1993). Patients experience a variety of cognitive symptoms including memory problems, effortful processing, and poor attention (Alexander, 1995; Binder, 1997; Carroll et al., 2004; Hall, Hall, & Chapman, 2005; King, 1997) but these symptoms typically resolve within days or weeks after injury for a majority of patients (Frencham, Fox, & Maybery, 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). However, studies report 10-20% of patients with mild TBI experience persistent symptoms after the typical recovery period of three to six months, with many still experiencing symptoms years and even decades after the initial injury (Alexander, 1995; Bigler, 2003; Wood, 2004; Ruff, Camenzuli, & Mueller, 1996). Although chronic mild TBI patients represent the minority of all mild TBI patients, the sheer number of mild TBIs incurred every year make this phenomenon a public health concern with an economic cost estimated to exceed \$16 billion (Prevention & Control, 2003).

NEURAL BASIS OF CHRONIC MTBI

The etiology of chronic mild TBI is controversial. Despite that patients with chronic mild TBI self-report that cognitive symptoms do not resolve over time, several meta-analyses have shown that neuropsychological performance following mild TBI is within the normal range by three months post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Binder, Rohling, & Larrabee, 1997; Frencham et al., 2005; Karr, Areshenkoff, & Garcia-Barrera, 2014; Schretlen & Shapiro, 2003). Additionally, patients typically have normal radiological outcomes when assessed with conventional neuroimaging, such as computed topography (CT) and magnetic resonance imaging (MRI; Borg et al., 2004; Shenton et al., 2012). The disparity between subjective, self-reported cognitive difficulty in chronic mild TBI and the absence of objective indicators of persistent neurocognitive impairment contributes to an ongoing examination of the etiology of persistent cognitive symptoms in chronic mild TBI.

While many researchers suggest that persistent symptoms in chronic mild TBI are psychogenic, others report that long-term neurological dysfunction underlies these symptoms. The primary pathophysiological effect of mild TBI is diffuse axonal injury which prompts a neurometabolic cascade that ultimately leads to neuronal dysfunction (Giza & Hovda, 2014; Iverson, 2005). Axonal injury and dysregulated neural transmission appear to underlie the cognitive deficits observed in acute and sub-acute mild TBI (Giza & Hovda, 2014). However, following mild injuries, neurometabolic activity returns to baseline within several days, consistent with the time course of resolution of cognitive symptoms in typical patients (Giza & Hovda, 2014; Hovda et al., 1999; McCrea, Guskiewicz, Marshall, & et al., 2003). Some studies report that neurological recovery is longer or incomplete for some individuals, which may contribute

to persistent symptoms. Using more sensitive neuroimaging techniques than CT or structural MRI, such as diffusion tensor imaging (DTI), researchers have identified diffuse axonal injury in mild TBI patients well after the typical recovery period (Scheid, Preul, Gruber, Wiggins, & Von Cramon, 2003; Smits et al., 2011).

Resource Allocation in Mild TBI

One possible explanation for persistent cognitive symptoms following mild TBI is impaired resource allocation. Neurotransmitter functioning, metabolic factors in the brain, and neural connectivity—all of which can be affected by mild TBI (Giza & Hovda, 2014)—can influence the amount of resources available to perform cognitive tasks (Just, Carpenter, & Miyake, 2003). Researchers have long speculated that cognitive deficits after mild TBI are caused by reduced resource capacity (Gronwall & Wrightson, 1975). In accordance with this theory, patients with mild TBI should have differences in resource allocation due to the compounded effects of reduced capacity and impaired neural transmission. In support of this theory, functional MRI (fMRI) studies of remote mild TBI have reported abnormal blood oxygen level dependent responses, indicative of impaired ability to utilize neural resources (Chen, Johnston, Collie, McCrory, & Ptito, 2007; Chen et al., 2004; Gosselin et al., 2011). Electrophysiological evidence also suggests that individuals with remote mild TBI are allocating fewer neural resources to complete cognitive tasks (Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000; Gaetz, Goodman, & Weinberg, 2000; Gosselin, Thériault, Leclerc, Montplaisir, & Lassonde, 2006; Lavoie, Dupuis, Johnston, Leclerc, & Lassonde, 2004; Weinberg, 2000). Often, these resource allocation differences are detected in the absence of behavioral or neuropsychological differences (Bernstein, 2002; Chen et al., 2004; Gosselin et al., 2011;

Segalowitz, Bernstein, & Lawson, 2001). Individuals with mild TBI typically perform similarly to controls on easier tasks; however, the effects of subtle processing deficits become more apparent with more demanding tasks (Bernstein, 2002; Segalowitz et al., 2001).

In addition to sufficient resource capacity, adaptive modulation of neural resources is also required to maintain optimal performance under changing task demands (Egner & Hirsch, 2005; Hillyard, Vogel, & Luck, 1998; Lavie, 2010; Scolari & Serences, 2009). Resource allocation in healthy controls increases parametrically with cognitive load, such that more difficult tasks evoke greater resource allocation, as indicated by increased neural activity (Beatty, 1982; Beatty & Lucero-Wagoner, 2000; Cabestrero, Crespo, & Quirós, 2009; Granholm & Verney, 2004; Kok, 2001; Polich, 2007; Polich & Kok, 1995; Zekveld & Kramer, 2014). However, patients with acute and sub-acute mild TBI do not exhibit the same linear pattern as uninjured controls. In one pair of fMRI studies of acute and sub-acute mild TBI, patients increased neural activation between low and moderate working memory load conditions, but the effect plateaued between moderate and high load (McAllister et al., 1999; McAllister et al., 2001). Interestingly, despite the increased resource allocation at low and moderate load, no performance differences were observed between groups until the highest level of cognitive load. These studies suggest that cognitive resource allocation is impaired in earlier stages following mild TBI, particularly during demanding tasks with high cognitive load. Thus, considering evidence of extended or incomplete neurological recovery for those with chronic mild TBI, the ability to optimally modulate neural resource allocation may be compromised in this population. Furthermore, research using healthy volunteers has

demonstrated that subjective ratings of mental effort during cognitive tasks reflect the amount of resources allocated to performing cognitive tasks (Howells, Stein, & Russell, 2012). Therefore, poor resource allocation may explain why patients with chronic mild TBI report cognitive tasks as more effortful, even in the absence of performance decrements.

NEURAL GAIN

The mechanism by which adaptive, load-dependent resource allocation is proposed to occur is neural gain modulation. Neural gain is the increase in neural sensitivity to incoming stimuli to enhance information processing (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013). It is modulated by the locus coeruleus norepinephrine (LC-NE) network, which works to flexibly tune neural sensitivity to incoming neural signals—whether excitatory or inhibitory—to optimize behavioral performance in the face of changing task demands. The LC-NE network receives top-down input from the prefrontal cortex, which is thought to relay goal- and performance-related information (Aston-Jones & Cohen, 2005; Eldar et al., 2013).

Neural gain can be modulated globally and/or locally. Global neural gain reflects brain-wide, domain-general neural sensitivity. Pupillometry, the measurement of pupil diameter in response to sensory, cognitive, or motor events, is a reliable index of global neural gain (Granholm, Asarnow, Sarkin, & Dykes, 1996; Granholm & Verney, 2004; Unsworth & Robison, 2015; Van Der Meer et al., 2010; Verney, Granholm, & Marshall, 2004). The pupil is predominantly innervated by the LC-NE pathway; accordingly, larger pupil diameter reflects greater global neural gain. A large body of literature has demonstrated that pupil diameter is correlated with task demands. As task demands

increase, cognitive load pupil diameter also increases (Beatty, 1982; Cabestrero et al., 2009; Granholm et al., 1996; Rajkowski, Kubiak, & Aston-Jones, 1993; Zekveld & Kramer, 2014). This pattern of results has been used to support the neural efficiency hypothesis which states that some individuals process cognitive information with greater efficiency such that tasks require relatively less mental effort. More efficient cognitive processing and reduced effort are associated with smaller pupil diameter (Verney et al., 2004).

Distinct from brain-wide, domain-general global neural gain, attentional gain amplifies neural responses specific to attended stimuli and attenuates neural responses to unattended stimuli (Kim, Grabowecky, Paller, Muthu, & Suzuki, 2007; Scolari & Serences, 2009). It is commonly studied using attention-related event-related potentials (ERPs) and time-frequency analyses of electroencephalographic signals (EEG; (Doesburg, Bedo, & Ward, 2016; Foxe & Snyder, 2011; Hillyard & Anllo-Vento, 1998). By increasing the neural sensitivity to attended stimuli and/or decreasing neural sensitivity to unattended stimuli, the signal-to-noise ratio is increased, thereby sharpening the focus of attention (Aston-Jones & Cohen, 2005; Eldar et al., 2013; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010). The ability to selectively filter relevant stimuli from irrelevant stimuli and enhance attentional processing is dependent on modulation of attentional gain (Scolari & Serences, 2009). The N1 and P1 components of the ERP dissociate neural responses to attended and unattended visual stimuli (Hillyard & Anllo-Vento, 1998). Typically, N1 and P1 amplitudes are enhanced over the hemisphere contralateral to the spatial location where attention is directed (Hillyard & Anllo-Vento, 1998; Luck, Heinze, Mangun, & Hillyard, 1990). This pattern indicates that visuospatial

attention is influenced by modulations in attentional gain to increase neural responsivity to incoming, task-relevant sensory information and/or increased sensitivity to information in attended locations. Additionally, ERSPs are a direct measurement of neural gain because they index changes in summation and/or synchronization of neural activity at various oscillatory frequencies in response to task events (Zagha & McCormick, 2014). Specifically, an increase in oscillatory power indicates amplification of neural gain and a decrease in oscillatory power indicates attenuation of neural gain. Spectral activity is known to increase linearly with load in healthy controls, with the effects of increased load largely affecting top-down, endogenous attention but not bottom-up, exogenous attention (Jensen, Gelfand, Kounios, & Lisman, 2002; Meltzer et al., 2008; Michels et al., 2010). Taken together, these robust pupillary and electrophysiological findings indicate that the positive linear relationship between resource allocation and cognitive load is likely a result of adaptive modulation of neural gain.

CURRENT PROGRAM OF RESEARCH

While the ability to flexibly allocate brain-wide neural resources in response to increases in cognitive load is critical to maintaining normal cognitive performance in healthy controls, patients with mild TBI exhibit different patterns of resource allocation while completing cognitive tasks, particularly during more difficult tasks (McAllister et al., 2001). Accordingly, it is plausible that this group difference in resource allocation under greater cognitive load is due to poor modulation of global neural gain. Attentional neural gain may also be important for understanding subjective cognitive complaints and cognitive performance in chronic mild TBI, as attention is central to all other cognitive processes for its role in selecting information for further processing (Parasuraman, 2000).

Due to the necessity of attention to all cognitive processes, deficits in attentional gain modulation may also underlie the variety of cognitive difficulties reported in chronic symptomatic mild TBI.

To further understand the neural basis of chronic mild TBI and reconcile the disparity between subjective cognitive complaints and neuropsychological performance, it is critical to understand neural gain modulation in response to changing task demands in this population. In the following series of empirical studies, I directly test the theory that patients with chronic mild TBI have an impaired ability to modulate neural gain, and that this impairment may underlie the self-reported cognitive symptoms in this population. Poor modulation of neural gain may contribute to inefficient cognitive processing that ultimately results in normative behavioral responses but causes patients to report greater cognitive effort as tasks become more difficult. To quantify neural gain modulation, changes in pupil diameter, ERP indices of attentional gain, and event-related spectral perturbations (ERSPs) were measured in individuals with self-reported persistent symptoms following mild TBI while they performed a cued attention task under varying levels of cognitive load. The cue-target combinations in the task were designed to evoke both top-down (e.g., cued) and bottom-up (e.g., stimulus captured) attention; instructions for how to respond to the target were varied to induce three distinct levels of cognitive load. See Appendix for a power analysis for the proposed series of studies.

Study One

The first study of this series measured ERSPs to evaluate how cognitive load affects top-down and bottom-up attentional processing in chronic mild TBI. Accordingly, this study tests the hypothesis that the chronic mild TBI group would exhibit alterations

in ERSPs in response to changes in cognitive load, when compared to uninjured controls. Specifically, we predicted that, while controls would show an effect of load on top-down attentional processing, as reflected in ERSPs, the chronic mild TBI group would not. Each frequency band is functionally relevant for different cognitive processes; this study was partially exploratory because it agnostically examined the effect of cognitive load on all frequencies between 5Hz and 80Hz to gain insight into what specific cognitive processes are adversely affected by maladaptive neural gain modulation in chronic mild TBI.

Study Two

The second study of this series builds upon the first by differentiating specific types of neural gain—i.e., global neural gain and attentional gain—as well as evaluating specific mechanisms of selective attention—i.e., attended vs. unattended stimulus processing. If individuals with chronic symptomatic mild TBI poorly modulate global neural gain as proposed above, this would be reflected by larger pupil diameter during cognitive tasks, particularly those which impose greater cognitive load, and it would be negatively associated with cognitive performance. Additionally, poor modulation of attentional gain would be reflected in group differences in attention-related ERP components. Thus, in this study, we compared baseline pupil diameter, N1 ERP amplitude, and P1 ERP amplitude between groups and evaluated the relationship of these variables with self-reported symptoms and neuropsychological performance. Additionally, the relationship between task performance and global and attentional gain are investigated to test how neural gain modulation is related to behavioral outcomes on the cued attention task.

Study Three

The third and final study of this research program is a methodological investigation of the clinical utility of pupil diameter as an index of impaired neural gain modulation in mild TBI. Changes in pupil diameter in response to cognitive tasks have been reliably and robustly linked to neural gain modulation (Alnaes et al., 2014; Granholm et al., 1996; Rajkowski et al., 1993). However, the state of pupillometry research is lacking in clear guidance for selection of pupillary metrics that are best at identifying cognitive load effects and group differences in cognitive processing. Additionally, although pupillometry is sensitive to neurological dysfunction in many clinical populations, such as schizophrenia and ADHD (Granholm & Verney, 2004; Karatekin, Bingham, & White, 2009; Verney et al., 2004), it has not been used to study cognition in mild TBI. Therefore, to identify which pupillary metrics are most suitable to measure global neural gain modulation in chronic mild TBI samples, this study compares psychometric properties of several commonly used pupillary metrics, including internal consistency, sensitivity to group, cognitive load, and group * cognitive load effects, and replicability of findings. Ultimately, this study is intended to provide meaningful methodological advances to cognitive pupillometry and to further its inclusion in clinical assessments of impaired cognitive processing in a variety of patient populations.

References

- Alexander, M. P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*, 45(7), 1253-1260.
- Alnaes, D., Sneve, M. H., Espeseth, T., Endestad, T., van de Pavert, S. H. P., & Laeng, B. (2014). Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *Journal of vision*, 14(4), 1-1.
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, 28, 403-450.
- Bazarian, J. J., McClung, J., Shah, M. N., Ting Cheng, Y., Flesher, W., & Kraus, J. (2005). Mild traumatic brain injury in the United States, 1998–2000. *Brain Inj*, 19(2), 85-91.
- Beatty, J. (1982). Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychological bulletin*, 91(2), 276.
- Beatty, J., & Lucero-Wagoner, B. (2000). The pupillary system. *Handbook of psychophysiology*, 2, 142-162.
- Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild

traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society*, 11(03), 215-227.

Bernstein, D. M. (2002). Information processing difficulty long after self-reported concussion. *J Int Neuropsychol Soc*, 8(5), 673-682.

Bernstein, D. M. (2002). Information processing difficulty long after self-reported concussion. *Journal of the International Neuropsychological Society*, 8(05), 673-682.

Bigler, E. D. (2003). Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. *Arch Clin Neuropsychol*, 18(6), 595-621; discussion 623-597.

Binder, L. M. (1997). A review of mild head trauma. Part II: Clinical implications. *Journal of clinical and experimental neuropsychology*, 19(3), 432-457.

Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *J Clin Exp Neuropsychol*, 19(3), 421-431. doi:10.1080/01688639708403870

Borg, J., Holm, L., Cassidy, J. D., Peloso, P., Carroll, L., Von Holst, H., & Ericson, K. (2004). Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of rehabilitation medicine*, 36(0), 61-75.

- Cabestrero, R., Crespo, A., & Quirós, P. (2009). Pupillary dilation as an index of task demands. *Perceptual and motor skills*, 109(3), 664-678.
- Carroll, L., Cassidy, J. D., Peloso, P., Borg, J., Von Holst, H., Holm, L., . . . Pépin, M. (2004). Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of rehabilitation medicine*, 36(0), 84-105.
- Cassidy, J. D., Carroll, L., Peloso, P., Borg, J., Von Holst, H., Holm, L., . . . Coronado, V. (2004). Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of rehabilitation medicine*, 36(0), 28-60.
- Chen, J.-K., Johnston, K. M., Collie, A., McCrory, P., & Ptito, A. (2007). A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(11), 1231-1238.
- Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage*, 22(1), 68-82. doi:10.1016/j.neuroimage.2003.12.032
- Doesburg, S. M., Bedo, N., & Ward, L. M. (2016). Top-down alpha oscillatory network interactions during visuospatial attention orienting. *Neuroimage*, 132, 512-519.

- Dupuis, F., Johnston, K. M., Lavoie, M., Lepore, F., & Lassonde, M. (2000). Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport*, 11(18), 4087-4092.
- Egner, T., & Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature neuroscience*, 8(12), 1784.
- Eldar, E., Cohen, J. D., & Niv, Y. (2013). The effects of neural gain on attention and learning. *Nature neuroscience*, 16(8), 1146-1153.
- Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in psychology*, 2, 154.
- Frencham, K. A., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *J Clin Exp Neuropsychol*, 27(3), 334-351.
- Gaetz, M., Goodman, D., & Weinberg, H. (2000). Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj*, 14(12), 1077-1088.
- Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269.

- Giza, C. C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery*, 75(0 4), S24.
- Gosselin, N., Bottari, C., Chen, J.-K., Petrides, M., Tinawi, S., de Guise, E., & Ptito, A. (2011). Electrophysiology and functional MRI in post-acute mild traumatic brain injury. *Journal of neurotrauma*, 28(3), 329-341.
- Gosselin, N., Thériault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery*, 58(6), 1151-1161.
- Granholm, E., Asarnow, R. F., Sarkin, A. J., & Dykes, K. L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology*, 33(4), 457-461.
- Granholm, E., & Verney, S. P. (2004). Pupillary responses and attentional allocation problems on the backward masking task in schizophrenia. *International Journal of Psychophysiology*, 52(1), 37-51.
- Gronwall, D., & Wrightson, P. (1975). Cumulative effect of concussion. *Lancet*, 2(7943), 995-997.
- Hall, R. C., Hall, R. C., & Chapman, M. J. (2005). Definition, diagnosis, and forensic implications of postconcussional syndrome. *Psychosomatics*, 46(3), 195-202.
- Head, J. (1993). Definition of mild traumatic brain.. Injury. *J Head Trauma Rehabil*, 8(3), 86-87.

- Hillyard, S. A., & Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of Sciences*, 95(3), 781-787.
- Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 353(1373), 1257-1270.
- Hovda, D., Prins, M., Becker, D., Lee, S., Bergsneider, M., & Martin, N. (1999). Neurobiology of concussion. *Sports Related Concussion*. St. Louis, Quality Medical Publishing, Inc, 12-51.
- Howells, F. M., Stein, D. J., & Russell, V. A. (2012). Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance. *Metabolic brain disease*, 27(3), 267-274.
- Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Current opinion in psychiatry*, 18(3), 301-317.
- Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. *Cereb Cortex*, 12(8), 877-882.
- Just, M. A., Carpenter, P. A., & Miyake, A. (2003). Neuroindices of cognitive workload: Neuroimaging, pupillometric and event-related potential studies of brain work. *Theoretical Issues in Ergonomics Science*, 4(1-2), 56-88.

- Karatekin, C., Bingham, C., & White, T. (2009). Regulation of cognitive resources during an n-back task in youth-onset psychosis and attention-deficit/hyperactivity disorder (ADHD). *International Journal of Psychophysiology*, 73(3), 294-307.
doi:<http://dx.doi.org/10.1016/j.ijpsycho.2009.05.001>
- Karr, J. E., Areshenkoff, C. N., & Garcia-Barrera, M. A. (2014). The neuropsychological outcomes of concussion: A systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*, 28(3), 321.
- Kim, Y. J., Grabowecky, M., Paller, K. A., Muthu, K., & Suzuki, S. (2007). Attention induces synchronization-based response gain in steady-state visual evoked potentials. *Nature neuroscience*, 10(1), 117.
- King, N. (1997). Mild head injury: neuropathology, sequelae, measurement and recovery. *British Journal of Clinical Psychology*, 36(2), 161-184.
- Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*, 38(3), 557-577.
- Lavie, N. (2010). Attention, distraction, and cognitive control under load. *Current Directions in Psychological Science*, 19(3), 143-148.
- Lavoie, M. E., Dupuis, F., Johnston, K. M., Leclerc, S., & Lassonde, M. (2004). Visual p300 effects beyond symptoms in concussed college athletes. *J Clin Exp Neuropsychol*, 26(1), 55-73.

- Luck, S. J., Heinze, H., Mangun, G., & Hillyard, S. A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. *Electroencephalography and clinical neurophysiology*, 75(6), 528-542.
- McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., . . . Yanofsky, N. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. *Neurology*, 53(6), 1300-1308.
- McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage*, 14(5), 1004-1012.
doi:10.1006/nimg.2001.0899
- McCrea, M., Guskiewicz, K. M., Marshall, S. W., & et al. (2003). Acute effects and recovery time following concussion in collegiate football players: The ncaa concussion study. *JAMA*, 290(19), 2556-2563. doi:10.1001/jama.290.19.2556
- Meltzer, J. A., Zaveri, H. P., Goncharova, I. I., Distasio, M. M., Papademetris, X., Spencer, S. S., . . . Constable, R. T. (2008). Effects of Working Memory Load on Oscillatory Power in Human Intracranial EEG. *Cerebral Cortex*, 18(8), 1843-1855. doi:10.1093/cercor/bhm213

- Michels, L., Bucher, K., Lüchinger, R., Klaver, P., Martin, E., Jeanmonod, D., & Brandeis, D. (2010). Simultaneous EEG-fMRI during a working memory task: modulations in low and high frequency bands. *PloS one*, 5(4), e10298.
- Parasuraman, R. (2000). *The Attentive Brain*: MIT Press.
- Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical neurophysiology*, 118(10), 2128-2148.
- Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biol Psychol*, 41(2), 103-146.
- Powell, J. M., Ferraro, J. V., Dikmen, S. S., Temkin, N. R., & Bell, K. R. (2008). Accuracy of mild traumatic brain injury diagnosis. *Archives of physical medicine and rehabilitation*, 89(8), 1550-1555.
- Prevention, N. C. f. I., & Control. (2003). *Report to Congress on mild traumatic brain injury in the United States: Steps to prevent a serious public health problem*: Centers for Disease Control and Prevention.
- Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1993). *Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention*. Paper presented at the Society for Neuroscience Abstracts.
- Rohling, M. L., Binder, L. M., Demakis, G. J., Larrabee, G. J., Ploetz, D. M., & Langhinrichsen-Rohling, J. (2011). A meta-analysis of neuropsychological outcome after mild traumatic brain injury: Re-analyses and reconsiderations of

- Binder et al.(1997), Frencham et al.(2005), and Pertab et al.(2009). *The Clinical Neuropsychologist*, 25(4), 608-623.
- Ruff, R. M., Camenzuli, L., & Mueller, J. (1996). Miserable minority: Emotional risk factors that influence the outcome of a mild traumatic brain injury. *Brain Inj*, 10(8), 551-566.
- Scheid, R., Preul, C., Gruber, O., Wiggins, C., & Von Cramon, D. Y. (2003). Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3 T. *American Journal of Neuroradiology*, 24(6), 1049-1056.
- Schretlen, D. J., & Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry*, 15(4), 341-349.
- Scolari, M., & Serences, J. T. (2009). Adaptive allocation of attentional gain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(38), 11933-11942. doi:10.1523/JNEUROSCI.5642-08.2009
- Scolari, M., & Serences, J. T. (2009). Adaptive allocation of attentional gain. *Journal of Neuroscience*, 29(38), 11933-11942.
- Segalowitz, S. J., Bernstein, D. M., & Lawson, S. (2001). P300 event-related potential decrements in well-functioning university students with mild head injury. *Brain and Cognition*, 45(3), 342-356.

- Shenton, M., Hamoda, H., Schneiderman, J., Bouix, S., Pasternak, O., Rath, Y., . . . Koerte, I. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging and Behavior*, 6(2), 137-192.
- Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J., . . . van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology*, 53(8), 553-563.
- Sosin, D. M., Snizek, J. E., & Thurman, D. J. (1996). Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj*, 10(1), 47-54.
- Unsworth, N., & Robison, M. K. (2015). Individual differences in the allocation of attention to items in working memory: Evidence from pupillometry. *Psychonomic bulletin & review*, 22(3), 757-765.
- Van Der Meer, E., Beyer, R., Horn, J., Foth, M., Bornemann, B., Ries, J., . . . Wartenburger, I. (2010). Resource allocation and fluid intelligence: Insights from pupillometry. *Psychophysiology*, 47(1), 158-169.
- Verney, S. P., Granholm, E., & Marshall, S. P. (2004). Pupillary responses on the visual backward masking task reflect general cognitive ability. *International Journal of Psychophysiology*, 52(1), 23-36.
- Weinberg, M. G., Hal. (2000). Electrophysiological indices of persistent post-concussion symptoms. *Brain Inj*, 14(9), 815-832.

- Wood, R. (2004). Understanding the 'miserable minority': A diathesis-stress paradigm for post-concussional syndrome. *Brain Inj*, 18(11), 1135-1153.
- Zagha, E., & McCormick, D. A. (2014). Neural control of brain state. *Current opinion in neurobiology*, 29, 178-186.
- Zekveld, A. A., & Kramer, S. E. (2014). Cognitive processing load across a wide range of listening conditions: insights from pupillometry. *Psychophysiology*, 51(3), 277-284.

Chapter Two: Effects of Cognitive Load and Varied Attentional Demands on Spectral Power in Chronic Mild Traumatic Brain Injury

INTRODUCTION

Neural gain is thought to facilitate cognitive functions like visuospatial attention, wherein the processing of incoming sensory information can be either enhanced or reduced in accordance with attentional demands. When neural gain is high, neural networks are more responsive to incoming signals which helps focus attention. When neural gain is low, neural networks are less responsive to incoming signals which reduces the focus of attention (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013). Within the neural gain framework, top-down, endogenous control of attention depends on higher neural gain to focus on task-relevant stimuli to accomplish goal-directed behaviors. In contrast, bottom-up attention captured by salient stimuli in the environment is better served by relatively lower neural gain, facilitating the diffusion of attention (Kim, Grabowecky, Paller, Muthu, & Suzuki, 2007; Scolari & Serences, 2009).

Cognitive Load and Neural Gain

It has been suggested that cognitive load may influence attentional processing through its effects on neural gain (Eldar et al., 2013). Cognitive load has been defined as the cognitive burden imposed by a given task. In one of the earliest experiments measuring cognitive load in healthy participants, cognitive load, modulated by task difficulty, was a significant predictor of performance decrements on a visual detection task (Kahneman, Beatty, & Pollack, 1967). In this experiment, participants' pupil

diameters—a robust index of neural gain—increased linearly with cognitive load.

Similarly, response time for detecting a target stimulus among an array of distractors also increased. This classic study demonstrated that neural gain increases linearly with cognitive load.

However, subsequent research has provided a more nuanced understanding of the effect cognitive load has on visuospatial attention. For example, some research has shown that increased cognitive load impairs attention processing because high load requires additional processing resources which reduces the resources available for attentional processing (Dalton, Santangelo, & Spence, 2009; Lavie, 2005; Lavie & De Fockert, 2005). In contrast, other studies suggest that focal task-engagement is increased under high load, thereby decreasing susceptibility to distracting stimuli (Kim, Kim, & Chun, 2005; SanMiguel, Corral, & Escera, 2008; Sörqvist & Marsh, 2015). In a behavioral study, Hu et al. (2016) reported that high cognitive load only impaired controlled attention, while bottom-up attention was independent of cognitive load. Taken together, these results suggest that only attentional mechanisms that rely upon executive control are negatively affected by limited resources.

The effect of load-dependent neural gain modulation on visuospatial attention is well-documented in cognitively normal individuals, but its contributions to attentional deficits in chronic mild TBI remain to be fully understood. In particular, poor neural gain modulation may underlie the attentional deficits reported in chronic mild TBI. Most patients who sustain a mild TBI fully recover within 3-6 months post-injury; however, an estimated 10-20% experience persistent symptoms, with attentional impairments among

the most cited (Pare, Rabin, Fogel, & Pepin, 2009; Parks et al., 2015; Pontifex, O'Connor, Broglio, & Hillman, 2009; Sterr, Herron, Hayward, & Montaldi, 2006).

Neural Gain in Mild TBI

The etiology of persistent symptoms following mild TBI is unclear, though some research indicates that diffuse axonal damage—the hallmark neuropathology following mild TBI—does not completely resolve for some patients and that frontal networks are particularly vulnerable (Johnson, Stewart, & Smith, 2012; Lipton et al., 2009; Smith, Meaney, & Shull, 2003; Thatcher, Biver, McAlaster, & Salazar, 1998). Prior research suggests that neural gain is modulated by the locus coeruleus in combination with substantial input from frontal networks to adaptively optimize performance under changing cognitive demands (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013). Given that frontal networks are thought to be critical for modulating neural gain to optimize performance, it follows that patients with chronic mild TBI may demonstrate impairments of visuospatial attention because of a diminished capacity for modulating neural gain.

Previous studies have demonstrated that top-down and bottom-up (e.g., endogenous and exogenous) attentional processing are differentially affected by mild TBI (Broglio, Pontifex, O'Connor, & Hillman, 2009; Duncan, Kosmidis, & Mirsky, 2005; Pontifex et al., 2009; van Donkelaar et al., 2005). In an fMRI study of selective attention in acute and sub-acute mild TBI (i.e., days to weeks post-injury) compared to healthy controls, individuals with mild TBI were unable to modulate neural activity in top-down attention networks; in contrast, healthy controls had greater activation for top-down attention compared to bottom-up attention (Mayer et al., 2012). Importantly, these neural

differences were observed in the absence of behavioral performance and neuropsychological differences between groups.

In addition to the differential effects of various attentional demands on neural gain in mild TBI, cognitive load has been shown to affect neural gain in this population. Studies manipulating cognitive load have demonstrated that patients with mild TBI show similar neural activation under lower levels of cognitive load compared to healthy controls, but that activation increases as load increases to moderate levels before reaching asymptote or even declining under the highest levels of cognitive load (Bryer, Medaglia, Rostami, & Hillary, 2013; Chen et al., 2012; McAllister, Sparling, Flashman, Guerin, et al., 2001; McAllister, Sparling, Flashman, & Saykin, 2001). Interestingly, while mild TBI participants in these studies show greater neural activation under moderate levels of cognitive load, performance typically remains undifferentiated between groups at this load level; it is not until high levels of cognitive load when performance deficits typically become evident, coinciding with the plateau or decline in neural activity (McAllister, Sparling, Flashman, Guerin, et al., 2001; McAllister, Sparling, Flashman, & Saykin, 2001). This pattern of neural activation and concomitant performance suggests that individuals with mild TBI may not be able to increase neural gain beyond a certain threshold, resulting in behavioral decrements for highly-demanding tasks.

What remains unknown is how changes in cognitive load and attentional demands interact to affect neural gain. Additionally, studies of mild TBI commonly include patients in either the acute or sub-acute stages; and those that focus exclusively on patients with *chronic* mild TBI often include both symptomatic and asymptomatic patients (Duncan et al., 2011). This heterogeneity of mild TBI samples limits the ability

to adequately characterize the long-term effects of mild TBI. Therefore, in the current study, we tested symptomatic patients with a remote history of mild TBI (i.e., 3 months to 10 years post-injury) and uninjured controls using a cued attention task that independently manipulated cognitive load and attentional demands. In the task, trials varied by cue-target combination to evoke both top-down and bottom-up attention; task instructions varied by block, such that three levels of task difficulty were provided.

Event Related Spectral Perturbations

In accordance with prior studies of cognitive load (Jensen, Gelfand, Kounios, & Lisman, 2002; Jensen & Tesche, 2002; Meltzer et al., 2007; Michels et al., 2010; Onton, Delorme, & Makeig, 2005; Simos, Papanikolaou, Sakkalis, & Micheloyannis, 2002), neural gain was measured using event-related spectral perturbations (ERSPs). ERSPs reflect changes in neural oscillatory activity relative to baseline in response to experimental events; an increase in spectral power (dB) is observed when more neurons become active and/or active neurons increase synchronicity, while a decrease in spectral power is observed when a population of neurons become less active and/or desynchronize. An increase in oscillatory power indicates amplification of neural gain and a decrease in oscillatory power indicates attenuation of neural gain (Zagha & McCormick, 2014).

In visuospatial attention tasks, alpha (8-12Hz) activity is typically suppressed over the visual cortex contralateral to the attended location and enhanced over the ipsilateral visual cortex (Doesburg, Bedo, & Ward, 2016; Foxe & Snyder, 2011). This pattern suggests that alpha oscillations are critical for inhibiting processing of task-irrelevant information. Changes in beta oscillations (14-30Hz) have also been implicated

in attentional processing. Historically, increased beta activity has been associated with top-down maintenance of sensorimotor expectancies that are modulated by contextual information and promotes controlled, inflexible behavioral responses (Engel & Fries, 2010). Recent research has demonstrated that beta synchronization may be related to reactivating task-relevant information under top-down control (Spitzer & Haegens, 2017). Gamma band (30-100Hz) synchronization has also been implicated in supporting selective attention and is thought to be the mechanism by which neural gain is increased for attended stimuli (Doesburg, Roggeveen, Kitajo, & Ward, 2007; Fries, Reynolds, Rorie, & Desimone, 2001; Fründ et al., 2008; Ray, Niebur, Hsiao, Sinai, & Crone, 2008). Increased gamma power has been observed following spatial cues (Fan et al., 2007; Fründ et al., 2008; Ray et al., 2008). Theta, alpha, and gamma power are known to increase linearly with task difficulty and working memory load (Jensen, Gelfand, Kounios, & Lisman, 2002; Jensen & Tesche, 2002; Meltzer et al., 2007; Onton, Delorme, & Makeig, 2005; Simos, Papanikolaou, Sakkalis, & Micheloyannis, 2002); spectral power in these frequency bands are also greater for attended stimuli than unattended stimuli (Fan et al., 2007; Fründ et al., 2008; Klimesch, 1999; Pesonen, Hämäläinen, & Krause, 2007; Ray et al., 2008). Together, evidence suggests that in healthy controls these oscillatory mechanisms are instrumental in facilitating visuospatial attention and are dynamically modulated to optimize performance in response to changing task demands and increased cognitive load.

Event Related Spectral Perturbations in Mild TBI

Alpha power is reduced immediately following mild TBI and this effect persists chronically for many individuals (Arakaki et al., 2018; Guay, De Beaumont, Drisdelle,

Lina, & Jolicoeur, 2018; Slobounov, Sebastianelli, & Hallett, 2012; Yadav & Ciuffreda, 2015). In a study of symptomatic mild TBI patients 1 month to 7 years post- injury, resting state EEG was characterized by a decrease in alpha power (Korn, Golan, Melamed, Pascual-Marqui, & Friedman, 2005). In a more recent study measuring event-related alpha perturbations during a visuospatial attention task, alpha activity was abnormal in chronic mild TBI patients who reported subjective attentional deficits, although it did not correspond to any group differences in task performance (Yadav & Ciuffreda, 2015). In addition to decreased alpha power, additional studies using resting state EEG measurements have shown a decrease in beta power in individuals two to four months following sports-related concussion (Thompson, Sebastianelli, & Slobounov, 2005). In one study of patients with mild to severe TBI eight months or more prior to testing, decreased beta power was associated with performance on an executive attention task for the mild TBI group but not controls (Shah et al., 2017). These results are consistent with known properties of beta—particularly its integration with top-down mechanisms to control behavior and resolve cognitive conflict and to facilitate allocation of sustained attention. Finally, although less is known about gamma activity in mild head injury, gamma power is also reduced following mild head injury. In a study of adolescents with sports-related concussion, gamma power was reduced during a vigilance task compared to uninjured controls (Munia, Haider, Schneider, Romanick, & Fazel-Rezai, 2017). Reduced gamma band has also been reported in patients with diffuse axonal injury—the hallmark characteristic of head injury (Molteni, Bianchi, Butti, Reni, & Zucca, 2008; Slewa-Younan et al., 2002).

Hypothesis

Previous research on changes in neural activity following mild TBI suggests that patients may have an impaired ability to modulate neural gain in response to increased task difficulty (McAllister et al., 2001). Although limited research has specifically investigated this phenomenon in chronic mild TBI, synthesis of the extant literature suggests that persistent cognitive symptoms following mild TBI may be related to the effect of load-dependent neural gain modulation on attentional processes. Our primary hypothesis was neural gain, reflected in fluctuations in ERSP power, associated with top-down attention, would be sensitive to cognitive load among controls, but that load would have no effect on neural gain for either top-down or bottom-up attention within the chronic mild TBI group. Because prior research in both healthy controls and TBI has demonstrated fluctuations in neural gain across a wide range of frequencies in response to cognitive load and attentional demands, we did not make a priori predictions about specific time-frequency bands.

METHODS

Participants

Nineteen participants with chronic mild TBI and 26 uninjured controls were recruited for participation in this study. Participants between 18 and 55 without a history of neurological conditions other than TBI were included. Inclusion in the mild TBI group required that participants acquired a mild traumatic brain injury between 3 months and 10 years prior to testing and endorse persistent neurobehavioral symptoms. Mild TBI was defined as loss of consciousness <30 minutes, post-traumatic amnesia < 24 hours, and/or any alterations of consciousness following injury (Head, 1993). Approval to conduct this

study was obtained from the Uniformed Services University of the Health Sciences Institutional Review Board and all participants provided written informed consent prior to testing.

Procedure

At the start of the testing session, demographic information was obtained using a structured interview and detailed histories of head injuries were obtained from each participant using the OSU-TBI ID (Corrigan & Bogner, 2007). Participants also completed the Neurobehavioral Symptom Inventory, a 22-item (5-point scale) inventory of neurobehavioral symptoms assessing cognitive, affective, and somatosensory symptoms (King et al., 2012). Participants then performed a computerized cued attention task while EEG data were continuously recorded.

Cued Attention Task

Stimuli were controlled and delivered via a desktop computer using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA) and presented on a 24 inch, 1920x1080 resolution LCD monitor. Participants were centered 24 inches in front of the stimulus monitor. Participants completed a target detection task while behavioral responses and EEG data were recorded. In the target detection task (see Figure 1), participants were asked to shift their gaze to the location of a target as quickly as possible after it appears, while simultaneously making a manual response (i.e., button press). Cues were either left- or right-facing white arrows and were presented in the center of the screen over a gray background 200ms prior to target onset. Targets were blue or green circles that appeared either to the left or right of center. Targets and cues remained on

screen together for 1500ms following target onset. Between each trial, a fixation cross was displayed; the duration of the fixation cross was randomly selected between 520 and 1020 seconds. Figure 3 shows a graphical depiction of the task. Cue-target combinations were randomly presented. The cues validly predicted the location of the target for 47% of trials; cues invalidly predicted the target location for 26.5% of trials. Additionally, 26.5% of trials were uncued.

Cognitive load was modulated by varying the instructions for how to manually respond to the targets; there were three conditions with increasing cognitive load. In the low load condition—target detection/simple response time, “SRT”—participants were instructed to press a center button on the response device when the target appears. In the moderate load condition—target discrimination, “0-back”—participants were asked to press a button (above center) if the target was blue and a different button (below center) if the target was green. In the high load condition—“1-back”—participants were asked to determine whether the color of the target (either blue or green) matched or did not match the color of the target on the previous trial. Participants pressed a button (above center) to select a “same” response and a different button (below center) to select a “different” response. Cognitive load conditions varied randomly between blocks (Load: low, moderate, high); cue-target combinations (Cue type: valid, invalid, or uncued) varied randomly within blocks. There was a total of 6 blocks, with two sequential blocks for each load condition and 120 trials per block. Video instructions and 6, 8, or 12 practice trials were provided at the beginning of each load condition, respectively. Participants could replay the instructional video and/or repeat the practice block if needed prior to beginning the experiment.

ERSP Pre-Processing and Measurement

EEG data were recorded using a 64-channel BioSemi ActiveTwo recording system with active, sintered Ag/AgCl electrodes conforming to the standard International 10-20 System of electrode placement. EOG recordings were taken from electrodes placed below and in the outer canthi of the left eye. EEG data were sampled at 256 Hz with a low-pass fifth order sinc filter using ActiView software. Electrode offsets were kept below 25 k Ω . EEG data were processed off-line using Matlab toolboxes EEGLab (Delorme & Makeig, 2004) and ERPlab (Lopez-Calderon & Luck, 2014). Data were bandpass filtered offline between .1 and 125 Hz and referenced to the common average. The data were visually inspected for extreme artifact. Segments of data containing extreme (e.g., $\leq 300\mu\text{V}$ or $\geq 300\mu\text{V}$) artifact were removed and channels containing extreme artifact or flatline were interpolated. Independent component analysis (ICA) was then used to identify and remove ocular artifact. Following ICA correction, the data were segmented into epochs time-locked to target onset from -400ms to 1200ms and baseline corrected using the 400ms pre-target interval. Trials with incorrect or omitted behavioral responses were removed from data prior to averaging. Following exclusion of participants due to poor ERSP data quality, our final sample size was 41, with 18 participants in the chronic mild TBI group and 23 control participants.

A time-frequency analysis was performed using EEGLAB (Delorme & Makeig, 2004) to measure the event-related oscillatory responses related to neural gain modulation during the task. Event-related spectral perturbation (ERSP) was computed in EEGLAB using Morlet wavelets over the target-locked EEG epochs spanning -400 ms to 1000 ms. The wavelet analysis was performed over 38 linearly spaced frequencies

between 5 and 80 Hz. The “cycles” parameter in EEGLAB was set to [2 .5] such that the number of significant wavelet cycles was 2 at 2 Hz and 16 at 85 Hz. All trials were normalized with respect to the baseline (divisive) period of -400 to 0 ms.

Averaged ERSPs were computed separately for each of the 3 (Load) X 3 (Cue) trial types for each participant (see Figure 2). Regions of interest (ROIs) in the ERSP data were then identified using a massive univariate analysis to test the main effects and interaction between the Load and Cue factors separately for each time and frequency in the 200 (times) by 38 (frequencies) in the time-frequency plane. The resulting family of p values were then submitted to the Benjamini, Krieger, and Yekutieli (2006) procedure for controlling the false discovery rate (FDR; see Hemmelmann, Horn, Süsse, Vollandt, and Weiss, 2005 for a comparison of error control methods in multiple comparisons of high dimensional EEG data). Only those points at which the p value exceeded a critical value defined by an FDR of $q < .0019$ were considered (see Figure 3). The topographical distribution of the statistical effects at each ROI in the time-frequency plane was then summarized by plotting the mean of the p -values over times and frequencies separately for each channel, revealing the optimal location(s) for measurement of the ERSP responses (see Figure 4). Based on inspection of the results of the massive univariate analysis and the topographical distributions of experimental effects, we identified two ERSP measures to characterize the main effects of Load and four ERSP measures to characterize the main effects of Cue. There were no significant interactions between Load and Cue in the massive univariate analysis. For the main effects of Load, we measured (1) mid-latency Beta between 200 ms and 475 ms over the 10-25 Hz frequency range at channels O1, Oz, and O2 and (2) long-latency Beta between 550ms and 1000ms

over the 13-40Hz frequency range at channels FCz, Cz, and CPz. For the main effects of Cue, we measured (1) short-latency Gamma between 50ms and 200ms over the 30-75Hz frequency range at channels CPz, Pz, and POz, (2) short-latency Beta between 0ms and 350ms over the 13-25Hz frequency range at channels O1, PO7, O2, and PO8, (3) mid-latency Theta between 200ms and 600ms over the 5-9Hz frequency range at channels O1, PO7, P7, O2, PO8, and P8, and (4) long-latency Beta between 550ms and 850ms over the 13-25Hz frequency range at channels O2, PO8, and P8. By focusing our analysis on those ROIs in the ERSP that are related the effects of cognitive load and attentional demands on neural gain across all participants in the present task, this analytic strategy assures that any conclusions about potential differences between groups can be confidently related to the underlying theoretical cognitive framework that served as the impetus for this study's design.

Statistical Analyses

Correct manual response times on the cued attention task were averaged over trials for each Load*Cue condition. Average response times were submitted to 2 (Group: controls/mild TBI) X 3 (Load: low/moderate/high) X 3 (Cue: valid/invalid/uncued) repeated measures ANOVAs. All ERSP metrics identified in the procedure described above were individually submitted to 2 (Group) X 3 (Load) X 3 (Cue) repeated measures ANOVAs with Greenhouse-Geisser sphericity corrections where appropriate. Significant effects were further explored using pairwise comparisons and simple effects analyses.

RESULTS

Participant Characteristics

Group demographics and injury characteristics are provided in Table 1. There were no group differences in age, education, or estimated verbal IQ, $p > .05$. Consistent with our inclusion criteria requiring persistent symptoms in the chronic mild TBI group, this group endorsed significantly greater neurobehavioral symptoms than controls, $p < .001$.

Task Performance

An interaction between Load and Cue was observed in response time, $F(3.124, 121.821) = 3.999$, $p = .009$, $\eta_p^2 = .093$. Simple effects analyses revealed that valid and invalid cues differed significantly from each other in the low, $p < .001$, and moderate load conditions, $p < .001$, but not in the high load condition, $p = .256$. A main effect of Load, $F(1.505, 58.690) = 78.449$, $p < .001$, $\eta_p^2 = .668$, revealed that response times increased linearly with load, with significant differences between all load conditions $p < .001$. Similarly, a main effect of Cue, $F(2,78) = 34.114$, $p < .001$, $\eta_p^2 = .467$, revealed that valid cues evoked the fastest response times, followed by invalid trials, and then uncued trials. All pairwise comparisons were significant, $p < .027$.

An effect of load on accuracy was observed, $F(2,74) = 62.610$, $p < .001$, $\eta_p^2 = .629$. Pairwise comparisons revealed that all load trials differed significantly from each other $p < .01$ (for all), with greatest accuracy during low load conditions ($M = 98.7\%$, $SE = .40$), followed by moderate load ($M = 97.2\%$, $SE = .60$), and high load conditions ($M = 84.9\%$, $SE = 1.70\%$). No group effect or interactions with group were demonstrated for performance accuracy.

Subjective Effort

Subjective effort ratings during the cued attention task differed by load, $F(2,74)=4.703$, $p = .012$, $\eta_p^2 = .113$. Pairwise comparisons revealed that the high load condition ($M = 4.56$, $SE = .41$) was rated as significantly more effortful than the low load condition ($M = 5.05$, $SE = .38$), $p = .008$, and marginally more effortful than the moderate load condition ($M = .5.78$, $SE = .37$), $p = .066$. The omnibus ANOVA did not reveal a group difference, $p > .1$, or a group * load interaction, $p > .1$. However, a post-hoc comparison of load revealed that the chronic mild TBI group ($M = 5.78$, $SE = .56$) rated the moderate load condition as more effortful than controls ($M = .4.32$, $SE = .52$), $p = .06$.

Load-Based Metrics

Mid-Latency Beta

The analysis revealed an effect of Load on mid-latency beta, $F(2,78) = 22.860$, $\eta_p^2 = .370$, wherein power was reduced significantly more in the moderate, $p < .001$, and high load conditions, $p < .001$, relative to the low load condition. No differences in mid-latency beta power were detected between moderate and high load, $p = .123$. Descriptive data are provided in Table 2. A main effect of cue was also observed in the omnibus test, $F(2,78) = 15.964$, $p < .001$, $\eta_p^2 = .290$; however, an interaction between Group and Cue, $F(2,78) = 3.891$, $p = .025$, $\eta_p^2 = .091$, suggests that neural gain modulation is not comparable between groups. Simple effects analyses revealed that mid-latency beta power was significantly different between all cue types in the group of control participants, such that valid cues evoked the largest reduction in beta, significantly less reduction following invalid cues, and the least following uncued trials. In contrast, none

of the simple effect comparisons between cues were significant within the mild TBI group, $p > .8$. This interaction is depicted in Figure 5a.

Long-Latency Beta

A significant Load effect on long-latency beta, $F(2,78) = 18.193$, $p < .001$, $\eta_p^2 = .318$, showed that power was significantly reduced more in the high load condition than low, $p < .001$, and moderate load conditions, $p < .001$. The difference between low and moderate load long-latency beta was non-significant, $p = .179$. Descriptive data are provided in Table 2. An effect of Cue was also observed, $F(1.375,61.488) = 3.547$, $p = .045$, $\eta_p^2 = .083$. This effect was driven by a significant difference in long-latency beta power between valid and uncued trials, $p = .001$. No other cue type comparisons were significant, $p > .1$. Descriptive data are provided in Table 2.

Cue-Based Metrics

Short-Latency Gamma

An effect of Cue on short-latency gamma was revealed, $F(1.557,60.737) = 14.656$, $p < .001$, $\eta_p^2 = .273$; however, this effect varied by group, as demonstrated by an interaction between group and cue, $F(1.557,60.737) = 3.789$, $p = .038$, $\eta_p^2 = .089$. Simple effects of cue within controls showed that gamma power was significantly greater for valid cues than invalid cues, $p < .001$, and uncued trials, $p < .001$, but that there were no effects of Cue in the mild TBI group, $p > .07$. This interaction is depicted in Figure 5b.

Short-Latency Beta

A main effect of Load on short-latency beta was observed, $F(2,78) = 11.225$, $p < .001$, $\eta_p^2 = .223$. Beta power was significantly lower in the high load condition compared to low, $p < .001$, and moderate load conditions, $p = .018$. Differences were also detected between low and moderate load conditions, $p = .043$. Descriptive data are provided in Table 2. A main effect of Cue was also demonstrated, $F(1.705,66.481) = 45.267$, $p < .001$, $\eta_p^2 = .537$. Beta power was significantly less reduced during uncued trials compared to valid, $p < .001$, and invalid trials, $p < .001$. Descriptive data are provided in Table 2.

Mid-Latency Theta

Load significantly influenced mid-latency theta, $F(2,78) = 6.885$, $p = .002$, $\eta_p^2 = .150$. A significant difference revealed that theta was reduced more in the high load condition relative to the low load condition, $p = .001$. Theta during the moderate load condition was also significantly more reduced than in the low load condition, $p = .023$, but did not differ from the high load condition, $p = .192$. Descriptive data are provided in Table 2. An effect of Cue was observed, $F(2, 78) = 36.022$, $p < .001$, $\eta_p^2 = .480$. Planned comparisons revealed that the difference was driven by significantly larger theta power for uncued trials than valid, $p < .001$, and invalid trials, $p < .001$. Valid and invalid trials did not differ significantly, $p = .350$. Descriptive data are provided in Table 2.

Long-Latency Beta

Results demonstrated a Load effect on long-latency beta, $F(2,78) = 11.666$, $p < .001$, $\eta_p^2 = .230$. Long-latency beta power was significantly reduced in the high load condition relative to the low, $p < .001$, and moderate, $p < .001$, load conditions. The low

and moderate load conditions did not differ significantly, $p = .268$. Descriptive data are provided in Table 2. A Cue effect was also revealed, $F(2,78) = 10.917$, $p < .001$, $\eta_p^2 = .219$. Power was less reduced for valid trials than for invalid, $p = .002$, and uncued trials, $p < .001$. No significant differences between long-latency beta power was detected between invalid and uncued trials, $p = .270$. Descriptive data are provided in Table 2.

DISCUSSION

Results indicate the presence of poor modulation of attentional processing in chronic mild TBI, as indexed by differences in event-related spectral perturbations. However, this deficit did not interact with changes in cognitive load, as was previously reported. It was predicted that only healthy controls, and not the chronic mild TBI group, would modulate neural gain in response to cognitive load, with differential effects of cognitive load on top-down and bottom-up attention. We found no significant three-way interactions between cognitive load, cue, and group. The effect of cognitive load on ERSP values was comparable for all three cue types in both groups, suggesting that cognitive load did not differentially affect either top-down or bottom-up attentional processes in either group. This result provides general support for the theory that greater cognitive load exhausts resources in a limited capacity system and thereby reduces resources available for top-down attentional processing (Dalton, Santangelo, & Spence, 2009; Lavie, 2005; Lavie & De Fockert, 2005). On one hand, response time differences between top-down and bottom-up attention trials were non-significant under the high load condition. This suggests that high cognitive load negatively impacted top-down attentional performance. On the other hand, we did not find neural evidence to explain this behavioral effect. ERSPs did not provide evidence that higher cognitive load affected

top-down attentional processing any differently than for bottom-up attentional process. Although this limited capacity theory can be reasonably extended to chronic mild TBI, the effect of cognitive load on top-down attention did not differ between the two groups.

Effects of Attentional Demands

Although group differences were not observed in cognitive load effects, attentional demands modulated neural gain for several frequency bands, evidenced by effects of cue on ERSP power. These effects also differed by group for some ERSP metrics. For instance, gamma power following target onset was not modulated by the chronic mild TBI group in response to varied attentional demands, but controls evidenced greater gamma power increase for valid trials than invalid or uncued trials. In addition to gamma modulation, mid-latency beta was modulated in response to cue type in controls but not in the chronic mild TBI group. In controls, the reduction in beta power was greatest for valid trials and minimal for uncued trials. The pattern of results from these interactions suggest that controls increase neural gain more for valid trials than for invalid or uncued trials. The invalid and uncued trials share a common characteristic: to successfully perform the task on these trials, attention should be less focused and more broadly distributed to allow for processing of the target stimuli that appeared in an unpredicted location. Therefore, we propose that the reduced attenuation of beta activity reflects a diffusion of attention that occurs when one must orient to a target that appears in an unexpected location. Diffusion of attention is consistent with the concept of an exploratory control state wherein disengaging attention from specific features in the environment permits processing of other features in the environment (Aston-Jones & Cohen, 2005; Jepma & Nieuwenhuis, 2011). According to the adaptive gain theory

(Aston-Jones & Cohen, 2005), frontal networks facilitate the adjustment of neural gain to optimally increase or decrease attentional focus on stimuli in the environment. Our findings that the chronic mild TBI group were unable to differentially modulate beta or short latency gamma in response to the varied cue-target combinations may indicate a disrupted ability to adaptively modulate the focus of their attention in response to changing attentional demands.

Neural gain of short latency beta and mid latency theta was enhanced in response to top-down attentional demands. The decrease in power in these frequency bands was greater for cued trials than for uncued trials, indicating that top-down attention was associated with a larger reduction in neural sensitivity to incoming stimuli. These effects indicate that top-down (i.e., both valid and invalid cues) and bottom-up attentional demands produced distinct changes in neural gain in the beta and theta frequency bands. These results are consistent with known properties of short latency beta and theta—particularly their integration with top-down mechanisms to control behavior (Engle & Fries, 2010; Klimesch, 1999; Nigbur, Ivanova, & Stürmer, 2011; Spitzer & Haegens, 2017). Curiously, long latency beta showed a different effect than described above: the reduction in oscillatory power was greatest for valid trials than invalid or uncued trials. Our results provide support for the temporal specificity of beta activity (van Ede, de Lange, Jensen, & Maris, 2011), whereby earlier beta activity regulates processing of cueing information and later beta activity regulates the diffusion of attention as necessitated by inaccuracy (i.e., invalid trials) or absence (i.e., uncued trials) of spatial cueing.

Effects of Cognitive Load

In contrast, the load effects observed across groups in our data suggest that the chronic mild TBI group, just like healthy controls, was modulating neural gain in response to changes in cognitive load. Several of the ERSP metrics were sensitive to manipulations of cognitive load, including short, mid, and long latency beta, and mid latency theta. Attenuation of neural gain in the theta frequency band was greater under moderate and high cognitive load than under low cognitive load. A similar trend was observed in beta metrics. Collectively, these results suggest that more demanding tasks reduce activity in the theta and beta frequency ranges. Recent research has demonstrated that increases in beta and theta power are functionally relevant to top-down, controlled cognition (Nigbur et al., 2011; Spitzer & Haegens, 2017). Accordingly, these results support previous accounts of cognitive load that additional processing needed for highly demanding tasks reduces the amount of neural resources available for attentional processing (Dalton, Santangelo, & Spence, 2009; Lavie, 2005; Lavie & De Fockert, 2005). However, previous research suggests that the effect of cognitive load on attention is specific to top-down attention; our data suggest that top-down and bottom-up attention are equally affected by the reduction of cognitive resources imposed by demanding tasks. This pattern is consistent with results from a related study conducted our lab (Ettenhofer, Hershaw, Engle, & Hungerford, 2018) that demonstrated the effect of cognitive load on saccadic response time did not differentially affect response times for cued or uncued trials.

We did not find load or cue differences at any time point in the alpha frequency band (8 – 13Hz). Prior research has suggested that alpha is independently sensitive to both mild TBI and cognitive load, so the absence of any effect on alpha oscillations is

somewhat unexpected. This may be due to our data-driven channel selection, which included channels from both hemispheres. By averaging over both contralateral and ipsilateral sites, we may have occluded any potential effects of cognitive load on alpha power. Nevertheless, we also did not observe any significant group differences. However, the absence of a significant group difference is not evidence that alpha activity is unaffected in the chronic stage of mild TBI. Given that some studies have found differences in alpha power in chronic mild TBI (Arakaki et al., 2018; 2018; Guay et al., 2018; 2018; Slobounov et al., 2012; 2012; Yadav & Ciuffreda, 2015; 2015) and that our methods did not permit evaluation of lateralization differences, more research is needed to understand the long-term effects of mild TBI on alpha activity.

Conclusion

Contrary to our expectations, both top-down and bottom-up attention were similarly affected by cognitive load in chronic mild TBI and healthy controls; however, our results do provide important insight into the long-term effects of mild TBI on attention. Controls were able to modulate neural gain in response to changing attentional demands, whereas the chronic mild TBI group was not. Regardless of whether the target appeared in the expected location, unexpected location, or appeared without prior expectation, the chronic mild TBI group processed the stimuli the same way. It is important to note that the absence of impaired manual performance on the task precludes any judgment that these neural differences are *dysfunctional*. However, it is evident that the attentional processing of visuospatial stimuli differs between the two groups and that mild TBI can result in long-term neurological differences. Future studies are warranted to

further investigate the relationships between oculomotor control and attentional gain modulation in this population.

References

- Arakaki X, Shoga M, Li L, Zouridakis G, Tran T, et al. 2018. Alpha desynchronization/synchronization during working memory testing is compromised in acute mild traumatic brain injury (mTBI). *PloS one* 13:e0188101
- Doesburg SM, Bedo N, Ward LM. 2016. Top-down alpha oscillatory network interactions during visuospatial attention orienting. *Neuroimage* 132:512-9
- Doesburg SM, Roggeveen AB, Kitajo K, Ward LM. 2007. Large-scale gamma-band phase synchronization and selective attention. *Cerebral cortex* 18:386-96
- Engel AK, Fries P. 2010. Beta-band oscillations—signalling the status quo? *Current opinion in neurobiology* 20:156-65
- Fan J, Byrne J, Worden MS, Guise KG, McCandliss BD, et al. 2007. The Relation of Brain Oscillations to Attentional Networks. *The Journal of Neuroscience* 27:6197-206
- Foxe JJ, Snyder AC. 2011. The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in psychology* 2:154
- Fries P, Reynolds JH, Rorie AE, Desimone R. 2001. Modulation of Oscillatory Neuronal Synchronization by Selective Visual Attention. *Science* 291:1560
- Fründ I, Schadow J, Busch NA, Naue N, Körner U, Herrmann CS. 2008. Anticipation of natural stimuli modulates EEG dynamics: physiology and simulation. *Cognitive Neurodynamics* 2:89-100

- Guay S, De Beaumont L, Drisdelle BL, Lina J-M, Jolicoeur P. 2018. Electrophysiological impact of multiple concussions in asymptomatic athletes: a re-analysis based on alpha activity during a visual-spatial attention task. *Neuropsychologia* 108:42-9
- Hemmelmann, C., Horn, M., Süsse, T., Vollandt, R., & Weiss, S. (2005). New concepts of multiple tests and their use for evaluating high-dimensional EEG data. *Journal of neuroscience methods*, 142(2), 209-217.
- Jensen O, Gelfand J, Kounios J, Lisman JE. 2002. Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral cortex* 12:877-82
- Jensen O, Tesche CD. 2002. Frontal theta activity in humans increases with memory load in a working memory task. *European journal of Neuroscience* 15:1395-9
- Klimesch W. 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research Reviews* 29:169-95
- Korn A, Golan H, Melamed I, Pascual-Marqui R, Friedman A. 2005. Focal cortical dysfunction and blood–brain barrier disruption in patients with postconcussion syndrome. *Journal of Clinical Neurophysiology* 22:1-9
- Meltzer JA, Zaveri HP, Goncharova II, Distasio MM, Papademetris X, et al. 2007. Effects of working memory load on oscillatory power in human intracranial EEG. *Cerebral Cortex* 18:1843-55

- Molteni E, Bianchi AM, Butti M, Reni G, Zucca C. 2008. Combined behavioral and EEG power analysis in DAI improve accuracy in the assessment of sustained attention deficit. *Annals of biomedical engineering* 36:1216
- Munia TT, Haider A, Schneider C, Romanick M, Fazel-Rezai R. 2017. A Novel EEG Based Spectral Analysis of Persistent Brain Function Alteration in Athletes with Concussion History. *Scientific reports* 7:17221
- Onton J, Delorme A, Makeig S. 2005. Frontal midline EEG dynamics during working memory. *Neuroimage* 27:341-56
- Pesonen M, Hämäläinen H, Krause CM. 2007. Brain oscillatory 4–30 Hz responses during a visual n-back memory task with varying memory load. *Brain research* 1138:171-7
- Ray S, Niebur E, Hsiao SS, Sinai A, Crone NE. 2008. High-frequency gamma activity (80–150 Hz) is increased in human cortex during selective attention. *Clinical Neurophysiology* 119:116-33
- Shah SA, Goldin Y, Conte MM, Goldfine AM, Mohamadpour M, et al. 2017. Executive attention deficits after traumatic brain injury reflect impaired recruitment of resources. *Neuroimage: clinical* 14:233-41
- Simos PG, Papanikolaou E, Sakkalis E, Micheloyannis S. 2002. Modulation of gamma-band spectral power by cognitive task complexity. *Brain topography* 14:191

- Slewa-Younan S, Green AM, Baguley IJ, Felmingham KL, Haig AR, Gordon E. 2002. Is 'gamma'(40 Hz) synchronous activity disturbed in patients with traumatic brain injury? *Clinical neurophysiology* 113:1640-6
- Slobounov S, Sebastianelli W, Hallett M. 2012. Residual brain dysfunction observed one year post-mild traumatic brain injury: combined EEG and balance study. *Clinical Neurophysiology* 123:1755-61
- Spitzer B, Haegens S. 2017. Beyond the status Quo: a role for beta oscillations in endogenous content (Re-) activation. *eneuro:ENEURO*. 0170-17.2017
- Thompson J, Sebastianelli W, Slobounov S. 2005. EEG and postural correlates of mild traumatic brain injury in athletes. *Neuroscience Letters* 377:158-63
- Yadav NK, Ciuffreda KJ. 2015. Objective assessment of visual attention in mild traumatic brain injury (mTBI) using visual-evoked potentials (VEP). *Brain injury* 29:352-65
- Zagha, E., & McCormick, D. A. (2014). Neural control of brain state. *Current opinion in neurobiology*, 29, 178-186.

Table 2.1. Participant Demographics and Injury Characteristics

	Uninjured Controls	Chronic mTBI	<i>p</i> ^a
<i>n</i>	23	18	--
Female, # (%)	17 (73.9%)	9 (50.0%)	.12
Race/Ethnicity			.13
Black, # (%)	9 (39.1%)	2 (11.1%)	
White, # (%)	11 (47.8%)	11 (61.1%)	
Hispanic / Latino, # (%)	0 (0.0%)	2 (11.1%)	
Asian, # (%)	2 (8.7%)	3 (16.7%)	
Other, # (%)	1 (4.3%)	0 (0.0%)	
Age in years, M (<i>SD</i>)	33.30 (9.76)	36.38 (10.58)	.34
Years education, M (<i>SD</i>)	16.85 (2.04)	15.39 (3.82)	.12
Estimated premorbid IQ, M (<i>SD</i>)	107.48 (11.09)	108.11 (9.96)	.85
Months Since Injury, M (<i>SD</i>)	--	37.94 (31.35)	
NSI total score, M (<i>SD</i>)	8.39 (10.43)	30.50 (13.87)	< .001**

Note. ^a *p*-value associated with independent samples *t*-test or chi-square test, where appropriate. **p* < .05; ****p* < .01.

Table 2.2. Descriptive Data for Significant Main Effects on Power (dB), M(SE)

	Load Effects		
	<u>Low</u>	<u>Moderate</u>	<u>High</u>
Mid-latency Beta	-.712 (.201)	-1.194 (.172)	-1.364 (.211)
Long-latency Beta ^L	-.373 (.120)	-.523 (.107)	-1.123 (.140)
Short-latency Beta	-.487 (.125)	-.635 (.109)	-.843 (.128)
Mid-latency Theta	-.646 (.239)	-.948 (.232)	-1.136 (.258)
Long-latency Beta ^C	-.844 (.184)	-.986 (.197)	-1.477 (.211)
	Cue Effects		
	<u>Valid</u>	<u>Invalid</u>	<u>Uncued</u>
Long-latency Beta ^L	-.559 (.120)	-.692 (.102)	-.769 (.098)
Short-latency Beta	-.846 (.127)	-.889 (.133)	-.231 (.102)
Mid-latency Theta	-1.231 (.223)	-1.140 (.241)	-.359 (.253)
Long-latency Beta ^C	-.871 (.191)	-1.172 (.197)	-1.263 (.175)

Note. All units are dB; ^L indicates ROI identified by Load effects; ^C indicates ROI identified by Cue effects

Figure 2.1: Task Schematic. Cue-target combination varied randomly within blocks;
Load varied randomly between blocks. Response to target varied by Load condition.

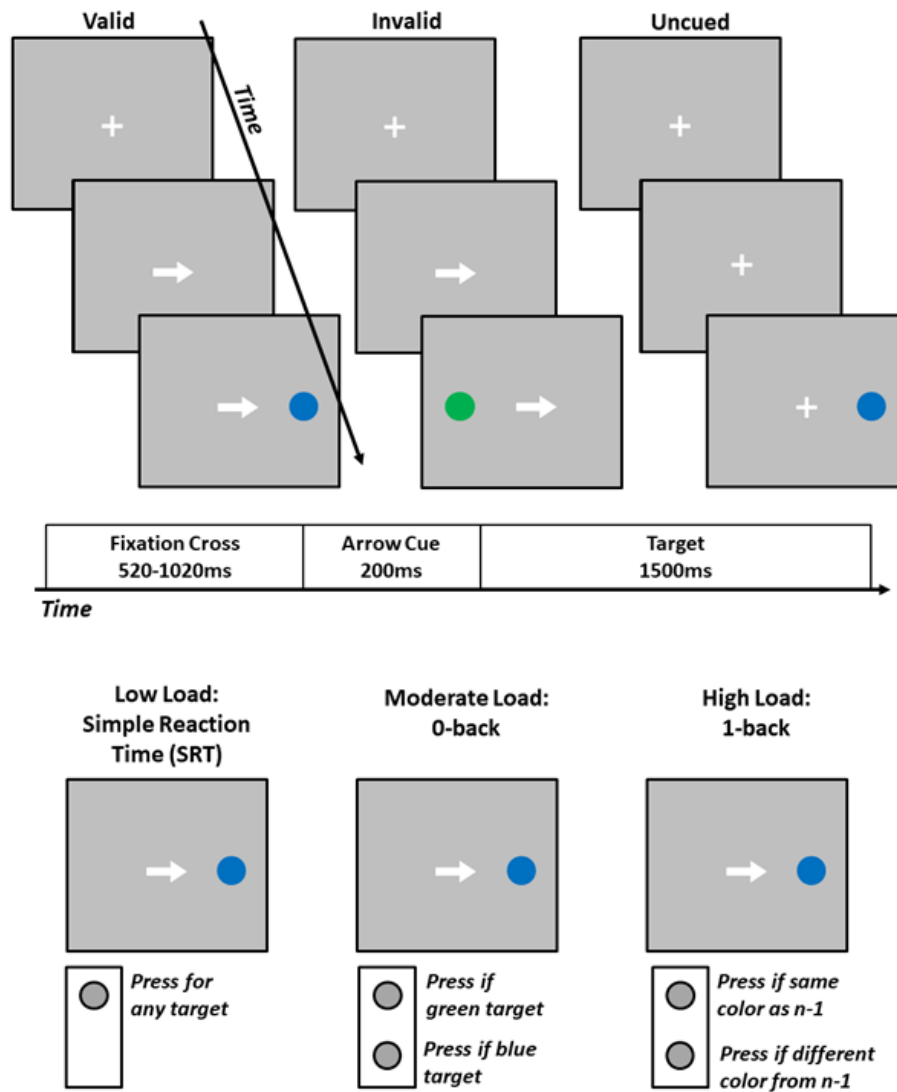


Figure 2.2: ERSPs. Grand average target-locked ERSP for a subset of midline and lateral channels.

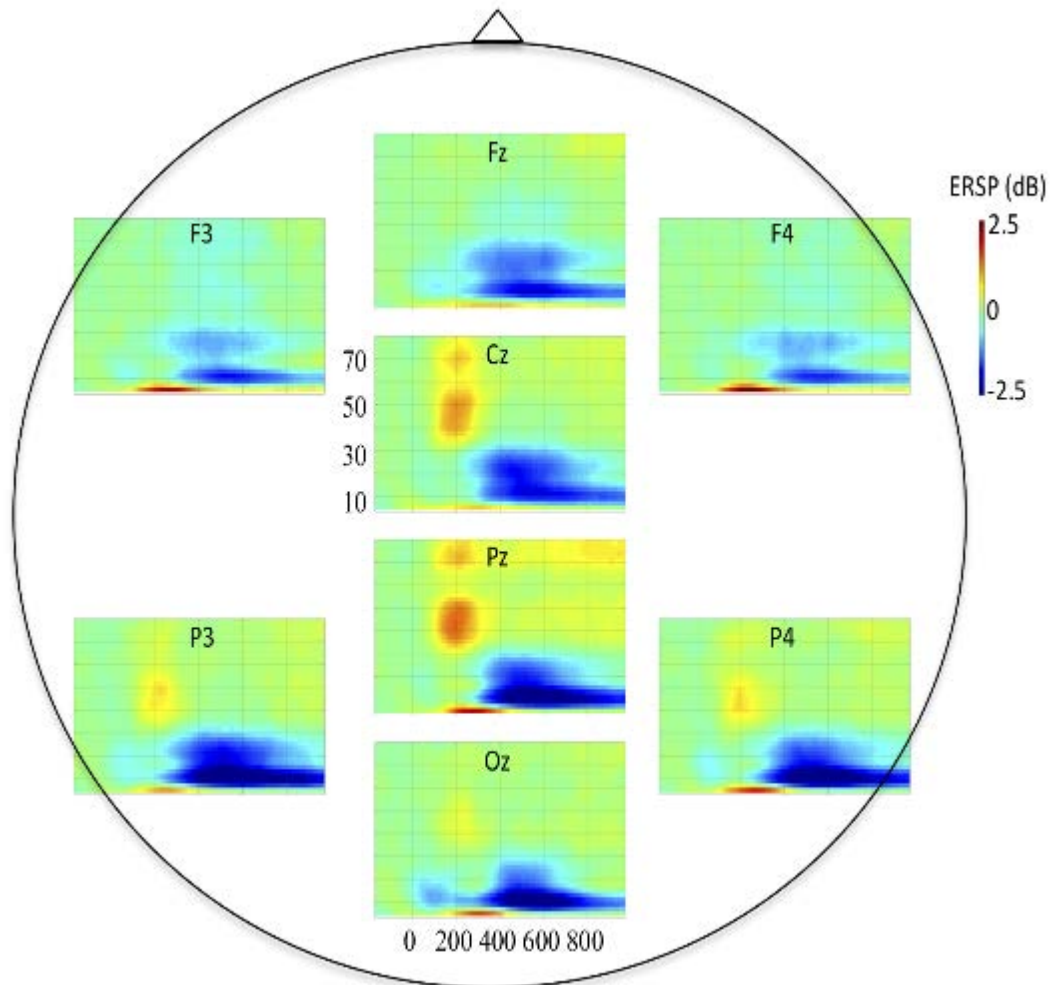


Figure 2.3: Probability Maps. p -values associated with the massive univariate time-frequency analysis for a selection of midline and lateral channels. Maps are masked for statistical significance using an FDR-corrected p -value of 0.0019.

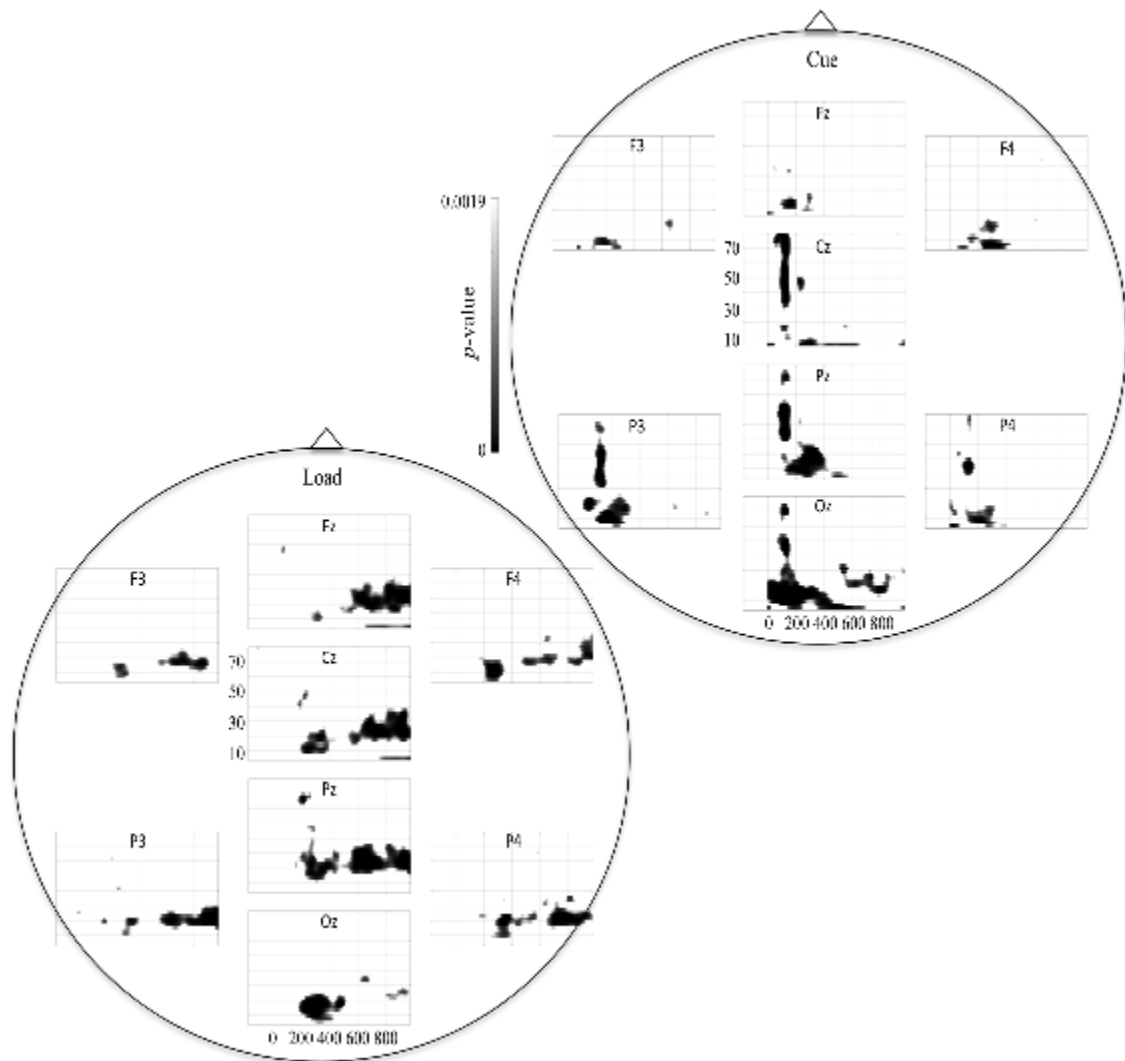


Figure 2.4: Topographical Plots. Topographical distributions of the average p-values within each of the time-frequency ROIs defined.

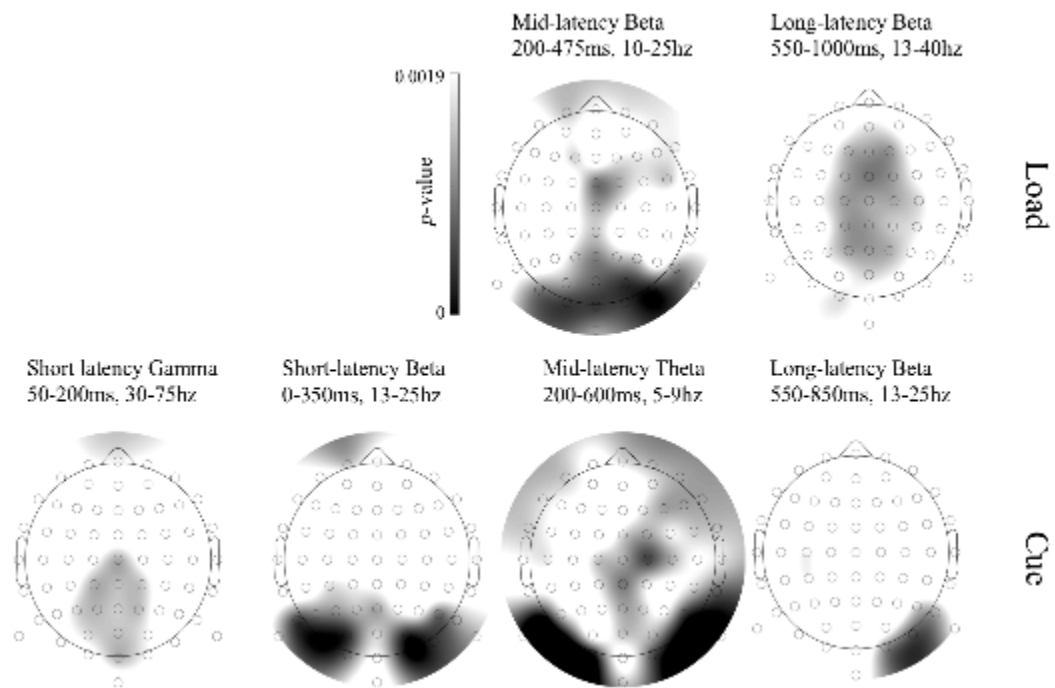
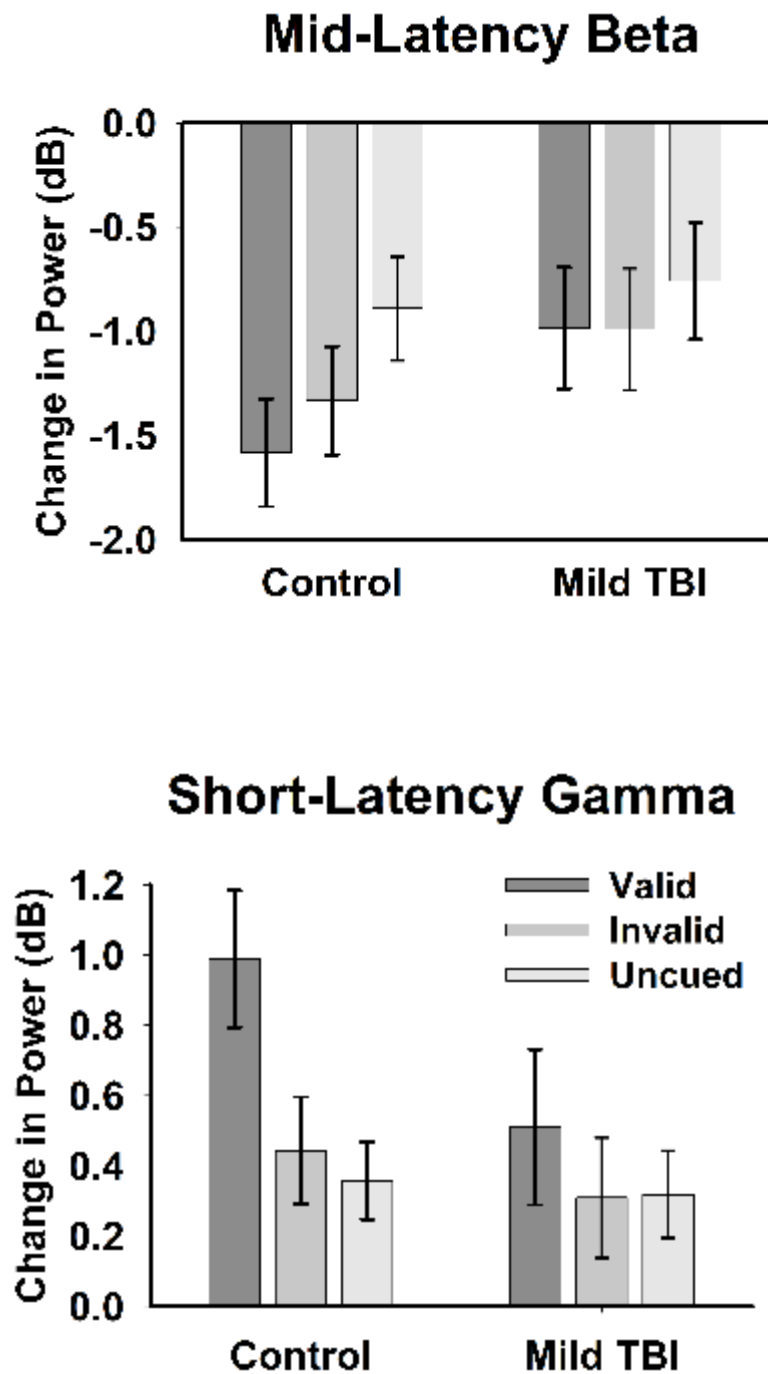


Figure 2.5: Group * Cue Interactions. The interaction between group and cue type on a) mid-latency beta and b) short-latency gamma.



CHAPTER 3: Attentional Gain Modulation in Chronic Mild Traumatic Brain Injury

INTRODUCTION

Difficulties in attention and other cognitive processes are commonly reported following mild traumatic brain injury (mTBI; Pare, Rabin, Fogel, & Pepin, 2009; Parks et al., 2015; Pontifex, O'Connor, Broglio, & Hillman, 2009; Sterr, Herron, Hayward, & Montaldi, 2006). For a minority of individuals who sustain mTBI, these symptoms persist beyond the typical three-month recovery period (Alexander, 1995; Bigler, 2003; Wood, 2004; Ruff, Camenzuli, & Mueller, 1996). Although many individuals reporting chronic cognitive difficulty perform within normal limits on neuropsychological assessments (Cooper, 2018; French, Lange, & Brickell, 2014; Spencer, Drag, Walker, & Bieliauskas, 2010), several neuroimaging and psychophysiological studies of chronic mTBI have identified alterations in attentional processing in the absence of observable cognitive deficits (Broglio, Pontifex, O'Connor, & Hillman, 2009; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; McAllister, Sparling, Flashman, Guerin, et al., 2001; Potter, Jory, Bassett, Barrett, & Mychalkiw, 2002; Slobounov et al., 2009). Additional information about the nature of TBI-related attentional changes could be instrumental in the development of improved methods for assessment and treatment of chronic mTBI.

Attentional Gain

Effective attentional processing is critically dependent on the ability to selectively filter stimuli that require further processing from those that do not (Desimone & Duncan,

1995; Duncan, 1998; Kastner & Pinsk, 2004; Theeuwes, 2010). This filtering process is thought to rely upon modulation of attentional gain (Scolari & Serences, 2009).

Attentional gain amplifies neural excitation to attended stimuli as well as neural inhibition to unattended stimuli and is commonly measured via attention-related event-related potentials (ERPs; Hillyard, Vogel, & Luck, 1998). This process increases the signal-to-noise ratio of the attended stimulus, sharpening the focus of attention (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010). In healthy individuals, attentional gain is adaptively modulated by executive control networks to optimize performance under conditions of changing task demands (Egner & Hirsch, 2005; Hillyard et al., 1998; Lavie, 2010; Scolari & Serences, 2009).

To date, few studies have examined the modulation of attentional processing in response to changing task demands in individuals with mild TBI. In one fMRI study, symptomatic mTBI volunteers at least 6 months post-injury were randomly assigned to receive a goal-directed attention regulation intervention or an educational (control) activity (Chen et al., 2011). Volunteers in the intervention group demonstrated improved attentional performance and greater neural activation to goal-relevant visual stimuli compared to goal-irrelevant visual stimuli. These results suggest that improved attention is related to increased neural gain, specifically increased signal-to-noise ratio, in chronic mTBI. However, this study was unable to discern whether this sharpening of attentional processing for goal-relevant stimuli relative to goal-irrelevant stimuli was due to increased sensitivity to task-relevant stimuli or reduced sensitivity to task-irrelevant stimuli (Chen et al., 2011).

The neural responses to attended and unattended visual stimuli can be dissociated by measuring the amplitude of the P1 and N1 components of the ERP during attention tasks, including cued attention tasks (Hillyard & Anllo-Vento, 1998). The amplitudes of these components are typically enhanced over the hemisphere contralateral to the spatial location where attention is directed. This pattern indicates that visuospatial attention is influenced by modulations in attentional gain to increase neural responsivity to incoming, task-relevant sensory information. Relative to attended locations, P1 amplitude is reduced for stimuli in unattended locations, suggesting that the modulatory effects of attentional gain act primarily on inhibition of sensory processing in the unattended location. In contrast, N1 is enhanced for stimuli at attended locations relative to unattended locations, indicating that the modulatory effects of attentional gain act primarily on enhancement of sensory processing in attended locations (Hillyard & Anllo-Vento, 1998; Mangun, 1995; Slagter, Prinssen, Reteig, & Mazaheri, 2016).

Individuals with mTBI often exhibit reduced N1 amplitude, even when behavioral performance is similar to uninjured controls (Gosselin, Thériault, Leclerc, Montplaisir, & Lassonde, 2006; Polo, Newton, Rogers, Escera, & Butler, 2002). In a study using a modified auditory oddball task, in comparison to uninjured controls, symptomatic and asymptomatic participants with recent concussions (average time since injury = 10 weeks) exhibited reduced N1 amplitude over the hemisphere contralateral to where their attention was directed (Gosselin et al., 2006). However, there were no group differences in N1 amplitude over the ipsilateral hemisphere. These differences in early attention processing were evident despite no performance differences on the oddball task or on a battery of neuropsychological tests. In a study of symptomatic TBI volunteers at least 12

months post-injury, a negative peak at a latency and scalp distribution consistent with N1 (labeled “N165” by study authors) was reduced in those with mTBI relative to uninjured controls when performing a visual continuous reaction time task (Polo et al., 2002). Although some studies report differences in N1 amplitude in symptomatic mTBI, other studies report no significant differences in N1 amplitude between individuals with mTBI and controls (Duncan, Kosmidis, & Mirsky, 2003; Duncan, Kosmidis, & Mirsky, 2005; Reinvang, Nordby, & Nielsen, 2000; Solbakk, Reinvang, & Nielsen, 2000). The discrepant findings have been attributed to differences in task demands and stimulus modalities between studies (Duncan, Summers, Perla, Coburn, & Mirsky, 2011).

The effects of mild TBI on visual P1 amplitude have received less attention. Reduced P1 amplitudes have been reported in adults with a history of childhood mTBI (Moore, Broglio, & Hillman, 2014). In contrast, other research has reported no group differences in P1 amplitude in chronic mTBI patients (Duncan et al., 2003; Duncan et al., 2005; Lachapelle, Bolduc-Teasdale, Ptito, & McKerral, 2008; Solbakk et al., 2000). In a study using a pattern-reversal paradigm to measure visual processing, no differences in P1 amplitude were observed between the mTBI and control groups (Lachapelle et al., 2008). Taken together, these studies provide mixed evidence for deficits in early attentional processing in mTBI. In the current study, we manipulate task difficulty to examine whether N1 and P1 amplitudes in chronic mild TBI and healthy controls diverge only at higher levels of cognitive load.

Global Neural Gain

Whereas attentional gain is specific to sensory processing and attentional mechanisms, increased global neural gain reflects non-specific, heightened neural

sensitivity throughout the brain. Greater global neural gain can potentially enhance processing of attended as well as unattended stimuli, and possibly increase distractibility (Eldar et al., 2013). Global neural gain is modulated by the locus coeruleus network and is reliably measured using pupil diameter, which is consistently reported to be sensitive to cognitive load (Beatty, 1982; Cabestrero, Crespo, & Quirós, 2009; Unsworth & Robison, 2015). As cognitive load increases, pupil diameter also increases until the amount of resources required exceeds cognitive capacity. Once cognitive capacity has been exceeded, pupil diameter plateaus or declines and performance deficits often become evident. Pupillary response to cognitive load reflecting global neural gain has not been reported in mTBI; however, this effect has been demonstrated in subjects with a number of other diagnoses, including mood disorders (Burkhouse, Siegle, & Gibb, 2014; Jones, Siegle, & Mandell, 2015) and schizophrenia (Granholm, Fish, & Verney, 2009; Granholm, Ruiz, Gallegos-Rodriguez, Holden, & Link, 2016; Steinhauer & Hakerem, 1992). For example, a study of mild cognitive impairment (MCI) found that, compared to controls and non-amnesic MCI volunteers, participants with single domain amnesic MCI (i.e., deficits in only one cognitive domain, such as attention, memory, or executive function) performed normally on an attention task but exhibited greater pupil diameter at low levels of cognitive load (Granholm et al., 2017). These results suggest that greater cognitive effort is required to maintain normal performance. However, individuals with multi-domain amnesic MCI (i.e., deficits in more than one cognitive domain) failed to demonstrate the expected changes in pupil diameter in response to increasing task demands, indicating that they were unable to adaptively modulate neural gain. The investigators concluded that pupil dilation in cognitively impaired populations reflects a

need for the allocation of additional resources to compensate for inefficient cognitive processing networks and can index the point at which maximum processing capacity is reached, compensatory efforts discontinue, and performance declines (Granholm et al., 2017).

Current Study

Little is known about the global neural gain and attentional gain in chronic mTBI. Given the potential for neural gain to impact the signal-to-noise ratio of stimulus processing and affect performance on an attention task as cognitive load increases, additional information about these mechanisms may enhance our understanding of attentional deficits in chronic mTBI. In the current study, we examined the ability of individuals with chronic mTBI to adaptively modulate global and attentional gain at varying levels of cognitive load, as well as how these two neural gain mechanisms relate to each other. Pupil diameter and EEG activity were recorded while volunteers with chronic mTBI and uninjured controls performed a cued attention task under low, moderate, and high levels of cognitive load. Baseline pupil diameter and P1 and N1 ERP amplitudes were evaluated as robust and reliable indices of global and attentional gain, respectively (Gilzenrat et al., 2010; Hillyard & Anllo-Vento, 1998; Hillyard et al., 1998; Jepma & Nieuwenhuis, 2011; Peysakhovich, Vachon, & Dehais, 2017; Slagter et al., 2016). We predicted that the chronic mTBI group would exhibit impaired modulation of global neural gain in response to increased cognitive load, evidenced by larger baseline pupil diameter regardless of cognitive load condition, whereas controls would exhibit a positive linear relationship. We also expected to observe reduced suppression of P1 in unattended locations and reduced enhancement of contralateral N1 in attended locations

relative to controls in response to increased cognitive load, with the greatest effects at higher levels of load. These effects of impaired modulation of global neural gain and attentional gain were expected in the absence of group differences on task performance at lower levels of load, but with group differences emerging under the highest level of load.

METHODS

Participants

Forty-five participants, ages 18-55, were recruited from the greater Washington, DC metro area for participation in this study. All study procedures were approved by the Uniformed Services University Institutional Review Board, and all participants provided written informed consent prior to testing. Participants were excluded for a history of any neurological condition (other than mTBI), uncorrected vision problems, or inability to provide written informed consent.

Twenty-six of the 45 study participants were healthy controls, defined as having no history of head trauma that resulted in loss of consciousness, post-traumatic amnesia, or alteration of consciousness. The remaining 19 participants comprised the chronic mTBI sample. Inclusion in the chronic mTBI group was permitted if participants had a history of mTBI or probable mTBI 3 months to 10 years prior to testing. Concomitant self-report neurobehavioral symptoms were also assessed (Neurobehavioral Symptom Inventory, NSI; (Cicerone & Kalmar, 1995; King et al., 2012). MTBI was defined according to American Congress of Rehabilitation Medicine criteria of loss of consciousness (LOC) less than or equal to 30 minutes, post-traumatic amnesia (PTA) less than or equal to 24 hours following injury (Head, 1993), and/or alterations of

consciousness (AOC) following a head injury (Malec et al., 2007). Sample characteristics and group differences are described in Results.

Procedure

After providing written informed consent, participants provided demographic information, including medical, occupational, and educational history during a semi-structured interview. Additional detailed TBI history was ascertained using the OSU TBI ID (Corrigan & Bogner, 2007). Participants then began the computerized target detection task, following which they completed questionnaires to assess self-reported psychological and neurobehavioral symptoms. Finally, a brief neuropsychological assessment was administered.

Cued Attention Task

Participants were seated 24 inches in front of a computer monitor and remote desktop eye tracker. Ambient luminance in the room was 29 lux. Eye tracking calibration using a 9-point calibration array was conducted prior to each block of the task to ensure measurement accuracy. Behavioral responses, EEG data, and pupil diameter were recorded during the cued attention task.

In the cued attention task, participants were instructed to shift their gaze to a target as quickly as possible after target onset, while simultaneously manually responding (i.e., button press) to the target. The instructions for responding to the targets were varied to create three levels of cognitive load. In the low load condition, a simple reaction time task ("SRT"), participants were instructed to press the center button on a response device when the target appeared. In the moderate load condition, participants were asked to

press a button above-center if the target was blue and a button below-center if the target was green (choice reaction time, “CRT”). In the high load condition, participants were asked to determine whether the color of the current target (either blue or green) matched or did not match the color of the target on the previous trial (“1-back”).

Targets were blue or green circles of equal luminance (2 lux) that appeared to the left or right of center and were preceded by a cue on 73.5% of trials. Cues were either left- or right-facing white arrows and were presented in the center of the screen over a gray background 200 ms prior to target onset. The cues’ validly predicted the location of the target on 47% of trials; cues invalidly predicted the target location on 26.5% of trials. The remaining 26.5% of trials were uncued. An inter-trial central fixation cross was displayed between 520 and 1020 ms (randomized) and persisted on uncued trials for an additional 200 ms. Targets and cues both remained on the screen for 1500 ms following target onset. Participants pressed a button above-center to indicate “same” and a button below-center to indicate “different.” Figure 1 is a graphical depiction of the task.

Cognitive load conditions (“load:” SRT, CRT, 1-back) varied randomly between blocks and cue-target combinations (“trial type:” valid, invalid, uncued) varied randomly within blocks. There was a total of 6 blocks, with two sequential blocks for each load condition and 120 trials per block. Video instructions and 6, 8, and 12 practice trials were provided at the beginning of each load condition block, respectively. Participants could elect to replay the instructional video and/or repeat the practice block, if desired, prior to beginning the experiment.

Following each the final block of each load condition, participants completed the TLX (Hart & Staveland, 1988) to assess the subjective ratings of cognitive effort. The

TLX assesses work load using 6 11-point (0 through 10) scales, including mental demand, physical demand, temporal demand, effort, performance, and frustration level. For the current analysis, we used responses for the ‘effort’ item as the measure for subjective cognitive effort.

Self-Reported Symptoms and Neuropsychological Performance

Participants completed the Neurobehavioral Symptom Inventory, a 22-item (5-point scale) inventory of neurobehavioral symptoms assessing cognitive, affective, and somatosensory symptoms (Corrigan & Bogner, 2007). Total NSI score was used for analysis. The brief neuropsychological assessment comprised the Symbol Search, Symbol-Digit Coding, and Digit Span subtests of the Wechsler Adult Intelligence Scale (Wechsler, 2014); Trail Making Test Parts A and B (Reitan, 1992), and the Hopkins Verbal Learning Test (Brandt, 1991). These metrics were standardized and combined into a Z score to measure global neuropsychological function.

Psychophysiological Data Collection and Processing

Apparatus

Stimuli were controlled and delivered via a desktop computer using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA). Stimuli were presented on a 24-inch, 1920 x1080 resolution LCD monitor. Pupil diameter was recorded from the right eye using an Applied Science Laboratories (ASL) D6 remote desktop eye tracker that detects pupil diameter and eye movements using an infrared light source directed at the participants’ eyes. Pupillary data were sampled continuously at 120 Hz. The camera was centered below the stimulus presentation monitor and participants were positioned in a

chin rest to maintain head position during testing. Pupil values were converted from pixels to millimeters using a scaling factor calibrated to a simulated eye of known size and distance from camera.

EEG data were recorded using a 64-channel BioSemi ActiveTwo recording system with active, sintered Ag/AgCl electrodes conforming to the International 10-20 System (Klem, Lüders, Jasper, & Elger, 1999). The electro-oculogram (EOG) was recorded from electrodes placed below and in the outer canthus of the left eye. EEG data were sampled at 256 Hz with a low-pass fifth order sinc filter using ActiView software. Due to the design of the BioSemi recording system, data were recorded in single-ended mode wherein the ground electrode is formed by the Common Mode sense active electrode and the Driven Right Leg passive electrode. Electrode offsets were kept below 25 k Ω .

Pupil Diameter

Pupillary data were processed off-line using custom MATLAB scripts (Version 8.4, Mathworks, Inc, 2014). In accordance with prior studies (Kang, Huffer, & Wheatley, 2014; Klingner, Kumar, & Hanrahan, 2008; Schacht, Dimigen, & Sommer, 2010), raw pupillary data were filtered using a 10 Hz low-pass FIR filter. Blinks and data loss (any missing data segments ≤ 500 ms) were corrected using a linear interpolation. There was no group difference in the ratio of interpolated data to usable data, $t(37) = -.520$, $p = .606$. Trials with total data loss (including blinks) of greater than 500 ms were excluded from analysis. Trials for which behavioral responses were incorrect or omitted were also excluded from analysis. Baseline pupil diameter was quantified as the average pupil diameter over a 200 ms pre-trial window when the fixation cross was onscreen.

ERPs

EEG data were processed off-line using Matlab toolboxes EEGLab (Delorme & Makeig, 2004) and ERPlab (Lopez-Calderon & Luck, 2014). Data were bandpass filtered between 1 and 40 Hz. Line noise was removed and bad channels were interpolated using the PREP pipeline (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015). Data were referenced offline to the common average and submitted to independent component analysis (ICA) to identify and remove components associated with eye blinks, horizontal eye movements, or muscular artifacts. Following ICA correction, segments of data containing $\pm 100 \mu\text{V}$ artifacts were rejected. The data were then time-locked to target onset, segmented between -200 –1500 ms from target onset, and baseline corrected using the 200 ms prestimulus interval. Trials with incorrect or omitted behavioral responses were removed from data prior to averaging. Correct trials were defined as trials during which an accurate response was made between 0 and 1000 ms after target onset. ERPs were grand-averaged across trials for the 6 conditions (load X trial type) for comparison within and between subjects. P1 and N1 ERP components were identified based upon visual inspection of grand-averaged waveforms and topographical distribution in consideration of conventional parameters (Hillyard & Anllo-Vento, 1998). Average contralateral P1 amplitude was measured at channels O1 and O2 between 100 and 175 ms after target onset; average contralateral N1 amplitude was measured between 175 and 250 ms after target onset at channels O1 and O2.

Statistical Analyses

Sample Characteristics

Group comparisons were conducted for gender, race, age, education, and estimated premorbid IQ. Chi-square goodness-of-fit analyses were computed on gender and race. Independent samples *t*-tests were computed on age, education, premorbid IQ, NSI score, and global neuropsychological function.

Task Performance

Reaction time (RT) data and accuracy were analyzed in separate 2 (group: control/chronic mTBI) x 3 (load condition: low/moderate/high) x 2 (trial type: valid/invalid) repeated measures analyses of variance (ANOVA). Post hoc comparisons using Fisher's LSD (Fisher, 1935; Williams & Abdi, 2010) were conducted to compare groups at each level of load, trial type, and load x trial type. Follow-up ANOVAs were computed separately for each group, with cognitive load and trial type as within-subject factors.

Subjective Effort

Responses to the TLX 'effort' item were entered into a 2 (group: control/chronic mTBI) x 3 (load condition: low/moderate/high) x 2 (trial type: valid/invalid) repeated measures analyses of variance (ANOVA). Post hoc comparisons using Fisher's LSD (Fisher, 1935; Williams & Abdi, 2010) were conducted to compare groups at each level of load, trial type, and load x trial type.

Global Neural Gain

Baseline pupil diameter was submitted to a 2 (group) x 3 (load condition) x 2 (trial type) repeated measures ANCOVA controlling for age to evaluate tonic modulation of pupil diameter. Age was included as a covariate for all analyses that included baseline

pupil diameter because it is a significant correlate (Zekveld, Kramer, & Festen, 2011).

Follow-up ANCOVAs were computed separately for each group, with cognitive load and trial type as within-subject factors, to examine the effects of the experimental manipulations within each group.

Attentional Gain

Contralateral P1 and N1 amplitudes were submitted to 2 (group) x 3 (load condition) x 2 (trial type) repeated measures ANOVAs. Follow-up ANOVAs were computed to examine the effects of experimental manipulations separately for each group, with cognitive load and trial type as within-subject factors.

Correlational Analyses

Pearson correlation coefficients were used to test the strength of associations of N1 amplitude, P1 amplitude, and baseline pupil diameter with RT and the global neuropsychological z-score. Relationships between baseline pupil diameter and P1 and N1 amplitudes were also tested. Partial correlation analyses controlling for age were used for tests including baseline pupil diameter. Correlation coefficients were only computed for measures specific to experimental conditions (i.e., N1 amplitude during low load/valid trials analyzed with RT on low load/valid trials). All correlational analyses were conducted separately for each group. To reduce the potential for Type I error, we limited our interpretations to broad patterns of correlations and did not interpret isolated significant correlations. Due to the small sample size and reduced power for both groups, correlations with medium to large effect sizes ($r > .3$) were also interpreted if they fit into

a broader pattern of meaningful results, including if the coefficients failed to reach statistical significance.

General Statistical Considerations

All analyses were performed using SPSS version 24. Greenhouse-Geisser corrections for sphericity violations are reported where appropriate. Alpha level was set to $\alpha=.05$, and trends of $p < .07$ were interpreted as marginally significant. All post-hoc comparisons were conducted using Fisher's test of Least Significant Difference (Fisher, 1935; Williams & Abdi, 2010).

RESULTS

Sample Characteristics

Demographics of the final sample ($n=39$) are presented in Table 1. One chronic mTBI participant and five control participants were excluded from analysis due to poor psychophysiological data quality. Consistent with rates of mTBI in the general population, groups differed by gender, $\chi^2(1, N = 39) = 4.127, p = .04$, wherein there was a significantly greater proportion of females in the control group (76%) than in the chronic mTBI group (44%). Subsequent analyses to test the effects of gender on measures of neural gain revealed no gender differences; therefore, it is not included as a covariate in the following analyses. No other significant between-group differences in demographic characteristics were observed. As expected due to inclusion criteria, the chronic mTBI group reported more neurobehavioral symptoms as indexed by NSI total score, $t(37) = -4.657, p < .001$ (chronic mTBI: $M = 28.50, SD = 15.11$; controls: $M =$

9.14, $SD = 10.75$). Groups did not differ significantly on the composite global neuropsychological z-score, $p = .79$ (chronic mTBI: $M = .032$, $SD = .60$; controls: $M = .079$, $SD = .49$).

Task Performance

An interaction between load and trial type on RT was observed, $F(1.723, 63.768) = 4.818$, $p = .02$, $\eta_p^2 = .115$. A test of simple comparisons determined that the interaction was driven by significant differences between valid and invalid trials under both low, $p < .001$, and moderate, $p < .001$, but not high load conditions, $p = .35$. No group effects or group interactions were observed for task performance. (Mean RTs are shown in Figure 2). Pairwise comparisons also did not reveal differences between groups at any level of load, trial type, or load x trial type.

An effect of load on accuracy was observed, $F(2,74) = 62.610$, $p < .001$, $\eta_p^2 = .629$. Pairwise comparisons revealed that all load trials differed significantly from each other $p < .01$ (for all), with greatest accuracy during low load conditions ($M = 98.7\%$, $SE = .40$), followed by moderate load ($M = 97.2\%$, $SE = .60$), and high load conditions ($M = 84.9\%$, $SE = 1.70\%$). No group effect or interactions with group were reported for performance accuracy.

Subjective Effort

Subjective effort ratings during the cued attention task differed by load, $F(2,74) = 4.703$, $p = .012$, $\eta_p^2 = .113$. Pairwise comparisons revealed that the high load condition ($M = 4.56$, $SE = .41$) was rated as significantly more effortful than the low load condition ($M = 5.05$, $SE = .38$), $p = .008$, and marginally more effortful than the

moderate load condition ($M = .5.78$, $SE = .37$), $p = .066$. The omnibus ANOVA did not reveal a group difference, $p > .1$, or a group * load interaction, $p > .1$. However, a post-hoc comparison of load revealed that the chronic mild TBI group ($M = 5.78$, $SE = .56$) rated the moderate load condition as more effortful than controls ($M = .4.32$, $SE = .52$), $p = .06$.

Baseline Pupil Diameter

Baseline pupil diameters are presented in Figure 3. In support of our hypothesis, the mTBI group had a larger baseline pupil diameter ($M = 5.002$ mm, $SE = .22$) than controls ($M = 4.410$ mm, $SE = .21$); however, these differences were only marginally significant, $F(1,36) = 3.801$, $p = .06$, $\eta_p^2 = .096$. A main effect of load was also significant, $F(2,72) = 3.329$, $p = .04$, $\eta_p^2 = .085$, wherein baseline pupil diameter was larger in the high cognitive load condition ($M = 4.844$, $SE = .15$) than the low ($M = 4.666$, $SE = .16$), $p < .01$, and moderate load conditions ($M = 4.607$, $SE = .15$), $p < .01$. Baseline pupil diameter did not differ between low and moderate conditions, $p = .32$. No other main effects or interactions on baseline pupil diameter were observed in the omnibus ANCOVA. Planned comparisons of group for each level of load revealed group differences in baseline pupil diameter: the chronic mTBI group had larger baseline pupil diameter than controls under low, $p = .05$, and moderate load conditions, $p = .04$. Group differences were not significant under high load, $p = .14$. When analyzed separately by group, no effects of load were observed in either group, $p > .09$.

P1 Amplitude

P1 amplitudes are depicted in Figure 4a and ERP waveforms are depicted in Figure 4c-d. An interaction between group and load was observed in P1 amplitude, $F(2,74) = 6.021, p < .01, \eta_p^2 = .140$. Tests of load effects within each group revealed that P1 amplitude differed by load in the chronic mTBI group, $F(2,34) = 4.994, p = .01, \eta_p^2 = .227$, but not in the control group, $F(2,40) = 2.067, p = .14, \eta_p^2 = .094$. In contrast to our hypothesis, P1 suppression was reduced (i.e., larger amplitude) in the chronic mTBI group in the low load condition ($M = .989, SE = .60$) compared to the moderate load ($M = .429, SE = .55, p = .03$, and the high load conditions ($M = .449, SE = .55, p = .02$. P1 amplitude did not differ between moderate and high loads, $p = .90$, in the chronic mTBI group. Additionally, a main effect of validity revealed P1 amplitude to valid trials ($M = .963, SE = .36$) was larger than invalid ($M = .670, SE = .36$) trials, $F(1, 37) = 5.896, p = .02, \eta_p^2 = .137$.

N1 Amplitude

N1 amplitudes are presented in Figure 4b. An interaction between load and group was also observed for N1 amplitude, $F(2,74) = 5.452, p = .01, \eta_p^2 = .128$. Post-hoc ANOVAs separated by group revealed that N1 amplitude differed by load in the chronic mTBI group, $F(2,34) = 7.856, p < .01, \eta_p^2 = .316$, but not in controls, $F(2,40) = .159, p = .85, \eta_p^2 = .008$. Contrary to our hypothesis, N1 amplitude in chronic mTBI was reduced in the low load condition ($M = 1.064, SE = .38$) relative to the moderate ($M = .342, SE = .37, p < .01$, and high load conditions ($M = .137, SE = .41, p < .01$. N1 amplitude in this group did not differ between moderate and high load conditions, $p = .46$.

Correlations

Correlation analyses are presented in Table 2. Evaluation of patterns within the correlation matrix revealed several important findings. When examining relationships between task performance (RT) and attentional gain, faster responses were associated with enhanced P1 (i.e., reduced suppression) across nearly all experimental conditions (load*trial type) for controls. Faster response times were also associated with attenuated N1 amplitude (i.e., reduced enhancement) among the control group, and although some coefficients failed to reach significance, medium-to-large effect sizes were observed across nearly all experimental conditions. Relationships between measures of neural gain and subjective effort were also observed within the control group. Greater baseline pupil diameter was associated with lower ratings of subjective effort during low cognitive load. Less P1 suppression was also associated with lower ratings during moderate and high load conditions; and reduced N1 enhancement was associated with lower subjective effort during valid trials during all three load conditions. Relationships between baseline pupil diameter and N1 and P1 amplitude were not present in the control group.

However, for individuals with chronic mTBI, the negative relationship between P1 and N1 amplitudes and RT was evident only in the moderate load condition. Additionally, examination of correlations between pupillary and ERP measures of neural gain and composite neuropsychological z-score revealed medium-to-large associations in the chronic mTBI group only. Larger baseline diameter and smaller P1 amplitude across all experimental conditions and larger N1 during invalid trials were associated with lower neuropsychological z-scores in the mTBI group. In the chronic mTBI group, medium-to-large correlations were observed between baseline pupil diameter and N1 amplitude. Results indicated that larger baseline pupil diameter was associated with enhanced N1

amplitude in chronic mTBI. Unlike controls, measures of neural gain were not associated with subjective effort in chronic mild TBI, with the exception of N1 amplitude during high load invalid trials which was related to greater subjective effort.

DISCUSSION

Previous research suggests that increased global neural gain, which is sensitive to changes in cognitive load, may influence attentional gain and performance on attention tasks by amplifying sensitivity to attended and/or unattended stimuli (Eldar et al., 2013). The aim of the present study was to evaluate neural gain modulation in chronic mTBI at varying levels of cognitive load to better characterize the cognitive sequelae of this condition. Furthermore, we sought to examine how modulation of global neural gain and attentional gain may be related to performance on neuropsychological measures. Using pupillary and ERP metrics, we observed differences in global neural gain and attentional gain across different levels of cognitive load in participants with chronic mTBI. However, the chronic mTBI participants did not exhibit any differences in attention task performance or overall performance on neuropsychological tests. Importantly, the additional neural resources allocated in response to changing task demands were uniformly applied to higher load conditions rather than in a linear function and were associated with poorer task performance in some experimental conditions. Taken together, the results suggest that individuals with chronic mTBI modulate attentional gain to maintain the same level of cognitive performance as uninjured controls, but that this modulation is not always cognitively efficient.

The larger baseline pupil diameter observed in the chronic mTBI group indicates that this clinical population has greater global neural gain at low and moderate levels of

cognitive load relative to uninjured controls. The absence of a relationship between cognitive load and pupil diameter in the chronic mTBI sample indicates that these individuals have indiscriminately higher levels of global neural gain that is not adaptively modulated in response to task demands. Accordingly, individuals with chronic mTBI respond to low-load cognitive tasks with the same amount of global neural resources as they do for high-load cognitive tasks. However, when tasks are easier, greater neural resources are leveraged than the amount that is required to maintain normal performance in controls.

In contrast to global neural gain, attentional gain—indexed by P1 and N1 amplitudes—increased as a function of cognitive load and plateaued after the moderate load condition in the chronic mTBI group. Although these results are contrary to our prediction that the chronic mTBI group would not modulate attentional gain, they provide insight into attentional processing in this population. Specifically, the effects of increased attentional gain were stronger at higher levels of cognitive load: inhibition of processing (P1 suppression) and excitation of processing (N1 enhancement) were both enhanced in the moderate and high load conditions relative to low load. In comparison, these measures of attentional gain were not significantly modulated by load in the control group. These results are consistent with prior research in mTBI samples that showed neural activation increased and then plateaued between low and moderate levels of cognitive load (McAllister, Sparling, Flashman, Guerin, et al., 2001; McAllister, Sparling, Flashman, & Saykin, 2001). Our results do not fully corroborate these reports, as we did not observe performance decrements when attentional gain plateaued. In our sample, the extent to which the chronic mTBI group enhanced neural gain for moderate

load was sufficient to maintain normal performance for both the moderate and high load tasks. Taken together, the plateau effect in our data provides evidence that the modulation of attentional gain in the chronic mTBI group is not linear (up to the point of capacity) but follows an “all-or-none” pattern because the same amount of attentional resources was recruited for the moderate and high load conditions.

A negative relationship between neural activity and performance indicates efficient cognitive processing (Barulli & Stern, 2013; Fabiani, 2012; Fabiani, Low, Wee, Sable, & Gratton, 2006; Rypma et al., 2006). The attentional gain that the chronic mTBI group leveraged in response to the moderate load condition was negatively associated with task performance, such that reduced P1 suppression and reduced N1 enhancement were related to shorter response times. The relationship between attentional gain and performance did not extend to the low or high load conditions. By comparison, reduced attentional gain was related to faster responses across all three load conditions in uninjured controls. When interpreted from a cognitive efficiency framework, our data suggest that cognitive efficiency is reduced in chronic mTBI. In a previous study examining cognitive efficiency in moderate and severe TBI, Hillary and colleagues (Hillary et al., 2010) reported similar findings wherein faster response time on a working memory task was related to reduced neural activation in the prefrontal cortex. The authors interpreted these findings as evidence that increased frontal activity is the result of a “latent support mechanism” that operates to tolerate increases in task difficulty (Hillary et al., 2010). We propose that a similar mechanism to that described by Hillary et al. (2010) underlies the effects observed in the current study of chronic mTBI. Taken together, the results of the current study suggest that, although the chronic mTBI group

on average was able to maintain normal performance throughout the task, the amount of resources with which they responded to the moderate load condition was disproportionate to what was needed.

As an extension of the biased-competition theory of attention (Beck & Kastner, 2009; Desimone & Duncan, 1995; Kastner & Ungerleider, 2001), Mather and Sutherland (2011) proposed an arousal-biased competition theory that suggests selective processing of visual stimuli is moderated by the degree of arousal. Indeed, there is a large body of research showing that emotional arousal amplifies the processing of attended information (Chajut & Algom, 2003; De Martino, Kalisch, Rees, & Dolan, 2009; Edelstein & Levine, 2010). Although we did not use emotionally-valenced stimuli in our study, the networks involved in regulating emotional arousal and cognitive arousal overlap. One network that is critical to both is the locus coeruleus norepinephrine system (LC-NE; Sara, 2009). In fact, baseline pupil diameter—a reporter variable for tonic LC-NE activity—is a reliable index of general arousal, whether it is due to cognitive demands or emotional stimuli (Chiew & Braver, 2014; Granholm & Steinhauer, 2004). In accordance with this theory, we observed in the chronic mTBI group that baseline pupil diameter—which was greater than in controls—was associated with N1 amplitude, such that greater arousal (i.e., global neural gain) was related to enhanced processing of incoming sensory information across all experimental conditions. The fact that baseline pupil diameter was related to N1 but not P1 suggests that the effect of increased general arousal is specific to enhancement of attended stimuli but not inhibition of unattended stimuli. Interestingly, this relationship was not observed in controls. It is possible that the low levels of global neural gain and the reduced variability in this group were not sufficient to identify meaningful

relationship. Alternatively, this relationship may not exist in controls because they did not engage modulatory mechanisms of global neural gain or attentional gain, as evidenced by their consistent P1 and N1 amplitudes across the three load conditions.

It is critical to note that the difference between valid and invalid trials was not affected by load for either group in our study. Although P1 amplitude changed as a function of cognitive load in chronic mTBI, the difference between attended and unattended locations did not change by load. The same is true for N1 enhancement: N1 amplitude increased similarly for both valid (attended) and invalid (unattended) trials at all levels of cognitive load. By equally increasing the excitatory response to attended stimuli and the inhibitory response to unattended stimuli, the signal-to-noise ratio is maintained across load conditions. We interpret these results as evidence that attentional gain modulation in chronic mTBI does not function to increase the signal-to-noise ratio to improve attention but maintains the same signal-to-noise ratio to sustain normal performance in the face of increasing task demands. It seems that the general state of diffuse attention and heightened sensitivity to stimuli regardless of task-relevance is necessary to preserve normal task performance in this population. However, unlike many visuospatial attention tasks, our task did not contain visual distractors (i.e., noise) in the unattended location, which likely explains why diffuse attention did not negatively affect performance. Heightened attentional processing in unattended locations, as reported here, would likely produce different results if distractor stimuli were present in such locations. Additional studies using tasks that include visual distractors are needed to test whether increases in diffuse attentional gain occur in the context of competing visual stimuli; and, if it does, how it affects performance.

In our study, participants with chronic mTBI who exhibited increased global neural gain and increased attentional gain also had poorer neuropsychological performance. By comparison, these relationships were absent in controls. Although we surmised that greater neural gain at higher levels of cognitive load observed in the chronic mTBI group may underlie subjective reports of increased effort to perform cognitive tasks, the data did not fully corroborate this hypothesis. We found that greater neural gain was associated with subjective effort in the clinical sample, but only for invalid trials under high load. More research is warranted to test this relationship and determine why individuals with chronic mTBI often report that cognitive processing feels more effortful despite showing no performance deficits. Impaired attentional resource allocation likely has many downstream effects because attention serves as a “gatekeeper” for stimuli selected for further processing; Accordingly, the varied and non-specific cognitive symptoms commonly reported or observed in chronic mTBI, such as memory problems, poor concentration, or distractibility, may also be a consequence of impaired attentional gain modulation.

Limitations and Future Directions

Contrary to our hypotheses, the control group did not modulate neural gain or visuospatial attention processing with regard to cognitive load. We propose that our manipulation of cognitive load was not sufficient to elicit differences in pupil diameter or P1 and N1 amplitude in uninjured controls. For this reason, we are unable to measure the threshold at which controls begin to modulate attentional gain or make between-group comparisons for when and how these mechanisms differ. For example, it is possible that the response to a high cognitive load is the same for controls as it is for individuals with

chronic mTBI at lower levels of load, or it is possible that the mechanisms are different. Additional research should include more levels of cognitive load to quantify the pattern of gain modulation in normal controls under higher load.

Additionally, given the intersubject variability of our measures of neural gain combined with our small sample size, this study may have an increased risk of Type II error, i.e., failing to detect a true positive (for a discussion on intersubject variability for EEG measures, see Basile, Baldo, de Castro, and Gattaz, 2003). To accommodate this limitation, we reported and discussed ANOVA results with marginal p -values ($<.07$) and patterns of correlations with moderate-to-large effect sizes even if statistical significance was not reached. However, our data should still be interpreted with awareness of our reduced power for some analyses.

Conclusions

The results from this study provide evidence ability to modulate attentional gain is impaired in chronic mTBI. The overall pattern suggests that this population responds to increases in cognitive demand with a uniformly-applied “all or none” increases in neural resources, regardless of the relative difficulty of the task. Whereas this response is sufficient to maintain normal performance, it is cognitively inefficient and is related to poorer performance when tasks are only moderately difficult. It is possible that impaired modulation of attentional gain and subsequent cognitive inefficiency, while still sufficient to maintain normal performance, underlies subjective complaints of effortful cognitive processing in this population that are often uncorroborated by behavioral performance. Although causal relationships cannot be inferred from these results, they provide insight

into neurological factors that may be essential to achieving better long-term outcomes following mTBI.

References

- Alexander, M. P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*, 45(7), 1253-1260.
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience*, 28, 403-450.
- Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, 17(10), 10.1016/j.tics.2013.1008.1012. doi:10.1016/j.tics.2013.08.012
- Basile, L. F., Baldo, M. V., de Castro, C. C., & Gattaz, W. F. (2003). The generators of slow potentials obtained during verbal, pictorial and spatial tasks. *International journal of psychophysiology*, 48(1), 55-65.
- Beatty, J. (1982). Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychological Bulletin*, 91(2), 276.
- Beck, D. M., & Kastner, S. (2009). Top-down and bottom-up mechanisms in biasing competition in the human brain. *Vision Res*, 49(10), 1154-1165. doi:10.1016/j.visres.2008.07.012
- Bigdely-Shamlo, N., Mullen, T., Kothe, C., Su, K.-M., & Robbins, K. A. (2015). The PREP pipeline: standardized preprocessing for large-scale EEG analysis. *Frontiers in Neuroinformatics*, 9, 16.

- Bigler, E. D. (2003). Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. *Archives of Clinical Neuropsychology*, 18(6), 595-621; discussion 623-597.
- Brandt, J. (1991). The hopkins verbal learning test: Development of a new memory test with six equivalent forms. *Clinical Neuropsychologist*, 5(2), 125-142.
doi:10.1080/13854049108403297
- Broglio, S. P., Pontifex, M. B., O'Connor, P., & Hillman, C. H. (2009). The persistent effects of concussion on neuroelectric indices of attention. *Journal of Neurotrauma*, 26(9), 1463-1470.
- Burkhouse, K. L., Siegle, G. J., & Gibb, B. E. (2014). Pupillary reactivity to emotional stimuli in children of depressed and anxious mothers. *Journal of Child Psychology and Psychiatry*, 55(9), 1009-1016.
- Cabestrero, R., Crespo, A., & Quirós, P. (2009). Pupillary dilation as an index of task demands. *Perceptual and Motor Skills*, 109(3), 664-678.
- Chajut, E., & Algom, D. (2003). Selective attention improves under stress: implications for theories of social cognition. *Journal of Personality and Social Psychology*, 85(2), 231-248.
- Chen, A. J.-W., Novakovic-Agopian, T., Nycum, T. J., Song, S., Turner, G. R., Hills, N. K., . . . D'Esposito, M. (2011). Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury. *Brain*, 134(5), 1541-1554.

- Chiew, K. S., & Braver, T. S. (2014). Dissociable influences of reward motivation and positive emotion on cognitive control. *Cognitive, Affective, & Behavioral Neuroscience, 14*(2), 509-529. doi:10.3758/s13415-014-0280-0
- Cicerone, K. D., & Kalmar, K. (1995). Persistent postconcussion syndrome: The structure of subjective complaints after mild traumatic brain injury. *The Journal of Head Trauma Rehabilitation, 10*(3), 1-17.
- Cooper, D. B. (2018). Neuropsychological Performance and Subjective Symptom Reporting in Military Service Members With a History of Multiple Concussions Comparison With a Single Concussion, Posttraumatic Stress Disorder, and Orthopedic Trauma. *The Journal of Head Trauma Rehabilitation, 33*(2), 81-90. doi:10.1097/HTR.0000000000000375
- Corrigan, J. D., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University TBI Identification Method. *The Journal of Head Trauma Rehabilitation, 22*(6), 318-329. doi:10.1097/01.HTR.0000300227.67748.77
- De Martino, B., Kalisch, R., Rees, G., & Dolan, R. J. (2009). Enhanced processing of threat stimuli under limited attentional resources. *Cerebral Cortex, 19*(1), 127-133. doi:10.1093/cercor/bhn062
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9-21.

- Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, 18(1), 193-222.
- Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2003). Event-related potential assessment of information processing after closed head injury. *Psychophysiology*, 40(1), 45-59.
- Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2005). Closed head injury-related information processing deficits: an event-related potential analysis. *International Journal of Psychophysiology*, 58(2), 133-157.
- Duncan, C. C., Summers, A. C., Perla, E. J., Coburn, K. L., & Mirsky, A. F. (2011). Evaluation of traumatic brain injury: brain potentials in diagnosis, function, and prognosis. *International Journal of Psychophysiology*, 82(1), 24-40.
- Duncan, J. (1998). Converging levels of analysis in the cognitive neuroscience of visual attention. *Philosophical Transactions of the Royal Society B Biological Sciences*, 353(1373), 1307-1317. doi:10.1098/rstb.1998.0285
- Edelstein, R. S., & Levine, L. J. (2010). Emotion and memory narrowing: A review and goal-relevance approach *Cognition and Emotion* (pp. 178-220): Psychology Press.
- Egner, T., & Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature Neuroscience*, 8(12), 1784.

- Eldar, E., Cohen, J. D., & Niv, Y. (2013). The effects of neural gain on attention and learning. *Nature Neuroscience*, 16(8), 1146-1153.
- Fabiani, M. (2012). It was the best of times, it was the worst of times: A psychophysiological view of cognitive aging. *Psychophysiology*, 49(3), 283-304.
- Fabiani, M., Low, K. A., Wee, E., Sable, J. J., & Gratton, G. (2006). Reduced suppression or labile memory? Mechanisms of inefficient filtering of irrelevant information in older adults. *Journal of Cognitive Neuroscience*, 18(4), 637-650.
- Fisher, R. A. (1935). *The design of experiments*. Edinburgh: Oliver & Boyd
- French, L. M., Lange, R. T., & Brickell, T. A. (2014). Subjective cognitive complaints and neuropsychological test performance following military-related traumatic brain injury. *Journal of Rehabilitation Research and Development*, 51(6), 933.
- Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269.
- Gosselin, N., Thériault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery*, 58(6), 1151-1161.

Granholm, E., Fish, S. C., & Verney, S. P. (2009). Pupillometric measures of attentional allocation to target and mask processing on the backward masking task in schizophrenia. *Psychophysiology*, 46(3), 510-520.

Granholm, E., Ruiz, I., Gallegos-Rodriguez, Y., Holden, J., & Link, P. C. (2016). Pupillary responses as a biomarker of diminished effort associated with defeatist attitudes and negative symptoms in schizophrenia. *Biological Psychiatry*, 80(8), 581-588. doi:10.1016/j.biopsych.2015.08.037

Granholm, E., & Steinhauer, S. R. (2004). Pupillometric measures of cognitive and emotional processes. *International Journal of Psychophysiology*, 52(1), 1-6. doi:10.1016/j.ijpsycho.2003.12.001

Granholm, E. L., Panizzon, M. S., Elman, J. A., Jak, A. J., Hauger, R. L., Bondi, M. W., . . . Kremen, W. S. (2017). Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease. *Journal of Alzheimer's disease : JAD*, 56(4), 1419-1428. doi:10.3233/JAD-161078

Hart, S. G., & Staveland, L. E. (1988). Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research. In *Advances in psychology* (Vol. 52, pp. 139-183). North-Holland.

Head, J. (1993). Definition of mild traumatic brain.. Injury. *Journal of Head Trauma and Rehabilitation*, 8(3), 86-87.

Hillary, F. G., Genova, H. M., Medaglia, J. D., Fitzpatrick, N. M., Chiou, K. S., Wardecker, B. M., . . . DeLuca, J. (2010). The nature of processing speed deficits

- in traumatic brain injury: is less brain more? *Brain Imaging and Behavior*, 4(2), 141-154.
- Hillyard, S. A., & Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of Sciences*, 95(3), 781-787.
- Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 353(1373), 1257-1270.
- Jepma, M., & Nieuwenhuis, S. (2011). Pupil diameter predicts changes in the exploration–exploitation trade-off: Evidence for the adaptive gain theory. *Journal of Cognitive Neuroscience*, 23(7), 1587-1596.
- Jones, N. P., Siegle, G. J., & Mandell, D. (2015). Motivational and emotional influences on cognitive control in depression: A pupillometry study. *Cognitive, Affective, & Behavioral Neuroscience*, 15(2), 263-275.
- Kang, O. E., Huffer, K. E., & Wheatley, T. P. (2014). Pupil dilation dynamics track attention to high-level information. *PloS one*, 9(8), e102463.
- Kastner, S., & Pinsk, M. A. (2004). Visual attention as a multilevel selection process. *Cognitive, Affective, & Behavioral Neuroscience*, 4(4), 483-500.

- Kastner, S., & Ungerleider, L. G. (2001). The neural basis of biased competition in human visual cortex. *Neuropsychologia*, 39(12), 1263-1276.
- King, P. R., Donnelly, K. T., Donnelly, J. P., Dunnam, M., Warner, G., Kittleson, C., . . . Meier, S. T. (2012). Psychometric study of the Neurobehavioral Symptom Inventory. *Journal of Rehabilitation Research & Development*, 49(6), 879-890.
- Klem, G. H., Lüders, H. O., Jasper, H., & Elger, C. (1999). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, 52(3), 3-6.
- Klingner, J., Kumar, R., & Hanrahan, P. (2008). *Measuring the task-evoked pupillary response with a remote eye tracker*. Paper presented at the Proceedings of the 2008 symposium on Eye tracking research & applications.
- Lachapelle, J., Bolduc-Teasdale, J., Ptito, A., & McKerral, M. (2008). Deficits in complex visual information processing after mild TBI: electrophysiological markers and vocational outcome prognosis. *Brain Injury*, 22(3), 265-274.
- Lavie, N. (2010). Attention, distraction, and cognitive control under load. *Current Directions in Psychological Science*, 19(3), 143-148.
- Wood, R. (2004). Understanding the ‘miserable minority’: A diathesis-stress paradigm for post-concussional syndrome. *Brain Injury*, 18(11), 1135-1153.
- Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, 8, 213.

- Malec, J. F., Brown, A. W., Leibson, C. L., Flaada, J. T., Mandrekar, J. N., Diehl, N. N., & Perkins, P. K. (2007). The Mayo classification system for traumatic brain injury severity. *Journal of Neurotrauma*, 24(9), 1417-1424.
- Mangun, G. R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology*, 32(1), 4-18. doi:doi:10.1111/j.1469-8986.1995.tb03400.x
- Mather, M., & Sutherland, M. R. (2011). Arousal-Biased Competition in Perception and Memory. *Perspectives on Psychological Science*, 6(2), 114-133.
doi:10.1177/1745691611400234
- Mayer, A. R., Mannell, M. V., Ling, J., Gasparovic, C., & Yeo, R. A. (2011). Functional Connectivity in Mild Traumatic Brain Injury. *Human brain mapping*, 32(11), 1825-1835. doi:10.1002/hbm.21151
- McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage*, 14(5), 1004-1012.
doi:10.1006/nimg.2001.0899
- McAllister, T. W., Sparling, M. B., Flashman, L. A., & Saykin, A. J. (2001). Neuroimaging findings in mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, 23(6), 775-791.
- Moore, R. D., Broglio, S. P., & Hillman, C. H. (2014). Sport-related concussion and sensory function in young adults. *Journal of Athletic Training*, 49(1), 36-41.

- Pare, N., Rabin, L. A., Fogel, J., & Pepin, M. (2009). Mild traumatic brain injury and its sequelae: characterisation of divided attention deficits. *Neuropsychological Rehabilitation*, 19(1), 110-137. doi:10.1080/09602010802106486
- Parks, A. C., Moore, R. D., Wu, C.-T., Broglio, S. P., Covassin, T., Hillman, C. H., & Pontifex, M. B. (2015). The association between a history of concussion and variability in behavioral and neuroelectric indices of cognition. *International Journal of Psychophysiology*, 98(3, Part 1), 426-434.
doi:http://dx.doi.org/10.1016/j.ijpsycho.2015.08.006
- Peysakhovich, V., Vachon, F., & Dehais, F. (2017). The impact of luminance on tonic and phasic pupillary responses to sustained cognitive load. *International Journal of Psychophysiology*, 112, 40-45.
doi:https://doi.org/10.1016/j.ijpsycho.2016.12.003
- Polo, M. D., Newton, P., Rogers, D., Escera, C., & Butler, S. (2002). ERPs and behavioural indices of long-term preattentive and attentive deficits after closed head injury. *Neuropsychologia*, 40(13), 2350-2359.
- Pontifex, M. B., O'Connor, P. M., Broglio, S. P., & Hillman, C. H. (2009). The association between mild traumatic brain injury history and cognitive control. *Neuropsychologia*, 47(14), 3210-3216.
doi:https://doi.org/10.1016/j.neuropsychologia.2009.07.021

- Potter, D. D., Jory, S. H., Bassett, M. R., Barrett, K., & Mychalkiw, W. (2002). Effect of mild head injury on event-related potential correlates of Stroop task performance. *Journal of the International Neuropsychological Society*, 8(6), 828-837.
- Reinvang, I., Nordby, H., & Nielsen, C. S. (2000). Information processing deficits in head injury assessed with ERPs reflecting early and late processing stages. *Neuropsychologia*, 38(7), 995-1005. doi:[https://doi.org/10.1016/S0028-3932\(99\)00153-0](https://doi.org/10.1016/S0028-3932(99)00153-0)
- Reitan, R. M. (1992). *Trail Making Test: Manual for administration and scoring*: Reitan Neuropsychology Laboratory.
- Ruff, R. M., Camenzuli, L., & Mueller, J. (1996). Miserable minority: Emotional risk factors that influence the outcome of a mild traumatic brain injury. *Brain Injury*, 10(8), 551-566.
- Rypma, B., Berger, J. S., Prabhakaran, V., Bly, B. M., Kimberg, D. Y., Biswal, B. B., & D'esposito, M. (2006). Neural correlates of cognitive efficiency. *Neuroimage*, 33(3), 969-979.
- Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, 10(3), 211.
- Schacht, A., Dimigen, O., & Sommer, W. (2010). Emotions in cognitive conflicts are not aversive but are task specific. *Cognitive, Affective, & Behavioral Neuroscience*, 10(3), 349-356.

- Scolari, M., & Serences, J. T. (2009). Adaptive allocation of attentional gain. *Journal of Neuroscience*, 29(38), 11933-11942.
- Slagter, H. A., Prinssen, S., Reteig, L., & Mazaheri, A. (2016). Facilitation and inhibition in attention: functional dissociation of pre-stimulus alpha activity, P1, and N1 components. *Neuroimage*, 125, 25-35.
- Slobounov, S. M., Zhang, K., Pennell, D., Ray, W., Johnson, B., & Sebastianelli, W. (2009). Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study. *Exp Brain Res*.
doi:10.1007/s00221-009-2141-6
- Solbakk, A.-K., Reinvang, I., & Nielsen, C. S. (2000). ERP indices of resource allocation difficulties in mild head injury. *Journal of Clinical and Experimental Neuropsychology*, 22(6), 743-760.
- Spencer, R. J., Drag, L. L., Walker, S. J., & Bieliauskas, L. A. (2010). Self-reported cognitive symptoms following mild traumatic brain injury are poorly associated with neuropsychological performance in OIF/OEF veterans. *Journal of Rehabilitation Research and Development*, 47(6), 521-530.
- Steinhauer, S. R., & Hakerem, G. (1992). The pupillary response in cognitive psychophysiology and schizophrenia. *Annals of the New York Academy of Sciences*, 658(1), 182-204.

- Sterr, A., Herron, K. A., Hayward, C., & Montaldi, D. (2006). Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussion syndrome. *BMC Neurology*, 6, 7-7. doi:10.1186/1471-2377-6-7
- Theeuwes, J. (2010). Top-down and bottom-up control of visual selection. *Acta Psychologica*, 135(2), 77-99. doi:http://dx.doi.org/10.1016/j.actpsy.2010.02.006
- Unsworth, N., & Robison, M. K. (2015). Individual differences in the allocation of attention to items in working memory: Evidence from pupillometry. *Psychonomic Bulletin & Review*, 22(3), 757-765.
- Wechsler, D. (2014). Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV).
- Williams, L. J., & Abdi, H. (2010). Fisher's least significant difference (LSD) test. *Encyclopedia of Research Design*, 218, 840-853.
- Zekveld, A. A., Kramer, S. E., & Festen, J. M. (2011). Cognitive load during speech perception in noise: The influence of age, hearing loss, and cognition on the pupil response. *Ear and Hearing*, 32(4), 498-510.

Table 3.1. Participant Characteristics, Symptoms, and Neuropsychological Performance

	Uninjured Controls	Chronic mTBI	p^a
<i>n</i>	21	18	--
Female, # (%)	16 (76.2%)	8 (44.4%)	.04*
Race/Ethnicity			.35
Black, # (%)	8 (38.1%)	3 (16.7%)	
White, # (%)	10 (47.6%)	10 (55.6%)	
Hispanic / Latino, # (%)	1 (4.8%)	2 (11.1%)	
Asian, # (%)	1 (4.8%)	3 (16.7%)	
Other, # (%)	1 (4.8%)	0 (0.0%)	
Age in years, M (<i>SD</i>)	34.67 (10.08)	36.33 (10.52)	.62
Years education, M (<i>SD</i>)	16.93 (2.11)	15.50 (3.81)	.15
Estimated premorbid IQ, M (<i>SD</i>)	107.24 (10.35)	108.33 (9.86)	.74
Months Since Injury (<i>SD</i>)	--	40.61 (34.17)	
NSI total score, M (<i>SD</i>)	9.14 (10.75)	28.50 (15.11)	.01**
Neuropsychological z-score (<i>SD</i>)	0.079 (0.49)	0.032 (0.60)	.79

Note. ^a p -value associated with independent samples t -test or chi-square test, where appropriate. * $p < .05$; *** $p < .01$.

Table 3.2. Correlation Coefficients

	Uninjured Controls				Chronic mTBI			
	RT	DBP D†	NP	Effort	RT	BPD†	NPNP	Effort
Baseline Pupil Diameter†								
<i>Low/Valid</i>	-.378	--	.016	-.448*	-.119	----	-.358	.092
<i>Low/Invalid</i>	-.396	--	-.012	-.457*	-.252	----	-.486	.047
<i>Moderate/Valid</i>	-.150	--	.057	-.192	-.132	----	-.443	.257
<i>Moderate/Invalid</i>	-.407	--	.045	-.154	-.159	----	-.528^	.218
<i>High/Valid</i>	-.111	--	.078	-.148	.369	----	-.356	-.083
<i>High/Invalid</i>	-.122	--	.077	-.133	.385	----	-.337	-.039
P1 Amplitude								
<i>Low/Valid</i>	-.532*	.083	.300	-.131	-.208	.099	.256	-.191
<i>Low/Invalid</i>	-.512*	-.033	.358	-.058	.098	-.207	.345	-.299
<i>Moderate/Valid</i>	-.449*	-.103	.200	-.407^	-.506*	.010	.396	.145
<i>Moderate/Invalid</i>	-.435*	-.005	.126	-.446*	-.475*	.042	.438^	.003
<i>High/Valid</i>	-.232	-.097	.055	-.477*	-.164	.271	.324	.009
<i>High/Invalid</i>	-.424^	-.064	.076	-.316	-.235	.046	.351	.202
N1 Amplitude								
<i>Low/Valid</i>	-.410	.293	.402^	-.413^	-.095	-.472^	.216	-.217
<i>Low/Invalid</i>	-.397	.131	.266	-.074	.178	-.313	.322	-.301
<i>Moderate/Valid</i>	-.455*	.065	.210	-.418^	-.454*	-.379	.173	-.197
<i>Moderate/Invalid</i>	-.370	.029	.069	-.320	-.400	-.383	.438^	-.166
<i>High/Valid</i>	-.329	-.046	.252	-.382^	-.200	-.313	.267	.324
<i>High/Invalid</i>	.193	.118	.073	-.199	-.229	-.330	.311	.557**

Notes. * $p < .05$; ^ $p < .09$; †indicates partial correlation coefficients; BPD=baseline pupil diameter; NP Z=global neuropsychological z-score.

Figure 3.1. Task Schematic. Cue validity varied randomly within blocks and task instructions varied randomly between blocks (SRT, CRT, or 1-back).

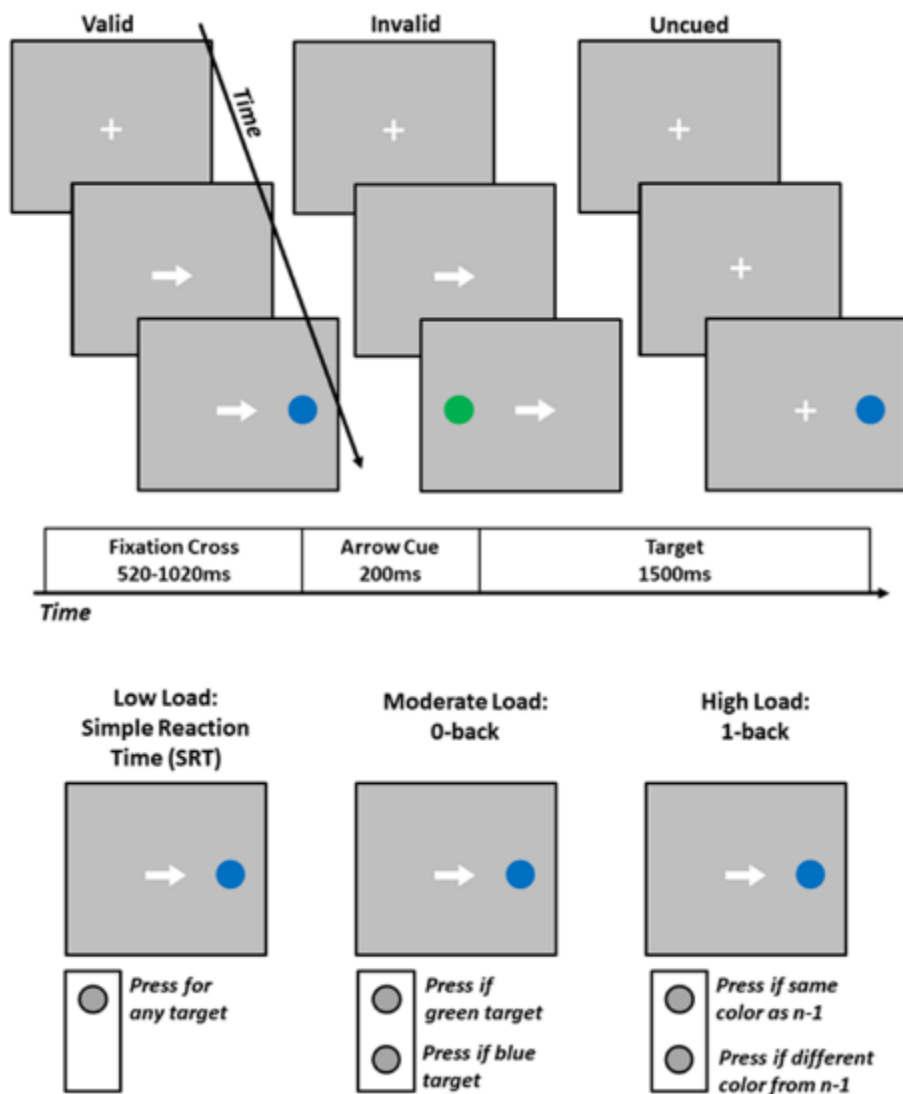


Figure 3.2. Response Time. Load and trial type interacted, $p = .02$, wherein differences in RT between valid and invalid trials were significant at low and moderate loads, $p < .05$.

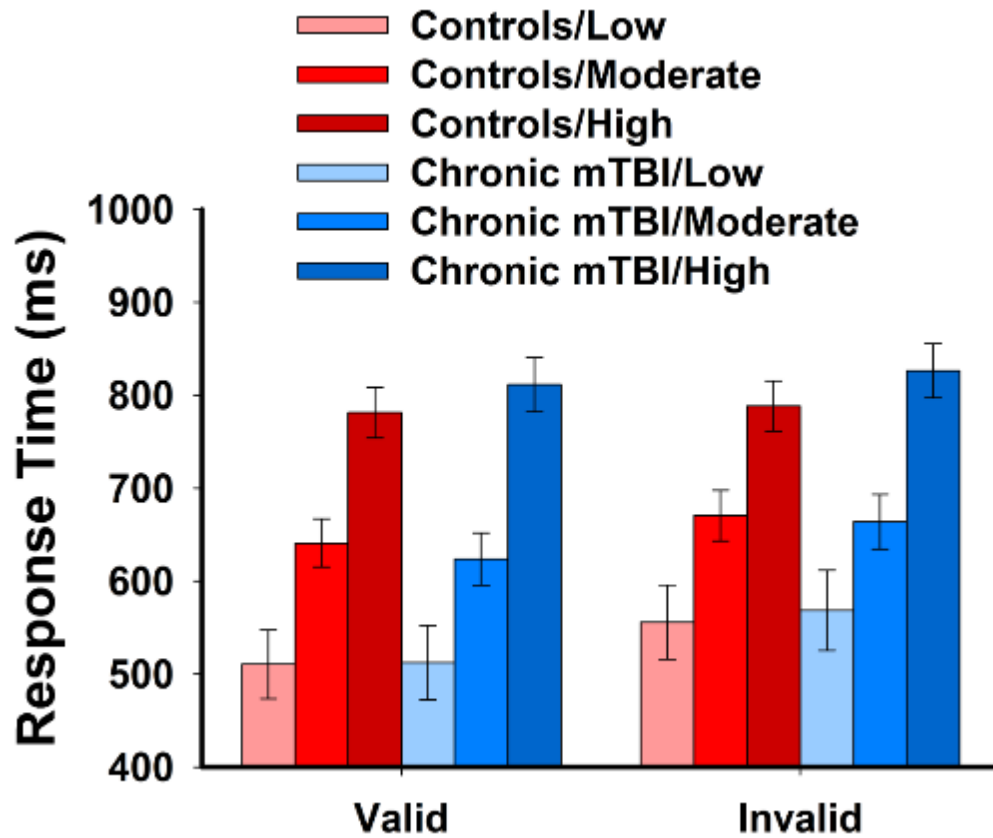


Figure 3.3. Baseline Pupil Diameter. Groups differed marginally, $p = .06$; this difference was significant, $p < .05$, at low and moderate loads. A main effect of load was also observed, $p = .04$.

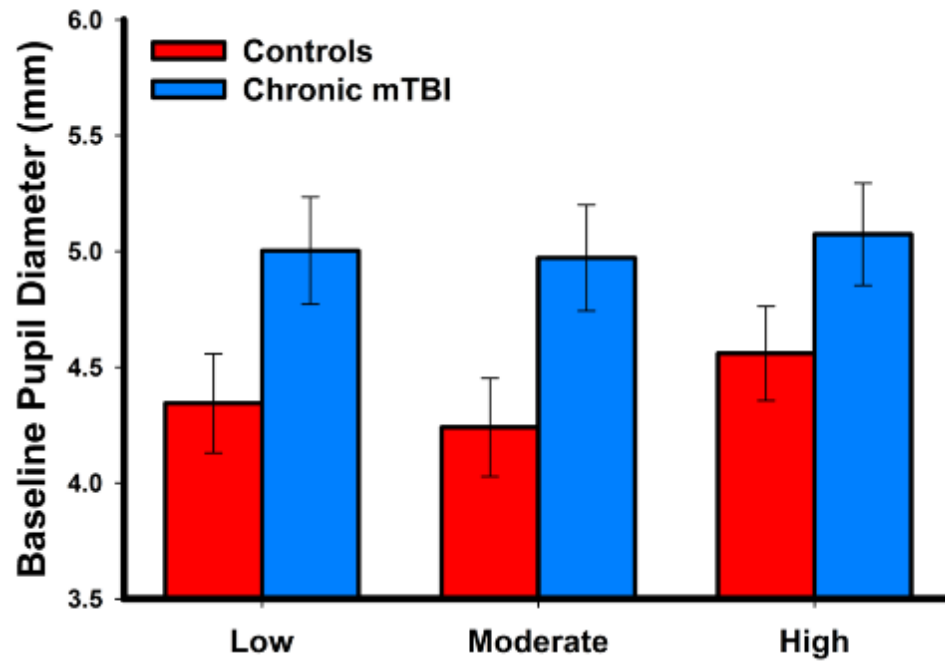
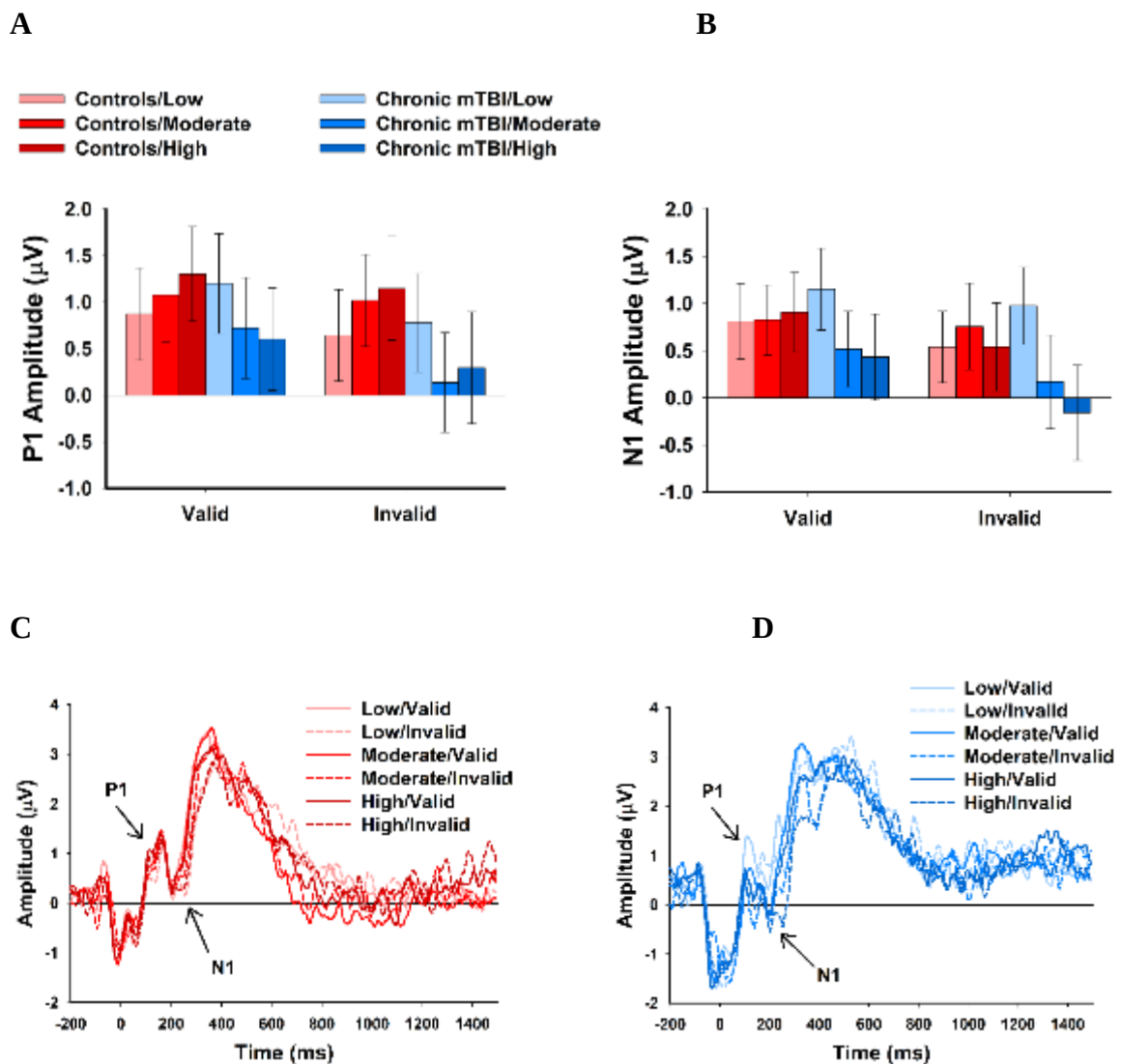


Figure 3.4. ERP Results. A) P1 amplitude differed by trial type, $p = .02$; an interaction between group and load was observed, $p < .01$, wherein the effect of load was significant in chronic mTBI but not controls; B) N1 amplitude revealed an interaction between group and load, $p = .01$, wherein the effect of load was significant in chronic mTBI but not controls; C) Contralateral ERP waveforms at O1/O2 for the control group. D) Contralateral waveforms at O1/O2 for the chronic mTBI group.



Chapter 4: Insights into Cognitive Pupillometry: Evaluation of the Utility of Pupillary Metrics for Assessing Cognitive Load in Normative and Clinical Samples

INTRODUCTION

Applications of Cognitive Pupillometry

Since the 1960s, pupillometry has been used to study information processing in healthy and clinical populations (Janisse, 1973). Pupillary responses have been linked to cognitive and emotional mechanisms, including changes in global resource allocation and cognitive arousal (Beatty, 1982b; Beatty and Lucero-Wagoner, 2000; Granholm and Verney, 2004; Unsworth and Robison, 2015; Verney et al., 2001), novelty processing and attention orienting (Murphy et al., 2011; Steiner and Barry, 2011; Wang and Munoz, 2015) and emotion processing (Bradley et al., 2002; Kinner et al., 2017). Early pupillometry research established that fluctuations in pupil diameter reliably track changes in information processing. In a classic study using a digit span task, Beatty and Kahneman (1966) demonstrated that pupil diameter increased linearly as the number of digits held in working memory increased, and decreased linearly as participants recounted the digits, effectively removing them from working memory. This work was among the first to suggest that changes in pupil diameter reflect variations in cognitive load, a hypothesis that has been subsequently and consistently supported (Cabestrero et al., 2009; Granholm et al., 1996; Siegle et al., 2008; Wong and Epps, 2016; Zekveld and Kramer, 2014). Subsequent research has demonstrated that cognition-related fluctuations in pupil diameter (in contrast to light reflexes) are largely influenced by the locus-

coeruleus norepinephrine (LC-NE) system which projects to nearly every cortical region and is strongly linked to arousal (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Beatty, 1982b; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Rajkowski, Kubiak, & Aston-Jones, 1993). Increased pupil dilation reflects the relative amount of attentional resources levied in response to a cognitive task. Cognitive load can also reduce the amplitude of the pupillary light reflex (Steinhauer et al., 2000; Verney et al., 2001). Thus, tasks with greater cognitive load require greater resource allocation as reflected by greater pupil diameter or attenuated constriction, regardless of the cognitive domain assessed by the task (Beatty, 1982b; Beatty and Lucero-Wagoner, 2000).

In addition to understanding normal cognitive function, cognitive load is an important consideration for understanding the nature of cognitive deficits in clinical populations. In populations characterized by abnormal or impaired resource allocation, cognitive deficits may become increasingly apparent as cognitive load increases (Cummins et al., 2008; Petrides, 2000). Patients may require additional neural resources or exhaust their available resources at lower levels of cognitive load compared to healthy controls, with or without concomitant performance decrements (Granholm et al., 2017; Mandrick et al., 2016; Li et al., 2016). For example, Granholm and colleagues (2017) demonstrated that amnesic single-domain mild cognitive impairment (MCI) patients exhibited differential effects of cognitive load on pupil diameter than normal controls, despite similar performance. They suggest that pupillary responses to changes in cognitive load may be a useful early biomarker for cognitive impairment before performance deficits become evident. Thus, pupillary measures of resource allocation in

response to tasks with varying cognitive loads may help inform neurocognitive assessment in clinical and healthy populations, even in the absence of behavioral deficits.

There has been an increase in the amount of published cognitive and affective pupillometry studies within the last 15 years. A large proportion of these studies investigated cognitive/affective processing in psychiatric conditions, notably schizophrenia and depression (Granholm et al., 2009; Granholm et al., 2016; Jones et al., 2015; Silk et al., 2007; Stone et al., 2016; Verney et al., 2001). This pattern is reflective of a recent trend of moving pupillometry from a basic research methodology towards clinical use in applied settings (Granholm et al., 2017; Graur and Siegle, 2013). Pupillometry may also be particularly useful for conditions that are most challenging to assess using conventional behavioral and neuropsychological measures (Sirois and Brisson, 2014), as it may reveal hidden cognitive deficits and/or improve prognostic accuracy (Granholm et al., 2017; Graur and Siegle, 2013). The added utility of pupillometry to neurocognitive assessment is due in large part to 1) the ability to measure neurocognitive processing and resource allocation in patients more accurately than behavioral or self-report measures; 2) the ability to measure an outcome that is not under voluntary control of patients, therefore eliminating the capability of influencing outcomes; and 3) the ability to measure neurocognitive processing less invasively and more cost-efficiently than neuroimaging techniques, such as PET or fMRI (Graur and Siegle, 2013; Sirois and Brisson, 2014).

Pupillary Metrics

Despite the increased use of pupillometry in research settings and recommendations from researchers to advance its translation into applied settings (Graur

and Siegle, 2013), there is no consensus on which metrics are best suited for particular applications or research questions (Sirois and Brisson, 2014). We wish to address this methodological gap in the literature by evaluating a variety of pupillary metrics in both a healthy and a clinical sample. Over the years, several metrics have been used to quantify pupillary activity during cognitive tasks. Analyses have included measuring pupil diameter in the time-frequency domain (e.g., the frequency of pupillary oscillatory activity; Grünberger et al., 1996; Naber, Alvarez, and Nakayama, 2013) and the time-domain (e.g., how diameter changes over time; Kamp and Donchin, 2015; Otero et al., 2011; Sirois and Brisson, 2014); however, the most common is a time-domain approach almost exclusively using a stimulus-locked approach. A commonly-used metric is the mean pupil diameter over a specified post-stimulus time window with a pre-stimulus baseline value subtracted (“baseline-corrected pupillary response” [BCPR]; Klingner, Tversky, and Hanrahan, 2011; Van Steenbergen and Band, 2013). Because it is an average, this metric is robust against random noise and spurious peaks in the pupillary signal. A similar approach involves computing the peak pupil diameter over a given time window as a proportion of the average or peak baseline, which permits more direct comparison between and within individuals (e.g., “peak dilation ratio”; Cavanagh et al., 2014; Heaven and Hutton, 2010). However, some researchers suggest using peak dilation with a pre-stimulus baseline subtracted to avoid the potential problem that means-based measures are influenced by the baseline diameter (Beatty and Lucero-Wagoner, 2000). Other metrics used in prior pupillometry research include peak dilation latency (Kuchinsky et al., 2013; Reinhard et al., 2007), peak-to-peak difference (Granholm et al.,

2009; Verney et al., 2001), and baseline pupil diameter over a pre-stimulus time window (Beatty, 1982a; Heitz et al., 2008).

Interestingly, task-evoked pupillary activity is typically measured at variable latencies following stimulus onset but has been observed to occur consistently prior to behavioral responses, regardless of trial type or response time; this pattern suggests that task-evoked pupillary activity reflects the outcome of task-related decision processes that facilitate behavioral performance (Aston-Jones and Cohen, 2005; Rajkowski et al., 2004). For this reason, time locking pupil activity to a response could potentially provide insight into cognitive processing that may otherwise be overlooked by time locking pupil activity to a stimulus, although the latter approach is considerably more common. Accordingly, this study will evaluate both stimulus-locked (i.e., post-stimulus) and response-locked (i.e., pre-response) pupillary metrics. In addition to mean-based and peak-based averages, intra-individual variability (e.g., within-subject standard deviation) of pupillary metrics also holds promise as a valuable metric to evaluate differences in information processing. Although largely excluded from the extant literature, greater intra-individual variability in behavioral and psychophysiological responses likely represents less precision in neurological responses to stimuli that may be indicative of underlying neuropathology (Dinstein et al., 2015) and/or trial-by-trial lapses in attention (Ghajar and Ivry, 2008; MacDonald et al., 2006; MacDonald et al., 2008; Taylor et al., 2011; Vaurio et al., 2009). In light of this, we will also evaluate the within-subject standard deviations of each pupillary metric.

Study Aims

To further advance the incorporation of pupillometry into neurocognitive assessment, the goal of the current study is to identify pupillary metrics that are psychometrically sound, sensitive to group and cognitive load differences and/or their interaction, and likely to replicate. To achieve the study aim, several pupillary metrics—selected based on their previous use in the extant literature, including cue- and response-locked means, peaks, peak latencies, and their standard deviations—were derived from raw pupil diameter in a clinical sample—symptomatic participants with remote history of mild TBI and uninjured control—as they completed a cued-attention task with varying levels of cognitive load. This comparison of pupillary outcomes between healthy controls and the mild TBI group is intended to serve as an example of the utility of various pupillary metrics to identify load-dependent cognitive processing differences in clinical populations. Prior research has demonstrated that neural activation patterns are atypical and vary by load in mild TBI, even when performance appears normal (Broglia et al., 2009; McAllister et al., 2001; Slobounov et al., 2009), making this task and clinical sample ideal candidates for testing the sensitivity of pupillary metrics to measure load effects in a clinical population. Empirical analyses were used to evaluate sensitivity to group and load effects for all metrics; additional bootstrapping analyses were computed to determine the replicability of results. Because this is an exploratory analysis of methodology with the goal of examining load effects on pupillary metrics in normal and clinical samples, no a priori hypotheses were tested; theoretical discussion of observed patterns will be reported in forthcoming papers.

METHODS

Participants

Forty-four participants, ages 18-55 years, were recruited using community and online advertisements in the greater Washington, DC metro area for participation in a parent study investigating saccadic impairment in TBI (Ettenhofer et al., under review). All participants provided written informed consent prior to testing, in accordance with the Uniformed Services University of the Health Sciences Institutional Review Board. Participants were excluded for history of any neurological condition (other than mild TBI), uncorrected vision problems, or inability to provide written informed consent. Twenty-five participants were included as healthy controls and 19 were included in the mild TBI group. Inclusion in the mild TBI group was permitted if participants had a history of mild TBI at least 3 months prior and no more than 10 years prior to testing, and reported persistent neurobehavioral symptoms (Neurobehavioral Symptom Inventory, NSI; Cicerone and Kalmar, 1995; King et al., 2012). Mild TBI was defined according to American Congress of Rehabilitation Medicine (ACRM) criteria of loss of consciousness (LOC) less than or equal to 30 minutes, alterations of consciousness (AOC) of any duration, and/or post-traumatic amnesia (PTA) less than or equal to 24 hours following injury (Head, 1993). ACRM criteria for mild TBI was assessed using the OSU TBI identification method, a validated and reliable method for evaluating lifetime history of head injury (Corrigan and Bogner, 2007). Prior to cognitive testing, all participants completed a brief demographic questionnaire, the Wechsler Test of Adult Reading (WTAR; Green et al., 2008) to obtain an estimated premorbid IQ score, the PTSD Checklist-Civilian (Weathers et al., 1994) to assess self-reported PTSD symptoms, the Center for Epidemiological Studies Depression Scale questionnaire (Radloff, 1977) to

assess self-reported depressive symptoms, and the NSI to assess self-report neurobehavioral symptoms.

Apparatus

Stimuli were controlled and delivered via a desktop computer using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA). Stimuli were presented on a 24 inch, 1920x1080 resolution LCD monitor and manual responses were recorded on a Cedrus RB-540 response box. Pupil diameter was recorded from the right eye using an Applied Science Laboratories (ASL) D6 remote eye tracker which detects pupil diameter and eye movements using an infrared light source directed at the participants' eyes. Pupillary data were continuously sampled at 120 Hz. The camera was centered below the stimulus presentation monitor and participants were positioned in a chin rest to maintain head position during testing. Output pupil values from the eye tracker were converted from pixels to millimeters using a scaling factor derived from calibration to a simulated eye of known size and distance from camera.

Procedure and Task Design

After providing written informed consent, and completing questionnaires, participants performed a computerized cued-attention task (see Figure 1). Participants were centered 24 inches in front of a stimulus computer and remote desktop eye tracker. Ambient luminance in the room was 29 lux for all testing sessions. Eye movement calibration using a 9-point calibration array was conducted prior to each block of the task to ensure eye tracking accuracy for the parent study. Following the initial calibration, participants completed the cued-attention task while behavioral responses and pupil

diameter were recorded. In the task, participants were instructed to shift their gaze to a lateral target as quickly as possible after target onset, while simultaneously making a manual response (i.e., button press). Targets were either blue or green circles (diameter angle 1.19° , 2 lux) that appeared either to the left or right of center and were preceded by an arrow cue on 73.5% of trials. Cues were either left- or right-facing white arrows (diameter angle 1.34° , 4 lux), and were presented in the center of the screen over a gray background (1 lux) 200ms prior to target onset. The cues validly predicted the location of the target for 47% of trials (“valid”); cues invalidly predicted the target location for 26.5% of trials (“invalid”). Additionally, 26.5% of trials were uncued (“uncued”), with an inter-trial central fixation cross persisting instead. The arrow cues and the central fixation cross were of similar luminance, precluding the possibility that any differences in the pupil response would be due to differences in the pupillary light reflex. The arrow cues or fixation cross (for uncued trials) remained onscreen after the target appeared. Targets and cues remained on screen together for 1500ms following target onset. Between each trial, a central fixation cross was displayed (diameter angle 1.34° , 4 lux); the duration of the inter-trial interval varied randomly between 520 and 1020 seconds. Instructions for how to respond to the targets were varied across task blocks to modulate cognitive load. There were three conditions of variable cognitive load: in the low load condition, participants were instructed to press the center button on the response device when the target appeared (simple reaction time, “SRT”). In the moderate load condition, participants were asked to press a button above-center if the target was blue and a button below-center if the target was green (“0-back”). In the high load condition, participants were asked to determine whether the color of the current target (either blue or green) matched

or did not match the color of the target on the previous trial (“1-back”). Participants pressed a button above-center to indicate “same” and a button below-center to indicate “different.” Figure 1 is a graphical depiction of the task. There was a total of 6 blocks, with two sequential blocks for each load condition and 120 trials per block. Cognitive load conditions varied randomly between blocks (e.g., 2 blocks of a given load condition were presented sequentially, but order of load conditions varied randomly); cue-target combinations (valid, invalid, or uncued trials) varied randomly within blocks. Video instructions and 6, 8, or 12 practice trials were provided at the beginning of each low, moderate, and high load condition block, respectively. Participants could elect to replay the instructional video and/or repeat the practice block if desired prior to beginning the experiment.

Pupillometry Acquisition and Processing

Pupillary data were processed off-line using custom MATLAB scripts (Version 8.4, Mathworks, Inc, 2014). In accordance with prior studies (Kang et al., 2014; Klingner et al., 2008; Schacht et al., 2010), raw pupillary data were filtered using a 10Hz low-pass FIR filter and blinks and data loss (any data segments $\leq 500\text{ms}$) were corrected using a linear interpolation. Trials with total data loss of greater than 500ms were excluded from further processing. A post-processing t-test comparing the amount of interpolated data between groups confirmed there was no group difference, $t(36)=-.285$, $p=.777$. On average, 159.6ms (8.4%) of data in the mild TBI group and 147.6ms (7.7%) of data in the control group was interpolated per each 1900ms data epoch. Trials for which behavioral responses were incorrect or omitted were also excluded from further processing. Participants with less than 15 usable trials (after data cleaning) in any one load condition

were excluded from analyses. A cue- and response-locked epoch was extracted from each trial. For cue-locked epochs, data were segmented -200ms to 1700ms around cue onset. Like cued trials, uncued trials were epoched to a timepoint that occurred 200ms prior to target onset, albeit without a cue appearing at that timepoint). Response-locked epochs were measured as the 1000ms immediately preceding a correct manual response. For pupillary metrics that are baseline corrected, baseline was defined as the average diameter over the 200ms pre-cue interval. The pupillary metrics evaluated in this study are presented in Table 1 and a corresponding graphical depiction of a prototypical pupillary waveform is provided in Figure 2. Values for each pupillary metric were computed for each trial and pooled across the three trial types (valid, invalid, and uncued) to obtain an average and standard deviation for each of the three load conditions.

Analytic Strategy

Internal Consistency

For each pupillary metric (mean and standard deviation), internal consistency was measured using a split-half reliability estimate using an odd-even method (i.e., correlating values of odd and even numbered trials) and a Spearman-Brown adjustment. These data were submitted to 5000 resamples (randomized with replacement) to compute an average reliability coefficient for each metric (e.g., “bootstrapped estimate;” see section 2.5.3). Our interpretations of the coefficients were informed by the guidelines set by Cicchetti (1994), whereby $r > .7$ is acceptable, $r > .8$ is good, and $r > .9$ is excellent.

Empirical Data Analyses

To assess group and load effects and group*load interactions, data from the original empirical sample were submitted to a 2 (group: mild TBI/controls) X 3 (load: low/moderate/high) repeated measures ANOVA. Results with $p < .05$ were interpreted as statistically significant and Greenhouse-Geisser corrections were applied to analyses with violations of sphericity assumption. To characterize the effects of load separately within both groups, tests of simple effects of load within each group were conducted using univariate ANOVAs with load as the within-subjects factor.

Replicability Analyses

While the ideal way to determine replicability is to repeat studies using similar samples (“external replication”), this is not always a practical approach. As an alternative, bootstrap resampling can be useful in determining if the effects observed in an original sample can generalize to similar independent samples by estimating the probability of replication. It is a non-parametric approach that creates a “bootstrapped resampling distribution” from a given data sample (“empirical sample”) by selecting thousands of “bootstrapped resamples” from the empirical sample using random sampling with replacement. Each of the thousands of resamples contains the same number of subjects as the empirical sample, although some subjects may be represented more than once or not at all in any given bootstrapped resample. The analysis of interest (e.g., ANOVA, regression) is then computed for each of the bootstrapped resamples, providing thousands of sample estimates of the statistic of interest (e.g., F , r^2 , or η^2). These thousands of estimates form the bootstrapped resampling distribution from which means and confidence intervals can be computed. The bootstrapped resamples are thought to represent thousands of potential random samples from the population; thus, the

confidence intervals around the estimates in the bootstrapped resampling distribution represent the likely range of that estimate in the population.

According to Banjanovic and Osborne (2016), if the confidence interval around effect size estimates is narrow and contains small, medium, or large effect sizes, the likelihood of the effects replicating in similar samples is higher than if the confidence interval has a wide range that does not primarily contain small, medium, or large effect sizes. In accordance with the above criteria, we considered an effect likely to replicate if the bootstrapped confidence intervals contained small, medium, or large effects sizes, implying that the effects observed in the empirical sample are likely to be observed again in independent samples using the same experimental parameters (Banjanovic and Osborne, 2016; Efron and Tibshirani, 1994; Thompson, 1993, 1995). If the lower limit of any confidence interval was near zero, we could not confidently predict that the effects would replicate. Additionally, the values of the average effect size from the bootstrapped resampling distribution (“average bootstrapped effect size”), together with effect size confidence intervals, should indicate the expected magnitude of the effect in subsequent studies (Banjanovic and Osborne, 2016; Efron and Tibshirani, 1994).

To perform the bootstrapping analysis, data from our empirical sample were submitted to a bootstrapping algorithm custom-written in Matlab to create 5000 bootstrapped resamples for each of the pupillary metrics (DiCiccio and Efron, 1996). A 2 (group: mild TBI/controls) X 3 (load: low/moderate/high) repeated measures ANOVA was applied to the 5000 bootstrapped resamples to create bootstrapped resampling distributions of partial eta squared, η_p^2 , for effects of group, load, and their interaction for all pupillary metrics. For each bootstrap distribution, the average η_p^2 and 95% confidence

intervals (percentile method) were computed. Simple effects of load within each group were analyzed using univariate ANOVAs and submitted to the same bootstrapping procedure. We used Cohen's (Cohen, 1988) guidelines for interpreting η_p^2 (small: $\eta_p^2 > .01$; medium: $\eta_p^2 > .06$; large: $\eta_p^2 > .14$).

RESULTS

Participants

Following data processing, six participants were excluded from further analyses due to missing data (less than 15 usable trials per load condition). The reason for low trial count in these participants was difficulty establishing a lock to participants' eyes. In total, 23 and 15 participants were included in the control and mild TBI groups, respectively. The average age of the final sample was 35.29 (SD=9.99) years with no significant group difference, $t(36) = -.748$, $p = .459$. The average years of education for the sample was 16.33 (SD=2.64), with no group difference, $t(36) = 1.51$, $p = .147$. There was a significant group difference in NSI score, $t(36) = -3.80$, $p < .01$. The average NSI score was 9.47 for controls and 25.4 for the mild TBI group. Group comparisons of self-reported PTSD symptoms [$M = 27.39$, $SD = 11.85$, $t(36) = -1.89$, $p = .076$], self-report depressive symptoms [$M = 13.39$, $SD = 9.06$, $t(36) = -1.50$, $p = .116$], and estimated premorbid IQ [$M = 107.68$, $SD = 10.11$, $t(36) = -.310$, $p = .754$] were also not significant. The mild TBI group sustained an average of 2.3 lifetime TBIs (SD=2.1) with 42.9 months average time since most recent injury (SD=36.6).

Manual Response Time

Although reported elsewhere in greater detail (Ettenhofer, Hershaw, Engle, and Hungerford, in press), we present here the results of a 2 (group) x 3 (load) repeated measures ANOVA on manual response times to complement our pupillary analyses. A main effect of load was observed, $F(1.48, 53,38)=68.773$, $p<.001$, $\eta_p^2=.656$. There was no significant effect of group, $p=.647$, or interaction, $p=.278$. Pairwise comparisons revealed that all comparisons were significant, $p<.001$, such that the low load condition had the fastest response time ($M=531\text{ms}$, $SE=29$), followed by moderate load ($M=648\text{ms}$, $SE=19$), and the high load condition had the slowest response times ($M=807\text{ms}$, $SE=20$).

Presentation of Results

Due to the large number of analyses conducted on pupillary data, we combined results into Table 2 to provide the most important results from internal consistency, empirical, and bootstrapped replicability analyses. Values included in Table 2 are those which represent meaningful results, including statistically significant effects from empirical analyses, non-trivial average effect sizes from bootstrapping analyses, and those results which exceed conventionally acceptable thresholds. Detailed results from all constituent analyses are presented in the Appendices (Tables B-F), as described in the following sections. Pupillary waveforms for the three load conditions in controls and the mild TBI group are shown in Figure 3.

Internal Consistency

As seen in Table 2 (“Reliability” column), nearly all pupillary metrics met conventional thresholds for “acceptable” internal consistency ($r>0.7$), with many exceeding the “excellent” threshold ($r>.9$). Of the 34 metrics tested, only 10 metrics did

not exceed $r > .7$. Detailed results from this analysis, including reliability coefficients for all tested metrics, are presented in Table A.

Group Effects

The 2x3 repeated measures ANOVAs on pupillary metrics using empirical data demonstrated that cue-locked peak dilation latency standard deviation and response-locked peak dilation latency mean and standard deviation were sensitive to group differences (see Table B, “Empirical η_p^2 ”). The mild TBI group exhibited shorter cue-locked latencies, longer response-locked latencies, and less response-locked latency variability than the control group. No other pupillary metrics were sensitive to group differences. The effect sizes were of medium magnitude for all three metrics and nearly identical to the corresponding average bootstrapped effect sizes. However, of all the pupillary metrics, only response-locked peak dilation latency mean produced bootstrapped confidence intervals containing primarily small to large effect sizes (see Table 2, “Group”). Table B includes all results from the analyses of group effects for all pupil metrics.

Load Effects

As demonstrated by significant load effects in the 2x3 repeated measures ANOVAs, some pupillary metrics detected differences in cognitive load, while others did not (see Table C for full results). Notably, cue- and response-locked peak dilation latency mean and response-locked peak dilation latency standard deviation were sensitive to load effects averaged across both groups. Pairwise comparisons for both cue- and response-locked means showed that latency was shortest in the low load condition ($p < .001$) than

the moderate and high load conditions, which did not differ from each other ($p > .142$). Response-locked dilation latency variability was significantly different between all three load manipulations, with low load generating the greatest amount of variability, $p < .01$, and high load generating the least, $p < .01$. The magnitudes of these three significant load effects metrics were medium-large to large and similar to the corresponding bootstrapped average η_p^2 . For all three metrics, confidence intervals contained small-medium to large effect sizes (see Table 2, “Load”). The empirical analysis yielded small to medium effect sizes for many other pupillary metrics, although they failed to reach statistical significance and the lower limits of their confidence intervals approached zero.

As shown in Table 2 (“Load: Controls”), empirical univariate ANOVAs showed that the following metrics were sensitive to load effects within controls: cue-locked peak dilation latency, response-locked peak dilation latency mean and standard deviation, response-locked peak constriction, response-locked peak constriction latency, response-locked peak to peak difference and standard deviation. All of these metrics followed the same pattern described above and had medium-large to large effect sizes. Subsequent bootstrapping analyses demonstrated that the bootstrapped average η_p^2 for these metrics was slightly larger in magnitude than their corresponding empirical effect sizes.

Additionally, although only a select group of metrics reached statistical significance, all the pupillary metrics in this study had small-medium to large average bootstrapped η_p^2 . Similarly, many of the pupillary metrics that did not yield significant load effects had bootstrapped confidence intervals containing small to large effect sizes (see Table 2, “Load: Controls”). This pattern was more prominent with response-locked metrics. Full results from this analysis are shown in Table D.

Within the mild TBI group, peak dilation latency standard deviation was sensitive to load (Table 2, “Load: Mild TBI”), such that variability decreased as load increased. The large empirical effect size was nearly identical to the bootstrapped average effect size. Additionally, the confidence interval contained medium-large to large effect sizes. Cue- and response-locked peak dilation latency mean, while not statistically significant in the empirical sample, had large effect sizes and bootstrapped confidence intervals that primarily contained small to large effect sizes. Most of the other metrics had small to medium empirical effect sizes and bootstrapped average effect sizes; however, the lower limit of their confidence intervals approximated zero and they did not produce significant results when submitted to empirical univariate ANOVAs (see Table E).

Group*Load Interaction

A significant interaction between group and cognitive load was identified with response-locked peak dilation standard deviation (see Table 2, “Group*Load”). The linear effect of load was larger in the mild TBI group than controls. The significant interaction demonstrated a medium empirical effect size; the bootstrapped average η_p^2 for this interaction was slightly larger than the empirical result. The bootstrapped confidence interval contained small to medium effect sizes. The 2x3 repeated measures ANOVAs on empirical data for the remaining pupillary metrics did not yield significant interactions. While nearly all bootstrapped average effect sizes were small-medium in size for this interaction, their confidence intervals approached zero and therefore the results are not likely to replicate (see Table F).

DISCUSSION

Pupillometry has great potential to be used for neurocognitive assessment, both in research and clinical settings, due to its ability to non-invasively measure neurocognitive function independent of behavioral methods. The goal of the current study was to address a methodological research gap by evaluating the utility of various pupillary metrics for neurocognitive assessment in a healthy and a mild TBI sample. Specifically, we examined the internal consistency, sensitivity to group and cognitive load effects, and replicability of pupillary metrics. Our reliability analyses indicated that most pupillary metrics tested in our study are reliable. Empirical analyses indicated that some of the tested variables were sensitive to group differences, experimental manipulations of cognitive load, and/or their interaction. Additional bootstrapping analyses of effect sizes revealed which metrics are likely to produce replicable effects of small, medium, or large magnitude. Given the combined reliability, sensitivity, and replicability of various metrics, our results demonstrate that a variety of pupillary metrics show promise for future studies of cognitive load, whether in normal samples or in clinical samples, although additional considerations should be taken into account when selecting pupillary metrics, as described below.

Internal consistency analyses of the pupillary metrics tested in our study revealed that nearly all metrics were highly reliable within a single testing session. The exceptions were cue- and response-locked Pupil Dilation Ratio means, response-locked Pupil Dilation Ratio standard deviation, cue- and response-locked BCPR means, and cue- and response-locked BCPR percent change means and standard deviations. In effect, metrics representing peak values and peak latencies were reliable; metrics computed using ratios or by averaging pupil diameter over a time window were not reliable.

A small number of pupillary metrics yielded statistically significant effects of group, cognitive load, or their interaction, including cue-locked peak dilation latency mean (cognitive load effect) and standard deviation (group effect) and response-locked peak dilation latency mean (group and cognitive load effects) and standard deviation (effects of group, cognitive load, and a group*cognitive load interaction). Response-locked peak dilation latency and its standard deviation demonstrated the greatest utility due to its sensitivity to group and cognitive load effects as well as their interaction. Although the empirical data revealed that most pupillary measures (all but peak dilation latency) were unable to detect significant group or cognitive load differences, the bootstrap analyses of effect sizes indicated that peak dilation, in addition to peak dilation latency, is likely able to detect a group*load interaction in other samples with sufficient power. The bootstrapped confidence interval around peak dilation contained primarily small to medium-large effect sizes. The bootstrapped average effect sizes for group, cognitive load, and interaction effects for many of the remaining metrics were small to large in magnitude; however, the lower limits of the confidence intervals around these averages approached zero and thus are unlikely to replicate in future samples.

In general, the pupillary metrics evaluated in this study performed better when cognitive load comparisons were conducted separately within each group. Within controls, means for cue- and response-locked peak dilation latency, response-locked peak constriction, peak constriction latency, and peak-to-peak difference, as well as standard deviations for response-locked peak dilation latency and peak-to-peak difference were sensitive to experimental manipulations of cognitive load. Additionally, all pupillary metrics tested in this study had small-medium to large bootstrapped average effect sizes

of load within controls. The largest average effect sizes observed were for peak dilation latency (both cue- and response-locked). Bootstrapped confidence intervals for these effect sizes within the control group suggest that the majority of response-locked metrics we evaluated (including means and standard deviations) and cue-locked peak dilation latency means are likely to replicate in similar samples, as evidence by intervals primarily containing small to large effect sizes.

A different pattern of findings for the assessment of cognitive load was observed within the mild TBI group. Although all pupillary metrics yielded average bootstrapped effect sizes ranging from small-medium to large, the empirical univariate ANOVA revealed that one metric in particular—response-locked peak dilation latency standard deviation was sensitive to cognitive load manipulations in mild TBI. The bootstrapped confidence intervals for effect sizes suggest that cue-locked peak dilation latency mean and response-locked peak dilation latency mean and standard deviation are likely to replicate similar cognitive load effects in similar clinical samples. Bootstrapping results for the remaining pupillary metrics did not provide confidence for their use in future research on cognitive load in mild TBI samples.

In light of a large body of literature that demonstrates that the effects of increased cognitive load are observed across a variety of cognitive processes, including attention, executive function, and memory (Cummins et al., 2008; Kessels et al., 2010; Najmi et al., 2015; Tomasi et al., 2007), our goal was to evaluate which pupillary metrics are most sensitive to differences in cognitive load. Our study used a modified cued-attention task to test the effect of cognitive load on various pupillary metrics. We evaluated cue effects on pupillary metrics to verify that pooling data across the different cue types in our task

did not differentially affect load differences. We found that load and cue interacted on peak constriction and peak to peak difference; however, as these two metrics underperformed in nearly all other analyses of sensitivity and replicability, the interaction does not greatly impact our overall conclusions. The minimal effects of cue on pupillary outcomes, by comparison to load manipulations, also indicate that pupillary responses to variations in load are more likely to yield information about cognitive status than responses to specific attentional demands.

Our evaluation of pupillary metrics indicates that the most sensitive and replicable metrics for assessing load effects during an attention task are pupil dilation latency mean and standard deviation, particularly when time locked to behavioral responses. Pupillary activity is known to increase prior to behavioral responses. This phenomenon suggests that the increase in pupil diameter preceding behavioral responses reflects a decision making process that, in turn, facilitates a correct response (Aston-Jones and Cohen, 2005; Gabay et al., 2011; Geva et al., 2013; Rajkowski et al., 2004). For this reason, although pupil dilation latency is temporally linked to behaviors, and thus will be highly related to RT, it is capable of informing investigators and clinicians of the neurocognitive processes involved in task performance, above and beyond what task performance can provide. In fact, in many neurological conditions characterized by subtle cognitive deficits, RT appears normal while neurocognitive processing is atypical. Our results corroborate this dissociation: manual performance of participants with mild TBI did not differ from controls on our task, however group differences were revealed on response-locked peak dilation latency.

In our study, response-locked peak dilation latency metrics were most sensitive to differences in group and load and produced large effect sizes for group, cognitive load, and interaction effects, as well as cognitive load effects assessed within groups that are all likely to replicate. We also demonstrated that response-locked peak dilation standard deviation is likely to replicate small to medium-large effect sizes for a group*load interaction, wherein this metric is likely to detect different effects of cognitive load between groups. Other metrics, such as peak dilation, peak constriction, peak constriction latency, and peak-to-peak difference (means and/or standard deviations) were sensitive to cognitive load manipulations and had large and replicable effects within controls only. Taken together, we conclude that peak-based metrics (peak values and peak latencies) are more reliable, sensitive, and likely to replicate than means-based metrics (e.g., BCPRs) or ratio-based metrics (e.g., pupil dilation ratio); in particular, response-locked peak dilation latency was the superior metric among the metrics we evaluated, as it was reliable, sensitive and likely to replicate all effects we tested in this study.

It is important to note that we found load effects within healthy controls for a more limited number of metrics than what is typically reported in the literature regarding load effects on pupillary response. One possible explanation for this discrepancy is that our task did not manipulate load enough to influence less sensitive pupillary metrics in controls. Indeed, in cognitively normal individuals, greater task difficulty may be needed to observe measurable differences in pupillary responses to task demands. The metrics we identified as most useful measuring cognitive load effects may be limited to cued attention tasks and not generalizable to other cognitive processes that were not directly manipulated by our paradigm. Without evaluating the outcomes from other cognitive

tasks, we cannot resolutely conclude that these results are generalizable to other tasks that modulate cognitive load; however, our goal for these results is to provide measured guidance for researchers when selecting measures of cognitive load—either in healthy controls or clinical populations.

Although certain metrics performed well in our clinical sample and our task, selection of pupillary metrics for future studies should take several factors into consideration. Depending on the research questions investigators seek to answer (i.e., load effects within controls only, simple group effects, or interactions between groups and cognitive load) or the populations under study, other metrics may be more likely to replicate small to large effect sizes. Pupillary metric selection should also take into account the theoretical framework of individual studies, as well as task design. For example, scientists interested in processes that are influenced by sympathetic activation may be better served by measures related to dilation, whereas those interested in parasympathetic activation would be advised to select constriction-based measures. We also demonstrated that both cue- and response-locked peak dilation latency means and standard deviation are robust metrics for assessing group differences in cognitive load. However, while these metrics are not entirely redundant, they share a lot of variance because the data epochs from which they are derived overlap in time (obviously, this feature would vary by task and epoch size). If an investigator is primarily interested in assessing stimulus processing, the preferred metric might be cue-locked pupil dilation latency, whereas an investigator interested in response processing may obtain more informative results with response-locked pupil dilation latency. Similarly, for questions that do not require consideration of the timing of cognitive processing, and instead focus

singularly on amount of cognitive resources, an investigator would be advised to select metrics other than latency-based measures, such as BCPRs, which are more reflective of sustained processing. Finally, stimulus-locked metrics may be the only option if tasks do not require discrete responses.

We analyzed pupillary data from individuals with persistent symptoms following mild TBI. Due to typically normal neuropsychological performance and difficulty identifying underlying neuropathology in this population, there is substantial debate whether the etiology of chronic mild TBI is neurological or psychological (Arciniegas et al., 2005; Bigler, 2008; Binder et al., 1997; Rohling et al., 2012). Other research has investigated differences in pupil diameter in other conditions that are often characterized by subtle behavioral deficits. For example, Granholm and colleagues (2017) recently reported increased pupil dilation in an amnesic mild cognitive impairment sample at higher cognitive loads, despite normal performance on digit span recall. Our findings that some pupillary metrics are more sensitive to neurocognitive processing differences chronic mild TBI—differences which conventional assessments often fail to detect—provide great promise that specific pupillary metrics are more likely than others to be sensitive to subtle cognitive processing differences in other neurocognitive conditions and may outperform conventional clinical assessments. However, further research is warranted to test these metrics in other populations, given that different underlying neuropathological mechanisms may differentially influence the effect of group and/or load on pupil dynamics. Furthermore, different processing demands may differentially influence pupillary dynamics. Although we tested our sample using a cued-attention task, pupil diameter has previously been shown to be sensitive to many other cognitive

processes. Before translating pupillary metrics into clinical practice, translational scientists will need to determine whether the pupillary metrics we noted as the most sensitive in symptomatic mild TBI also extend to other populations, tasks, and/or neural processes.

Limitations

Most pupillary metrics did not yield significant differences in the conventional empirical analyses. It is possible that some of the differences between the bootstrapping results and empirical results are due to non-normality of some of the underlying data distributions—an issue that bootstrapping has been shown to effectively address (Banjanovic and Osborne, 2016). However, our bootstrapping analyses suggest that this discrepancy is more likely due to limitations in statistical power. As our bootstrap average effect sizes and confidence intervals suggest, the effect sizes for several of these metrics were not trivial; therefore, these metrics would likely produce significant effects with larger sample sizes. The small sample size in our study also reduced statistical power to evaluate covariates that might influence pupillary outcomes, such as fatigue (Hopstaken et al., 2015), comorbid depression (Jones et al., 2015; Mestanikova et al., 2017), or psychotropic drugs such as opioids (Larson, 2008; Rosse et al., 1998), nicotine (Erdem et al., 2015), or caffeine (Abokyi et al., 2017). Before cognitive pupillometry is translated into clinical settings, further research is needed to understand how random variables such as these can affect pupil diameter, and consequently, the clinical interpretation of pupillary outcomes.

When external replicability is not feasible, bootstrapping methods have been useful for estimating the likelihood of replication. However, other methods for predicting

replication exist and have been empirically tested (Open Science Collaboration, 2015). A recent comparison of predictors of reproducibility, including p-values, effect sizes, and meta-analyses, reported that the best predictor of replicability is original p-values. There is no published comparison of internal replicability (i.e., bootstrapping) to the predicted reproducibility (i.e., original p-values) to identify which may be more apt for assessing replicability; however, the empirical and bootstrapped effect sizes in the current study arrive at the same conclusion regarding optimal pupillary metrics. The metrics with the largest empirical effect sizes had nearly identical bootstrapped effect sizes and satisfactory confidence intervals.

There are many pupillary metrics that clinical researchers can use to assess differences in cognitive processing between and within groups. In the current study, we evaluated pupillary metrics measured in the time-domain. Pupillary metrics measured in the frequency- or time-frequency domains have also been reported in the literature (Grünberger et al., 1996; Naber et al., 2013). However, the vast majority of cognitive pupillometry studies in the extant literature use time-domain analyses and frequency analyses of pupil diameter are relatively uncommon. Future studies evaluating the utility and replicability of frequency-domain pupillary metrics would be helpful and could potentially provide additional progress towards translating cognitive pupillometry into clinical settings. Furthermore, in our time-domain analysis of pupillary responses, we restricted the data epochs to 1700ms post-cue due to the timing sequence of the cognitive task we used. It is possible that analyses of pupillary responses with larger measurement windows (e.g., 4-5 seconds post-stimulus) might reveal different patterns of results.

In the current study, we refrained from using or implying the term “clinically meaningful” to describe effects because we believe the determination about whether an effect is clinically significant is beyond the scope of this paper. To interpret pupillary differences as *clinically* meaningful, changes in pupil metrics must correspond with changes or meaningful differences in brain states, clinical characteristics, or functional outcomes (which would vary across neurocognitive conditions and individuals). Our study design was underpowered to conduct these analyses; however, as pupillometry is further developed for translational applications, researchers will need to define clinically meaningful effects in terms of functional outcomes and symptoms specific to their populations and/or treatments of interest. Finally, the high trial loss observed in both groups reduced the amount of usable data in our study. Reliability of pupillary measurements is highly dependent on the technical aspects of the eye tracking hardware and with continued technological improvements we expect that data quality of future pupillometry studies will improve.

Conclusion

In an effort to advance translational efforts, our study evaluated the reliability, sensitivity to cognitive load manipulations in patients with chronic mild TBI and uninjured controls, and likelihood of replicability for several pupillary metrics. Our results highlighted certain pupillary metrics that are more likely than others to produce reliable, robust, and replicable effects in subsequent samples, particularly response-locked peak dilation latency mean and standard deviation. Additionally, we demonstrated that peak-based metrics and response-locked metrics are also more likely to produce replicable effects of group or load. With consideration given to their specific clinical

populations, research questions, task design, and sample size, future researchers can use these findings to inform their choice of pupillary metrics. As Graur and Siegle (2013) have stated before us, the realization of translating cognitive pupillometry into clinical settings will require that additional research gaps are addressed. For example, additional research is needed to establish normative data to serve as a basis of clinical comparison, determine what patient- or testing-related factors may influence reliability or validity, and develop clinically-feasible, standardized data collection, analysis, and interpretation procedures. Ideally, this study will help translational researchers focus their resources on metrics that are reliable, robust, and sensitive to cognitive processing differences in clinical populations.

References

- Abokyi, S., Owusu-Mensah, J., and Osei, K. (2017). Caffeine intake is associated with pupil dilation and enhanced accommodation. *Eye*, 31(4), 615.
- Arciniegas, D. B., Anderson, C. A., Topkoff, J., & McAllister, T. W. (2005). Mild traumatic brain injury: a neuropsychiatric approach to diagnosis, evaluation, and treatment. *Neuropsych Dis Treat*, 1(4), 311.
- Aston-Jones, G., and Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, 28, 403-450.
- Aston-Jones, G., Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *The Journal of Neuroscience*, 14(7), 4467-4480.
- Banjanovic, E. S., and Osborne, J. W. (2016). Confidence Intervals for Effect Sizes: Applying Bootstrap Resampling. *Pract Assess Res Eval*, 21.
- Beatty, J. (1982a). Phasic not tonic pupillary responses vary with auditory vigilance performance. *Psychophysiology*, 19(2), 167-172.
- Beatty, J. (1982b). Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychol Bull*, 91(2), 276.
- Beatty, J., and Kahneman, D. (1966). Pupillary changes in two memory tasks. *Psychon Sci*, 5(10), 371-372.

- Beatty, J., and Lucero-Wagoner, B. (2000). The pupillary system. *Handbook of psychophysiology*, 2, 142-162.
- Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *J Int Neuropsychol Soc*, 14(1), 1-22. doi: 10.1017/S135561770808017X
- Binder, L. M., Rohling, M. L., and Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *J Clin Exp Neuropsychol*, 19(3), 421-431.
- Bradley, M. M., Keil, A., & Lang, P. J. (2012). Orienting and emotional perception: facilitation, attenuation, and interference. *Front Psychol*, 3, 493.
- Broglio, S. P., Pontifex, M. B., O'Connor, P., & Hillman, C. H. (2009). The persistent effects of concussion on neuroelectric indices of attention. *J Neurotraum*, 26(9), 1463-1470.
- Cabestrero, R., Crespo, A., and Quirós, P. (2009). Pupillary dilation as an index of task demands. *Percept Motor Skill*, 109(3), 664-678.
- Cavanagh, J. F., Wiecki, T. V., Kochar, A., and Frank, M. J. (2014). Eye tracking and pupillometry are indicators of dissociable latent decision processes. *J Exp Psychol Gen*, 143(4), 1476.

- Cicchetti, D. V. (1994). Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol Assessment*, 6(4), 284.
- Cicerone, K. D., and Kalmar, K. (1995). Persistent postconcussion syndrome: The structure of subjective complaints after mild traumatic brain injury. *J Head Trauma Rehab*, 10(3), 1-17.
- Cohen, J. (1988). Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates. *Hillsdale, NJ*, 20, 26.
- Corrigan, J. D., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University TBI identification method. *The Journal of head trauma rehabilitation*, 22(6), 318-329.
- Cummins, T. D., Broughton, M., and Finnigan, S. (2008). Theta oscillations are affected by amnesic mild cognitive impairment and cognitive load. *Int J Psychophysiol*, 70(1), 75-81.
- DiCiccio, T. J., and Efron, B. (1996). Bootstrap confidence intervals. *Statistical science*, 189-212.
- Dinstein, I., Heeger, D. J., and Behrmann, M. (2015). Neural variability: friend or foe? *Trends Cogn Sci*, 19(6), 322-328.
- Efron, B., and Tibshirani, R. J. (1994). *An introduction to the bootstrap*: CRC press.

- Erdem, U., Gundogan, F. C., Dinc, U. A., Yolcu, U., Ilhan, A., & Altun, S. (2015). Acute effect of cigarette smoking on pupil size and ocular aberrations: a pre-and postsmoking study. *J Opthamol*, doi: 10.1155/2015/625470
- Ettenhofer, M.L., Hershaw, J.N., Engle, J.R., and Hungerford, L.D. (in press). Saccadic impairment in chronic traumatic brain injury: Examining the influence of cognitive load and injury severity. *Brain Injury*.
- Gabay, S., Pertzov, Y., & Henik, A. (2011). Orienting of attention, pupil size, and the norepinephrine system. *Atten Percept Psycho*, 73(1), 123-129.
- Geva, R., Zivan, M., Warsha, A., & Olchik, D. (2013). Alerting, orienting or executive attention networks: differential patters of pupil dilations. *Front Behav Neurosci*, 7, 145.
- Ghajar, J., and Ivry, R. B. (2008). The predictive brain state: timing deficiency in traumatic brain injury? *Neurorehab Neural Re*, 22(3), 217-227.
- Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269.
- Granholm, E., Asarnow, R. F., Sarkin, A. J., and Dykes, K. L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology*, 33(4), 457-461.

- Granholm, E., Fish, S. C., and Verney, S. P. (2009). Pupillometric measures of attentional allocation to target and mask processing on the backward masking task in schizophrenia. *Psychophysiology*, 46(3), 510-520.
- Granholm, E., Fish, S. C., and Verney, S. P. (2009). Pupillometric measures of attentional allocation to target and mask processing on the backward masking task in schizophrenia. *Psychophysiology*, 46(3), 510-520.
- Granholm, E., Ruiz, I., Gallegos-Rodriguez, Y., Holden, J., and Link, P. C. (2016). Pupillary responses as a biomarker of diminished effort associated with defeatist attitudes and negative symptoms in schizophrenia. *Biol Psychiat*, 80(8), 581-588. doi: 10.1016/j.biopsych.2015.08.037
- Granholm, E., and Verney, S. P. (2004). Pupillary responses and attentional allocation problems on the backward masking task in schizophrenia. *Int J Psychophysiol*, 52(1), 37-51.
- Granholm, E. L., Panizzon, M. S., Elman, J. A., Jak, A. J., Hauger, R. L., Bondi, M. W., et al. (2017). Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease. *J Alzheimers Dis*, 56(4), 1419-1428. doi: 10.3233/JAD-161078
- Graur, S., and Siegle, G. (2013). Pupillary Motility: Bringing Neuroscience to the Psychiatry Clinic of the Future. *Curr Neurol Neurosci*, 13(8), 1-9. doi: 10.1007/s11910-013-0365-0
- Green, R. E., Melo, B., Christensen, B., Ngo, L.-A., Monette, G., and Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the

- validity of the Wechsler Test of Adult Reading (WTAR). *J Clin Exp Neuropsych*, 30(2), 163-172.
- Grünberger, J., Linzmayer, L., Majda, E., Reitner, A., and Walter, H. (1996). Pupillary dilatation test and Fourier analysis of pupillary oscillations in patients with multiple sclerosis. *Eur Arch Psy Clin N*, 246(4), 209-212.
- Head, J. (1993). Definition of mild traumatic brain.. Injury. *J Head Trauma Rehabil*, 8(3), 86-87.
- Heaver, B., and Hutton, S. B. (2010). Keeping an eye on the truth: Pupil size, recognition memory and malingering. *Int J Psychophysiol*, 77(3), 306-306.
- Heitz, R. P., Schrock, J. C., Payne, T. W., and Engle, R. W. (2008). Effects of incentive on working memory capacity: Behavioral and pupillometric data. *Psychophysiology*, 45(1), 119-129.
- Hopstaken, J. F., van der Linden, D., Bakker, A. B., and Kompier, M. A. (2015). The window of my eyes: Task disengagement and mental fatigue covary with pupil dynamics. *Biol Psychol*, 110, 100-106.
- Janisse, M. P. (1973). Pupil size and affect: A critical review of the literature since 1960. *Can Psychologist-Pscho*, 14(4), 311.
- Jones, N. P., Siegle, G. J., and Mandell, D. (2015). Motivational and emotional influences on cognitive control in depression: A pupillometry study. *Cogn Affect Behav Ne*, 15(2), 263-275.

- Kamp, S. M., and Donchin, E. (2015). ERP and pupil responses to deviance in an oddball paradigm. *Psychophysiology*, 52(4), 460-471.
- Kang, O. E., Huffer, K. E., and Wheatley, T. P. (2014). Pupil dilation dynamics track attention to high-level information. *PloS One*, 9(8), e102463.
- Kessels, R. P., Meulenbroek, O., Fernández, G., & Olde Rikkert, M. G. (2010). Spatial working memory in aging and mild cognitive impairment: effects of task load and contextual cueing. *Aging, Neuropsychol C*, 17(5), 556-574.
- King, P. R., Donnelly, K. T., Donnelly, J. P., Dunnam, M., Warner, G., Kittleson, C., et al. (2012). Psychometric study of the Neurobehavioral Symptom Inventory. *J Rehabil Res Dev*, 49(6), 879-890.
- Kinner, V. L., Kuchinke, L., Dierolf, A. M., Merz, C. J., Otto, T., & Wolf, O. T. (2017). What our eyes tell us about feelings: Tracking pupillary responses during emotion regulation processes. *Psychophysiology*, 54(4), 508-518.
- Klingner, J., Kumar, R., and Hanrahan, P. (2008). *Measuring the task-evoked pupillary response with a remote eye tracker*. Paper presented at the Proceedings of the 2008 symposium on Eye tracking research and applications.
- Klingner, J., Tversky, B., and Hanrahan, P. (2011). Effects of visual and verbal presentation on cognitive load in vigilance, memory, and arithmetic tasks. *Psychophysiology*, 48(3), 323-332.

- Kramer, S. E., Lorens, A., Coninx, F., Zekveld, A. A., Piotrowska, A., & Skarzynski, H. (2013). Processing load during listening: The influence of task characteristics on the pupil response. *Language and cognitive processes*, 28(4), 426-442.
- Kuchinsky, S. E., Ahlstrom, J. B., Vaden, K. I., Cute, S. L., Humes, L. E., Dubno, J. R., and Eckert, M. A. (2013). Pupil size varies with word listening and response selection difficulty in older adults with hearing loss. *Psychophysiology*, 50(1), 23-34.
- Larson, M. D. (2008). Mechanism of opioid-induced pupillary effects. *Clin Neurophysiol*, 119(6), 1358-1364. doi: 10.1016/j.clinph.2008.01.106
- MacDonald, S. W., Nyberg, L., and Bäckman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends neurosci*, 29(8), 474-480.
- MacDonald, S. W. S., Nyberg, L., Sandblom, J., Fischer, H., and Bäckman, L. (2008). Increased Response-time Variability is Associated with Reduced Inferior Parietal Activation during Episodic Recognition in Aging. *J Cognitive Neurosci*, 20(5), 779-786. doi: 10.1162/jocn.2008.20502
- McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage*, 14(5), 1004-1012.
doi:10.1006/nimg.2001.0899

- Mestanikova, A., Ondrejka, I., Mestanik, M., Cesnekova, D., Visnovcova, Z., Bujnakova, I., et al. (2017). Pupillary light reflex is altered in adolescent depression. *Physiol Res*, 66, S277.
- Naber, M., Alvarez, G. A., and Nakayama, K. (2013). Tracking the allocation of attention using human pupillary oscillations. *Front Psychol*, 4, 919.
- Najmi, S., Amir, N., Frosio, K. E., & Ayers, C. (2015). The effects of cognitive load on attention control in subclinical anxiety and generalised anxiety disorder. *Cognition Emotion*, 29(7), 1210-1223.
- Open Science Collaboration. (2015). Estimating the reproducibility of psychological science. *Science*, 349(6251), aac4716.
- Otero, S. C., Weekes, B. S., and Hutton, S. B. (2011). Pupil size changes during recognition memory. *Psychophysiology*, 48(10), 1346-1353.
- Petrides, M. (2000). Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. *J Neurosci*, 20(19), 7496-7503.
- Radloff, E. S. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psych Meas*, 1(3), 385-401. doi: 10.1177/014662167700100306
- Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1993). *Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention*. Paper presented at the Society for Neuroscience Abstracts.

- Rajkowski, J., Majczynski, H., Clayton, E., and Aston-Jones, G. (2004). Activation of monkey locus coeruleus neurons varies with difficulty and performance in a target detection task. *J Neurophysiol*, 92(1), 361-371.
- Reinhard, G., Lachnit, H., and König, S. (2007). Effects of stimulus probability on pupillary dilation and reaction time in categorization. *Psychophysiology*, 44(3), 469-475.
- Rohling, M. L., Larrabee, G. J., & Millis, S. R. (2012). The "Miserable Minority" following mild traumatic brain injury: who are they and do meta-analyses hide them? *Clin Neuropsychol*, 26(2), 197-213.
- Rosse, R. B., Johri, S., Goel, M., Rahman, F., Jawor, K. A., and Deutsch, S. I. (1998). Pupillometric changes during gradual opiate detoxification correlate with changes in symptoms of opiate withdrawal as measured by the Weak Opiate Withdrawal Scale. *Clin Neuropharmacol*, 21(5), 312-315.
- Schacht, A., Dimigen, O., and Sommer, W. (2010). Emotions in cognitive conflicts are not aversive but are task specific. *Cogn Affect Behav Ne*, 10(3), 349-356.
- Siegle, G. J., Ichikawa, N., and Steinhauer, S. (2008). Blink before and after you think: blinks occur prior to and following cognitive load indexed by pupillary responses. *Psychophysiology*, 45(5), 679-687.
- Silk, J. S., Dahl, R. E., Ryan, N. D., Forbes, E. E., Axelson, D. A., Birmaher, B., and Siegle, G. J. (2007). Pupillary reactivity to emotional information in child and

adolescent depression: links to clinical and ecological measures. *Am J Psychiat*, 164(12), 1873-1880.

Sirois, S., and Brisson, J. (2014). Pupillometry. *Wires Cogn Sci*, 5(6), 679-692. doi: 10.1002/wcs.1323

Slobounov, S. M., Zhang, K., Pennell, D., Ray, W., Johnson, B., & Sebastianelli, W. (2009). Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study. *Exp Brain Res*. doi:10.1007/s00221-009-2141-6

Steiner, G. Z., & Barry, R. J. (2011). Pupillary responses and event-related potentials as indices of the orienting reflex. *Psychophysiology*, 48(12), 1648-1655.

Steinhauer, S. R., Condray, R., and Kasperek, A. (2000). Cognitive modulation of midbrain function: task-induced reduction of the pupillary light reflex. *Int J Psychophysiol*, 39(1), 21-30.

Stone, L. B., Silk, J. S., Siegle, G. J., Lee, K. H., Stroud, L. R., Nelson, E. E., et al. (2016). Depressed Adolescents' Pupillary Response to Peer Acceptance and Rejection: The Role of Rumination. *Wires Cogn Child Psychiat Hum D*, 47(3), 397-406. doi: 10.1007/s10578-015-0574-7

Taylor, B. A., Roberts, D. M., and Baldwin, C. L. (2011). The Role of Age-Related Neural Timing Variability in Speech Processing. *Hum Fac Eg Soc P*, 55(1), 162-166.

- Thompson, B. (1993). The use of statistical significance tests in research: Bootstrap and other alternatives. *J Exp Educ*, 61(4), 361-377.
- Thompson, B. (1995). Exploring the Replicability of a Study's Results: Bootstrap Statistics for the Multivariate Case. *Educ Psychol Meas*, 55(1), 84-94. doi: 10.1177/0013164495055001008
- Tomasi, D., Chang, L., Caparelli, E. C., & Ernst, T. (2007). Different activation patterns for working memory load and visual attention load. *Brain Res*, 1132, 158-165.
- Unsworth, N., and Robison, M. K. (2015). Individual differences in the allocation of attention to items in working memory: Evidence from pupillometry. *Psychon B Rev*, 22(3), 757-765.
- Van Steenbergen, H., and Band, G. P. (2013). Pupil dilation in the Simon task as a marker of conflict processing. *Front Hum Neurosci*, 7, 215.
- Vaurio, R. G., Simmonds, D. J., and Mostofsky, S. H. (2009). Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands. *Neuropsychologia*, 47(12), 2389-2396.
- Verney, S. P., Granholm, E., and Dionisio, D. P. (2001). Pupillary responses and processing resources on the visual backward masking task. *Psychophysiology*, 38(01), 76-83.

- Wang, C. A., & Munoz, D. P. (2015). A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. *Curr Opin Neurobiol*, 33, 134-140.
- Weathers, F., Litz, B., Herman, D., Huska, J., and Keane, T. (1994). The PTSD checklist-civilian version (PCL-C). *Boston, MA: National Center for PTSD*.
- Wong, H. K., and Epps, J. (2016). Pupillary transient responses to within-task cognitive load variation. *Comput Meth Prog Bio*, 137, 47-63. doi: <https://doi.org/10.1016/j.cmpb.2016.08.017>
- Zekveld, A. A., and Kramer, S. E. (2014). Cognitive processing load across a wide range of listening conditions: Insights from pupillometry. *Psychophysiology*, 51(3), 277-284.
- Zekveld, A. A., Kramer, S. E., and Festen, J. M. (2011). Cognitive load during speech perception in noise: The influence of age, hearing loss, and cognition on the pupil response. *Ear hearing*, 32(4), 498-510.

Table 4.1. Pupillary Metrics

<u>Metric</u>	<u>Definition</u>	<u>Published Studies</u>	<u>Representation in Figure 2</u>
Baseline Diameter	Average diameter over a pre-stimulus window	(Beatty, 1982a; Heitz et al., 2008)	a
Peak Dilation	Maximum diameter during a measurement window minus the average baseline diameter	(Beatty and Lucero-Wagoner, 2000; Zekveld, Kramer, and Festen, 2011)	$b_y - a$
Peak Dilation Latency	Time point at which peak dilation is reached	(Kuchinsky et al., 2013; Reinhard et al., 2007)	b_x
Peak Constriction	Minimum diameter during a measurement window minus the average baseline diameter	(Cabestrero et al., 2009; Granholm et al., 1996; Kramer et al., 2013)*	$c_y - a$
Peak Constriction Latency	Time point at which peak constriction is reached	(Cabestrero et al., 2009; Granholm et al., 1996; Kramer et al., 2013)*	c_x
Peak to Peak Difference	The difference between peak constriction and peak dilation during a measurement window	(Granholm et al., 2009; Verney et al., 2001)	$b_y - c_y$
Pupil Dilation Ratio	Peak dilation as a proportion of maximum diameter during a pre-stimulus baseline	(Heaver and Hutton, 2010; Otero et al., 2011)	$\frac{b_y}{baseline_{max}}$
Baseline-Corrected Pupillary Response (BCPR)	Average pupil diameter over a measurement window minus the average baseline diameter	(Klingner et al., 2011; Van Steenbergen and Band, 2013)	$d - a$
BCPR Percent Change	Average baseline-corrected pupillary response (BCPR) divided by baseline diameter	(Cavanagh et al., 2014)	$\frac{d - a}{a}$

Table 4.2. Bootstrapped and Empirical Results. Results of internal consistency, sensitivity, and replicability analyses are presented for those which exceed conventional thresholds for meaningful or significant results.

	<u>Reliability</u> $\hat{\alpha}$	<u>Sensitivity and Replicability Results†</u>				
		<u>Group</u>	<u>Load</u>	<u>Group*</u> <u>Load</u>	<u>Load:</u> <u>Controls</u>	<u>Load:</u> <u>Mild TBI</u>
Baseline						
<i>mean</i>	.91	--	--	--	--	--
<i>SD</i>	.83	--	--	--	--	--
Peak Dilation						
<i>cue-locked mean</i>	.89	--	--	--	--	--
<i>cue-locked SD</i>	.78	--	--	--	--	--
<i>response-locked mean</i>	.88	--	--	--	--	--
<i>response-locked SD</i>	.76	--	--	.026	--	--
Peak Dilation Latency						
<i>cue-locked mean</i>	.96	--	.117**	--	.126*	.158
<i>cue-locked SD</i>	.98	--	--	--	--	--
<i>response-locked mean</i>	.95	.089**	.189**	--	.315**	.121
<i>response-locked SD</i>	.96	--	.245**	--	.150**	.333**
Peak Constriction						
<i>cue-locked mean</i>	.91	--	--	--	.039	--
<i>cue-locked SD</i>	.73	--	--	--	.045	--
<i>response-locked mean</i>	.82	--	--	--	.121*	--
<i>response-locked SD</i>	.78	--	--	--	.086	--
Peak Constriction Latency						
<i>cue-locked mean</i>	.97	--	--	--	--	--
<i>cue-locked SD</i>	.98	--	--	--	--	--
<i>response-locked mean</i>	.97	--	--	--	.134*	--
<i>response-locked SD</i>	.94	--	--	--	--	--
Peak to Peak Difference						
<i>cue-locked mean</i>	.92	--	--	--	--	--
<i>cue-locked SD</i>	.71	--	--	--	--	--
<i>response-locked mean</i>	.92	--	--	--	.117*	--
<i>response-locked SD</i>	.73	--	--	--	.123*	--
Pupil Dilation Ratio						
<i>cue-locked mean</i>		--	--	--	--	--
<i>cue-locked SD</i>	.70	--	--	--	--	--
<i>response-locked mean</i>		--	--	--	--	--
<i>response-locked SD</i>		--	--	--	.086	--
BCPR						
<i>cue-locked mean</i>		--	--	--	--	--
<i>cue-locked SD</i>	.73	--	--	--	--	--
<i>response-locked mean</i>		--	--	--	.107	--
<i>response-locked SD</i>	.75	--	--	--	--	--
BCPR Percent Change						

<i>cue-locked mean</i>	--	--	--	--	--
<i>cue-locked SD</i>	--	--	--	.077	--
<i>response-locked mean</i>	--	--	--	--	--
<i>response-locked SD</i>	--	--	--	.093	--

Notes. ^ Bootstrapped average split-half reliability coefficients with Spearman-Brown adjustments; †values are average η^2_p for pupillary metrics that had meaningful effect size confidence intervals; significant effects from empirical ANOVAs, * $p < .05$ and ** $p < .01$.

Figure 4.1. Task Schematic. Three cue types were possible: valid, invalid, or uncued.

Trials were randomized within blocks. Cognitive load was manipulated by varying the response to targets: simple reaction time, 0-back, or 1-back.

Cognitive load varied randomly between blocks.

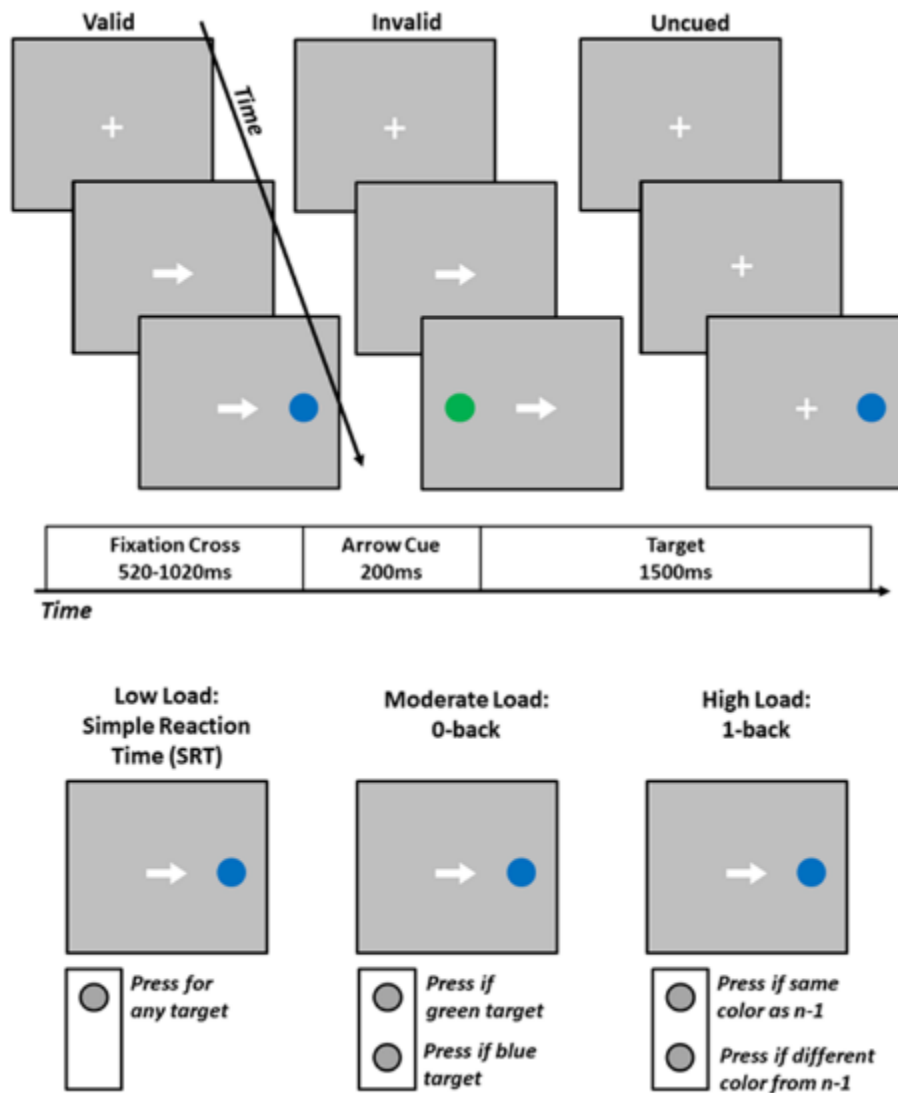


Figure 4.2. Prototypical Pupillary Waveform. Model pupillary waveform time-locked to stimulus onset; a) pre-stimulus baseline interval; b) peak dilation; c) peak constriction; and d) measurement window. The dashed vertical line represents a manual response. The light gray bar depicts the cue-locked epoch; the medium gray bay depicts the response-locked epoch; and the dark gray box represents the baseline window.

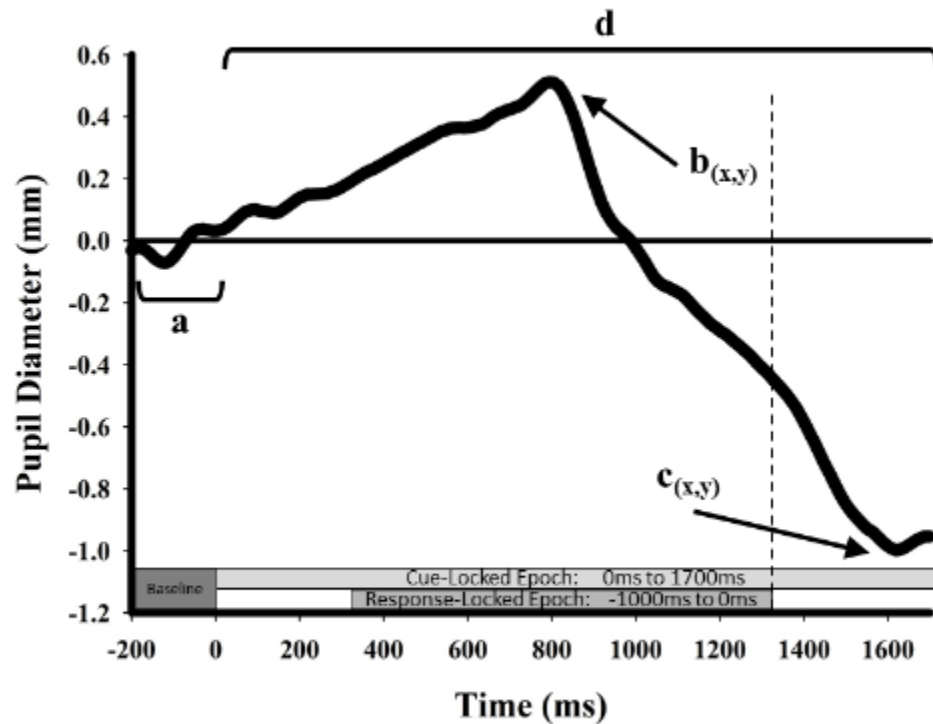
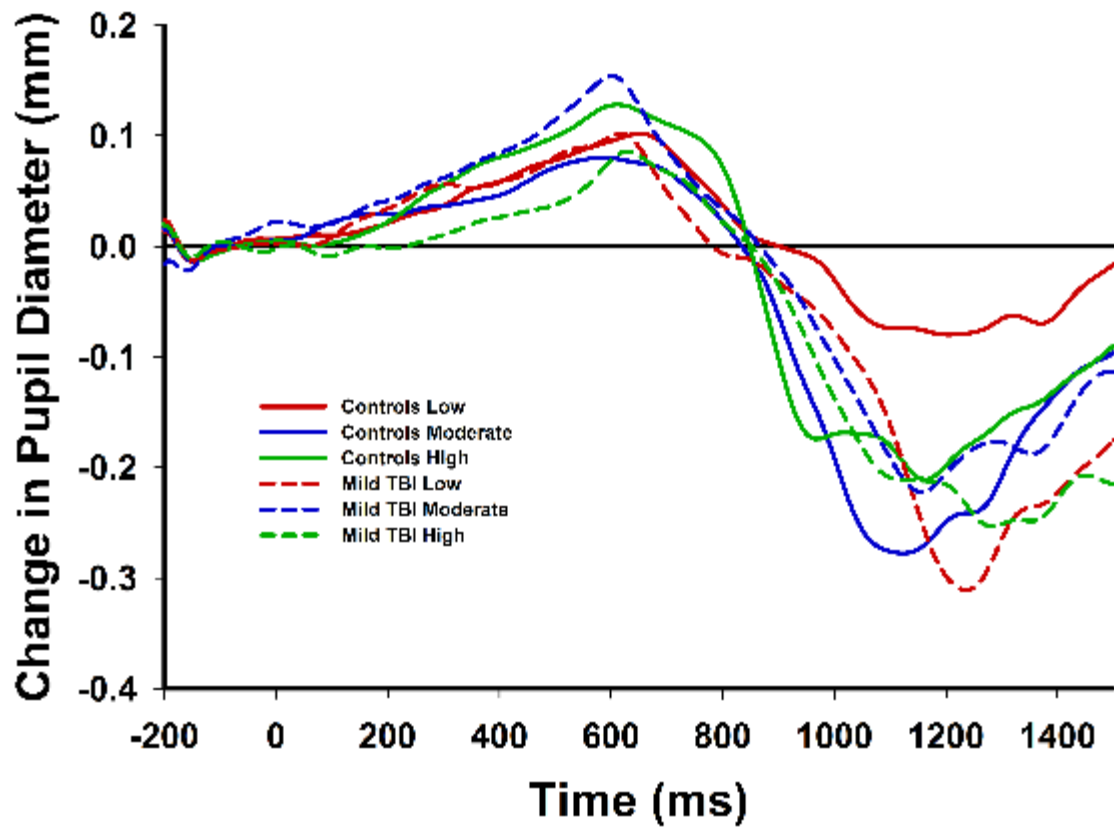


Figure 4.3. Cue-Locked Pupillary Waveforms. Pupillary responses following cue onset (-200ms to 1500ms) for controls (solid line) and mild TBI (dashed line) under low (red), moderate (blue), and high (green) cognitive load.



APPENDICES

Table 4.A. Internal Consistency

	<u>Coefficient*</u>	
	<u>Mean</u>	<u>SD</u>
<i>Baseline PD</i>	0.91	0.83
Cue-Locked Metrics		
<i>Peak Dilation</i>	0.89	0.78
<i>Peak Dilation Latency</i>	0.96	0.98
<i>Peak Constriction</i>	0.91	0.73
<i>Peak Constriction Latency</i>	0.97	0.98
<i>Peak to Peak Difference</i>	0.92	0.71
<i>Pupil Dilation Ratio</i>	0.27	0.70
<i>Baseline-Corrected Pupillary Response</i>	0.19	0.73
<i>Baseline-Corrected Pupillary Response Percent Change</i>	-0.71	0.34
Response-Locked Metrics		
<i>Peak Dilation</i>	0.88	0.76
<i>Peak Dilation Latency</i>	0.95	0.96
<i>Peak Constriction</i>	0.82	0.78
<i>Peak Constriction Latency</i>	0.97	0.94
<i>Peak to Peak Difference</i>	0.92	0.73
<i>Pupil Dilation Ratio</i>	0.24	0.55
<i>Baseline-Corrected Pupillary Response</i>	0.54	0.75
<i>Baseline-Corrected Pupillary Response Percent Change</i>	0.38	0.34

Note. *Bootstrapped average split-half reliability coefficients with Spearman-Brown adjustments. SD: standard deviation. Bold type indicates coefficient exceeded threshold for “acceptable”

Table 4.B. Group Effects

	<u>Empirical</u> η_p^2	Sensitivity and Replicability Results†		
		<u>Average</u> η_p^2	95% CI	95% CI
			<u>Lower</u> <u>Limit</u>	<u>Upper</u> <u>Limit</u>
Baseline				
<i>mean</i>	.033[^]	.032	.002	.078
<i>SD</i>	.001	.011	.000	.057
Peak Dilation				
<i>cue-locked mean</i>	.020	.029	.000	.107
<i>cue-locked SD</i>	.001	.011	.000	.059
<i>response-locked mean</i>	.025	.032	.000	.108
<i>response-locked SD</i>	.003	.014	.000	.070
Peak Dilation Latency				
<i>cue-locked mean</i>	.002	.013	.000	.066
<i>cue-locked SD</i>	.093**	.093	.008	.228
<i>response-locked mean</i>	.093**	.089	.018	.181
<i>response-locked SD</i>	.063**	.064	.001	.165
Peak Constriction				
<i>cue-locked mean</i>	.002	.014	.000	.073
<i>cue-locked SD</i>	.001	.009	.000	.043
<i>response-locked mean</i>	.006	.012	.000	.051
<i>response-locked SD</i>	.001	.006	.000	.030
Peak Constriction Latency				
<i>cue-locked mean</i>	.001	.012	.000	.061
<i>cue-locked SD</i>	.002	.011	.000	.054
<i>response-locked mean</i>	.001	.009	.000	.042
<i>response-locked SD</i>	.001	.010	.000	.050
Peak to Peak Difference				
<i>cue-locked mean</i>	.001	.013	.000	.066
<i>cue-locked SD</i>	.002	.009	.000	.042
<i>response-locked mean</i>	.001	.006	.000	.031
<i>response-locked SD</i>	.001	.007	.000	.035
Pupil Dilation Ratio				
<i>cue-locked mean</i>	.015	.019	.000	.075
<i>cue-locked SD</i>	.012	.021	.001	.072
<i>response-locked mean</i>	.014	.019	.000	.075
<i>response-locked SD</i>	.013	.020	.000	.073
Baseline-Corrected Pupillary Response				
<i>cue-locked mean</i>	.016	.022	.000	.075
<i>cue-locked SD</i>	.002	.008	.000	.039
<i>response-locked mean</i>	.017	.027	.000	.106
<i>response-locked SD</i>	.001	.010	.000	.054

Baseline-Corrected Pupillary
Response
Percent Change

<i>cue-locked mean</i>	.003	.021	.000	.098
<i>cue-locked SD</i>	.001	.009	.000	.042
<i>response-locked mean</i>	.002	.019	.000	.097
<i>response-locked SD</i>	.005	.011	.000	.051

Notes. †Indicates results from the bootstrapping analyses; **p<.01; *p<.05; ^p<.1; df=(1,112). SD: standard deviation. Bold type indicates effect size >.01

Table 4.C. Cognitive Load Effects

		Sensitivity and Replicability		
		<u>Empirical</u> η_p^2	Results†	
			Average η_p^2	95% CI Lower Limit Upper Limit
Baseline				
	<i>mean</i>	.009	.017	.001 .053
	<i>SD</i>	.012	.034	.001 .126
Peak Dilation				
	<i>cue-locked mean</i>	.029	.048	.003 .134
	<i>cue-locked SD</i>	.010	.029	.001 .105
	<i>response-locked mean</i>	.018	.038	.001 .120
	<i>response-locked SD</i>	.011	.031	.001 .116
Peak Dilation Latency				
	<i>cue-locked mean</i>	.103**	.117	.030 .240
	<i>cue-locked SD</i>	.006	.033	.001 .118
	<i>response-locked mean</i>	.189**	.189	.084 .312
	<i>response-locked SD</i>	.247**	.245	.095 .406
Peak Constriction				
	<i>cue-locked mean</i>	.011	.032	.001 .104
	<i>cue-locked SD</i>	.004	.018	.001 .068
	<i>response-locked mean</i>	.034	.046	.003 .135
	<i>response-locked SD</i>	.018	.032	.001 .107
Peak Constriction Latency				
	<i>cue-locked mean</i>	.006	.029	.001 .104
	<i>cue-locked SD</i>	.009	.027	.001 .086
	<i>response-locked mean</i>	.040	.055	.003 .159
	<i>response-locked SD</i>	.036	.050	.002 .153
Peak to Peak Difference				
	<i>cue-locked mean</i>	.016	.037	.001 .119
	<i>cue-locked SD</i>	.002	.017	.000 .065
	<i>response-locked mean</i>	.027	.039	.001 .123
	<i>response-locked SD</i>	.032	.046	.003 .125
Pupil Dilation Ratio				
	<i>cue-locked mean</i>	.025	.037	.003 .117
	<i>cue-locked SD</i>	.031	.040	.005 .124
	<i>response-locked mean</i>	.026	.040	.003 .124
	<i>response-locked SD</i>	.031	.043	.005 .127
Baseline-Corrected				
Pupillary Response				
	<i>cue-locked mean</i>	.010	.024	.001 .074
	<i>cue-locked SD</i>	.003	.019	.000 .069
	<i>response-locked mean</i>	.030	.050	.002 .158
	<i>response-locked SD</i>	.006	.024	.001 .092

Baseline-Corrected
Pupillary Response Percent
Change

<i>cue-locked mean</i>	.039	.050	.005	.129
<i>cue-locked SD</i>	.035	.045	.001	.120
<i>response-locked mean</i>	.040	.051	.003	.136
<i>response-locked SD</i>	.042	.052	.004	.133

Notes. †Indicates results from the bootstrapping analyses; **p<.01; *p<.05; ^p<.1; df=(2,224). SD: standard deviation. Bold type indicates effect size >.01

Table 4.D. Cognitive Load Effects within Controls

	<u>Empirical</u> η_p^2	<u>Sensitivity and Replicability</u> <u>Results</u>		
		<u>Average</u> η_p^2	95% CI	95% CI
			<u>Lower</u> <u>Limit</u>	<u>Upper</u> <u>Limit</u>
Baseline				
<i>mean</i>	.016	.034	.001	.111
<i>SD</i>	.011	.071	.003	.254
Peak Dilation				
<i>cue-locked mean</i>	.032	.057	.004	.158
<i>cue-locked SD</i>	.013	.047	.003	.166
<i>response-locked mean</i>	.011	.060	.001	.232
<i>response-locked SD</i>	.012	.064	.004	.235
Peak Dilation Latency				
<i>cue-locked mean</i>	.110*	.126	.031	.269
<i>cue-locked SD</i>	.011	.038	.001	.121
<i>response-locked mean</i>	.306**	.315	.147	.488
<i>response-locked SD</i>	.134**	.150	.028	.307
Peak Constriction				
<i>cue-locked mean</i>	.012	.039	.011	.133
<i>cue-locked SD</i>	.027	.045	.011	.140
<i>response-locked mean</i>	.100*	.121	.023	.299
<i>response-locked SD</i>	.058	.086	.011	.231
Peak Constriction Latency				
<i>cue-locked mean</i>	.001	.028	.001	.125
<i>cue-locked SD</i>	.031	.044	.002	.138
<i>response-locked mean</i>	.113*	.134	.013	.328
<i>response-locked SD</i>	.055	.077	.003	.225
Peak to Peak Difference				
<i>cue-locked mean</i>	.017	.045	.001	.146
<i>cue-locked SD</i>	.023	.043	.002	.134
<i>response-locked mean</i>	.095*	.117	.016	.303
<i>response-locked SD</i>	.092*	.123	.015	.290
Pupil Dilation Ratio				
<i>cue-locked mean</i>	.015	.031	.001	.099
<i>cue-locked SD</i>	.048	.067	.007	.180
<i>response-locked mean</i>	.040	.066	.007	.176
<i>response-locked SD</i>	.074^	.086	.013	.204
Baseline-Corrected Pupillary Response				
<i>cue-locked mean</i>	.029	.052	.003	.141
<i>cue-locked SD</i>	.010	.038	.002	.124
<i>response-locked mean</i>	.060	.107	.021	.277
<i>response-locked SD</i>	.016	.043	.002	.140

Baseline-Corrected Pupillary
Response Percent Change

<i>cue-locked mean</i>	.040	.058	.004	.143
<i>cue-locked SD</i>	.050	.077	.017	.199
<i>response-locked mean</i>	.036	.051	.005	.127
<i>response-locked SD</i>	.067	.093	.014	.256

Notes. **p<.01; *p<.05; ^p<.1; df=(2,66). SD: standard deviation. Bold type indicates effect size >.01

Table 4.E. Cognitive Load Effects within mild TBI

	<u>Empirical</u> η_p^2	<u>Sensitivity and Replicability Results</u>		
		<u>Average</u> η_p^2	95% CI <u>Lower</u> <u>Limit</u>	95% CI <u>Upper</u> <u>Limit</u>
Baseline				
<i>mean</i>	.005	.021	.001	.073
<i>SD</i>	.041	.064	.005	.184
Peak Dilation				
<i>cue-locked mean</i>	.036	.075	.003	.229
<i>cue-locked SD</i>	.041	.062	.005	.178
<i>response-locked mean</i>	.028	.059	.002	.170
<i>response-locked SD</i>	.039	.060	.005	.173
Peak Dilation Latency				
<i>cue-locked mean</i>	.105[^]	.158	.015	.394
<i>cue-locked SD</i>	.011	.089	.003	.300
<i>response-locked mean</i>	.100	.121	.023	.275
<i>response-locked SD</i>	.329**	.333	.106	.565
Peak Constriction				
<i>cue-locked mean</i>	.012	.068	.002	.214
<i>cue-locked SD</i>	.016	.058	.002	.186
<i>response-locked mean</i>	.005	.037	.001	.159
<i>response-locked SD</i>	.025	.052	.003	.159
Peak Constriction Latency				
<i>cue-locked mean</i>	.025	.087	.003	.312
<i>cue-locked SD</i>	.001	.067	.002	.253
<i>response-locked mean</i>	.005	.045	.001	.179
<i>response-locked SD</i>	.025	.068	.002	.243
Peak to Peak Difference				
<i>cue-locked mean</i>	.017	.072	.003	.227
<i>cue-locked SD</i>	.019	.059	.002	.188
<i>response-locked mean</i>	.010	.038	.001	.140
<i>response-locked SD</i>	.039	.060	.004	.163
Pupil Dilation Ratio				
<i>cue-locked mean</i>	.044	.075	.001	.173
<i>cue-locked SD</i>	.045	.061	.004	.185
<i>response-locked mean</i>	.046	.074	.006	.208
<i>response-locked SD</i>	.045	.062	.005	.184
Baseline-Corrected				
Pupillary Response				
<i>cue-locked mean</i>	.002	.044	.001	.173
<i>cue-locked SD</i>	.060	.078	.006	.209
<i>response-locked mean</i>	.023	.065	.002	.201
<i>response-locked SD</i>	.042	.063	.004	.185

Baseline-Corrected
Pupillary Response Percent
Change

<i>cue-locked mean</i>	.058	.081	.004	.219
<i>cue-locked SD</i>	.047	.065	.006	.169
<i>response-locked mean</i>	.056	.080	.004	.207
<i>response-locked SD</i>	.042	.064	.006	.162

Notes. **p<.01; *p<.05; ^p<.1; df=(2,42). SD: standard deviation. Bold type indicates effect size >.01

Table 4.F. Group*Cognitive Load Interaction Effects

		Sensitivity and Replicability Results		
		Empirical η_p^2	95% CI	
			Average η_p^2	95% CI Lower Limit Upper Limit
Baseline				
	<i>mean</i>	.001	.009	.000 .034
	<i>SD</i>	.014	.027	.001 .082
Peak Dilation				
	<i>cue-locked mean</i>	.008	.028	.001 .096
	<i>cue-locked SD</i>	.017	.028	.002 .083
	<i>response-locked mean</i>	.007	.024	.001 .077
	<i>response-locked SD</i>	.014	.026	.001 .079
Peak Dilation Latency				
	<i>cue-locked mean</i>	.001	.022	.000 .084
	<i>cue-locked SD</i>	.005	.032	.001 .117
	<i>response-locked mean</i>	.021	.033	.001 .097
	<i>response-locked SD</i>	.057**	.070	.004 .183
Peak Constriction				
	<i>cue-locked mean</i>	.001	.023	.001 .081
	<i>cue-locked SD</i>	.018	.029	.001 .088
	<i>response-locked mean</i>	.021	.034	.002 .104
	<i>response-locked SD</i>	.024	.034	.002 .089
Peak Constriction Latency				
	<i>cue-locked mean</i>	.005	.028	.001 .108
	<i>cue-locked SD</i>	.007	.025	.001 .092
	<i>response-locked mean</i>	.018	.033	.001 .103
	<i>response-locked SD</i>	.002	.021	.000 .079
Peak to Peak Difference				
	<i>cue-locked mean</i>	.001	.025	.001 .089
	<i>cue-locked SD</i>	.017	.029	.001 .087
	<i>response-locked mean</i>	.023	.035	.002 .105
	<i>response-locked SD</i>	.032	.044	.002 .122
Pupil Dilation Ratio				
	<i>cue-locked mean</i>	.029	.035	.001 .121
	<i>cue-locked SD</i>	.025	.036	.003 .119
	<i>response-locked mean</i>	.023	.041	.002 .128
	<i>response-locked SD</i>	.025	.040	.005 .121
Baseline-Corrected				
Pupillary Response				
	<i>cue-locked mean</i>	.008	.021	.001 .070
	<i>cue-locked SD</i>	.024	.036	.002 .095
	<i>response-locked mean</i>	.030	.030	.001 .106
	<i>response-locked SD</i>	.020	.032	.002 .088

Baseline-Corrected
Pupillary Response Percent
Change

<i>cue-locked mean</i>	.021	.033	.001	.111
<i>cue-locked SD</i>	.017	.029	.002	.081
<i>response-locked mean</i>	.008	.035	.001	.113
<i>response-locked SD</i>	.010	.025	.001	.076

Notes. **p<.01; *p<.05; ^p<.1; df=(2,224); SD: standard deviation. Bold type indicates effect size >.01

Chapter 5: Conclusion

Many patients with chronic mild TBI report persistent cognitive symptoms although research consistently demonstrates that they perform similarly to healthy controls on behavioral measures (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005; Karr, Areshenkoff, & Garcia-Barrera, 2014; Schretlen & Shapiro, 2003). This effect was replicated in our studies; task performance and global neuropsychological status were comparable between healthy controls and the chronic mild TBI sample. However, by comparison to controls, the chronic mild TBI group endorsed significantly more neurobehavioral symptoms and reported greater subjective cognitive effort during a moderately difficult cued attention task. Ultimately, the sample used in our studies provides further support for previous findings that subjective reports of cognitive difficulty in chronic mild TBI are not always corroborated with conventional behavioral measures and more sensitive measures are needed to assess cognitive processing in this population. The goal of this program of research was to investigate this discrepancy between subjective complaints in chronic mild TBI and unimpaired behavioral performance by examining underlying neural mechanisms.

Previous research has shown that patients with acute and sub-acute mild TBI do not efficiently allocate neural resources to complete cognitive tasks, particularly when task demands impose greater cognitive load (Chen, Johnston, Collie, McCrory, & Ptito, 2007; Chen et al., 2004; Gosselin et al., 2011). Interestingly, neural resource allocation is impaired even when behavioral performance falls within normal ranges. It is not until the upper limits of patients' cognitive capacity are reached under high cognitive load that

performance decrements are observed (Bernstein, 2002; Segalowitz, Bernstein, & Lawson, 2001). Additionally, research suggests that the amount of neural resources allocated to perform cognitive tasks is related to subjective reports of cognitive effort (Howells, Stein, & Russell, 2012). Neural resource allocation is regulated by neural gain modulation, which influences the sensitivity of neurons to incoming neural signals (Aston-Jones & Cohen, 2005; Eldar, Cohen, & Niv, 2013). In healthy controls is efficiently modulated to optimize behavioral performance under changing task demands (Aston-Jones & Cohen, 2005; Eldar et al., 2013).

PROPOSED THEORY

Considering these previous findings, I theorized that patients' subjective cognitive complaints may be reflecting increased neural recruitment that results from poor neural gain modulation. I hypothesized that patients with chronic mild TBI, in contrast to healthy controls, could not modulate neural gain in response to changing task demands and that this impaired ability to modulate neural gain would be related to cognitive outcomes. To test this set of hypotheses, I compared pupillary and electrophysiological measures between healthy controls and a chronic mild TBI sample as they completed a cued attention task with varying levels of difficulty. We hypothesized that if individuals with chronic mild TBI do, in fact, have an impaired ability to modulate neural gain, we would observe a different effect of task difficulty on neural gain in the clinical sample compared to healthy controls and that neural gain would not positively correlate with behavioral performance.

Study One

The first study in this series examined the effect of cognitive load on top-down and bottom-up attentional mechanisms in chronic mild TBI. Research has demonstrated that high cognitive load competes with cognitive resources needed for top-down processing (Lavie, 2010). We expected that in controls, increased cognitive load would affect top-down attention while bottom-up attention would be left unaffected; and in the chronic mild TBI group, we predicted no modulation of neural gain in response to greater cognitive load, and therefore no differential effects of cognitive load on attention. Unexpectedly, our results indicated that the chronic mild TBI group modulated neural gain similarly to controls. However, an unexpected but insightful result from this analysis revealed that individuals with chronic mild TBI were processing top-down and bottom-up attention differently than controls. Specifically, we observed that the clinical sample did not modulate neural gain in response to changing task demands. Where controls adaptively modulated the relative focus and diffusion of their attention, the chronic mild TBI group did not. We observed that the clinical sample exhibited more diffuse attentional processing for all attentional demands, including when focused attention would be the optimal approach.

Study Two

To further investigate the role of neural gain modulation in chronic mild TBI, the second study of this research program evaluated specific types of neural gain—global and attentional gain. In contrast to the first study, results demonstrated that individuals with chronic mild TBI modulate their neural gain differently than healthy controls who exhibit a linear relationship between neural gain and cognitive load. In the clinical sample, global neural gain did not differ as a function of cognitive load and they recruited significantly

more resources to complete the task at the same level as healthy controls. In effect, they are devoting the same amount of brain-wide resources to tasks, regardless of difficulty. The amount of resources they devote to less difficult tasks is more than is needed to maintain performance similar to controls. Differences in neural gain modulation were observed for attentional gain, as well. In healthy controls, there was no relationship between cognitive load and attentional gain as measured by early attention-related ERP components P1 and N1. However, in the chronic mild TBI sample, attentional gain increased between low and moderate loads and plateaued between moderate and high loads. These results suggest that individuals with chronic mild TBI respond to increased cognitive load with a uniform increase in attentional gain that is not modulated with respect to the relative load imposed by the task. The added processing resources were sufficient to maintain performance similar to controls but were not efficient because more resources were levied than were needed in the moderate load condition. We also discovered a relationship between increased neural gain and task performance and neuropsychological status in individuals with chronic mild TBI, supporting our hypothesis that neural gain is related to long-term functional outcomes in mild TBI.

General Theoretical Conclusions

The data from the first two studies in this series suggests that patients with chronic mild TBI have an impaired ability to modulate neural gain, both global neural gain and attentional gain. Overall, we found that individuals with chronic mild TBI exert more neural resources to complete cognitive tasks, independent of cognitive load (see Appendix for power analysis). In Study Two, we noted that patients had greater global neural gain; this is consistent with our results from Study One, wherein the clinical

sample demonstrated more diffuse attentional processing for all attentional demands—even those which evoke more focused attention in controls. Previous research suggests that greater global gain is related to more diffuse attention, which can result in greater distractibility (Aston-Jones & Cohen, 2005). Taken together, results from both studies provide support for this relationship; the chronic mild TBI group had both greater global neural gain and more diffuse attention due to an inability to modulate neural gain in response to changing attentional demands.

Furthermore, as demonstrated in Study Two, impaired neural gain modulation in response to changing task demands was evident in how individuals with chronic mild TBI processed attended and unattended information. The clinical sample was able to increase neural gain in response to a moderate increase in cognitive load but was unable to allocate additional resources in response to high cognitive load. This is consistent with previous reports that neural activity plateaus at moderate load (McAllister et al., 1999). Interestingly, the effect of cognitive load on attentional processing was similar for both attended and unattended locations, suggesting that the increase in neural gain in response to greater load doesn't change the signal-to-noise ratio of task-related stimuli, but works to preserve the same signal-to-noise ratio across different levels of cognitive load. We also found that neural gain during the most difficult experimental condition—high load, invalid trials—was related to greater subjective effort. This may explain why patients experience greater cognitive effort while performance is undifferentiated in chronic mild TBI: attentional performance is maintained through a consistent signal-to-noise ratio, but processing power is uniformly increased with greater cognitive load. Collectively, our data suggest that chronic mild TBI is characterized by impaired neural gain modulation,

and this may explain why this population experiences greater subjective effort, even when objective cognitive performance fall within normal ranges.

The extant literature provides mixed evidence for long-term neurological impairments following mild TBI. Several reasons have been proposed to explain the inconsistent results, including between-study differences in task difficulty and the heterogeneity of remote mild TBI samples, including both symptomatic and asymptomatic individuals (Duncan, Summers, Perla, Coburn, & Mirsky, 2011). To address these limitations, our study directly manipulated task difficulty to impose different levels of cognitive load. We also excluded from participation any individuals with remote history of mild TBI who did not experience persistent neurobehavioral symptoms. In doing so, we built upon previous research and provided nuance to the understanding of neural correlates of symptomatic chronic mild TBI.

STUDY THREE

After finding support for the inclusion of neural gain measures to identify cognitive processing impairments in chronic mild TBI, I conducted a methodological study to identify optimal measures of global neural gain in clinical and normative samples. Although pupil diameter is a well-established index of global neural gain (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010), the extant cognitive pupillometry literature reports pupillary outcomes using a variety of pupillary measures without clear indication of or consensus on which metrics are optimal for measuring neural gain modulation. Study Three, published in *The International Journal of Psychophysiology*, compared pupillary measures under varying levels of cognitive load in healthy controls and a sample of patients with chronic mild TBI. The analysis in this study considered

several important psychometrics when evaluating the utility of pupillary measures: internal consistency, sensitivity to group and cognitive load differences, and replicability. Ultimately, peak-based measures of the pupillary response were most sensitive to group and cognitive load differences and had high internal replicability. This study is an important addition to the cognitive pupillometry literature because there were no previously established standards or guidelines for researchers to consult when choosing which metric(s) to use. Additionally, identifying which pupillary metrics were most sensitive to group differences in neural gain modulation can accelerate the adaptation of pupillometry in clinical settings.

Applications

Historically, identifying individuals with residual neurological deficits due to mild TBI is complicated by the fact that many neuropsychological tests are not sensitive to subtle deficits (Iverson, 2005; McCrea, 2008). Differential diagnosis is also difficult because the constellation of symptoms is non-specific and resembles the symptoms reported in a variety of conditions, such as depression, anxiety, and chronic pain (Gasquoine, 2000; Iverson, 2006; Iverson & McCracken, 1997; Suhr & Gunstad, 2002). Considering that some individuals who report persistent symptoms after the typical recovery period show differences in neural resource allocation in the absence of detectable neuropsychological impairments (Howells et al., 2012), incorporating more direct measures of neurological function in clinical assessment of patients with a history of mild TBI may improve identification of residual neurological impairments of mild TBI in post-acute and chronic stages. Measuring neural gain modulation in clinical settings

may help identify the sources of impairment on a case-by-case basis; however, additional research is needed to establish clinical norms and standard measurement procedures.

The current program of research is distinguished in its inclusion of several measures of neural gain, cognitive performance metrics, and subjective effort. Regretfully, many studies of chronic mild TBI do not consider subjective ratings of cognitive effort that patients experience during task performance. As indicated in this research program, this is a critical variable to measure and include in the analysis and interpretation of long-term sequelae of mild TBI. Additionally, the multi-modal approach to measuring neural gain is an integral feature of this series of studies because it allowed us to make distinctions between different forms of neural gain (i.e., global and attentional) as well as make inferences about the functional significance of the various neural gain effects we observed.

Future Directions

Replication is integral to science; thus, it is critically important that the observed effects of mild TBI on neural gain modulation are replicated in additional samples. Additionally, it is important to test whether these effects extend to other cognitive domains. In this research program, participants completed a visuospatial attention task; however, mild TBI is known to affect other neurological processes differently, including other cognitive mechanisms such as memory and executive function, emotion processing such as emotion and mood regulation, behavioral control such as behavioral inhibition (Silver, McAllister, & Arciniegas, 2009). Accordingly, it is important to characterize the effect of impaired neural gain modulation on these other neurological processes by testing participants with a variety of tasks that can index these mechanisms.

It is important to consider, however, that the experimental manipulations of the task instructions may not have modulated cognitive load per se, but rather modulated the response set for each task. By requiring simple target detection, target discrimination, or working memory comparisons, it is possible that the effects observed reflect some combination of cognitive load modulation and response-set processing. Future research using a cognitive task with identical response sets across all levels of cognitive load may be helpful in dissociating these effects.

The results from the current series of studies generated new research questions. Specifically, we were able to demonstrate that neural gain modulation is impaired in chronic mild TBI but we did not discern what mechanism is responsible for this outcome. Extensive research has demonstrated that the locus coeruleus is responsible for modulating neural gain and that the LC-NE system receives input from the frontal lobe (Aston-Jones & Cohen, 2005; Eldar et al., 2013). Given that frontal regions are particularly vulnerable to injury (Marquez de la Plata et al., 2011; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011), it seems most plausible that the impairment in neural gain modulation is related to frontal damage sustained from mild TBI. Future empirical studies are warranted to test this theory and to identify the functional networks that ultimately contribute to poor neural gain modulation.

To integrate psychophysiological measures of neural gain into clinical settings, their utility must be demonstrated for a variety of clinical applications. In the current research program, we systematically identified which pupillary measures are most sensitive to group differences and cognitive load differences. However, there are many other clinical applications for which pupillary—and electrophysiological—metrics can be

used, such as predicting long-term outcomes and measuring intervention effectiveness. To realize the potential of incorporating objective measures of neural processing in applied settings, future studies will need to identify which measures provide the best predictive value of functional outcomes.

Overall, this research program contributes to both basic science and clinical research. Importantly, it furthers our understanding of a complex and controversial condition by shedding light on mechanisms that appear to contribute to self-reports of cognitive difficulty despite “normal” behavioral performance. We have provided direct evidence of impaired neural processing mechanisms that underlie persistent symptoms in the absence of behavioral deficits. These studies, in conjunction with work from many other researchers, provide evidence for long-term neurological impairment in *some* patients who experience mild TBI and support the inclusion of neurological measures in clinical assessment of cognitive outcomes in this population. Ideally, this research will encourage researchers and clinicians to use more sensitive, neural-based measures to understand the long-term consequences of mild TBI.

References

- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, 28, 403-450.
- Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society*, 11(03), 215-227.
- Bernstein, D. M. (2002). Information processing difficulty long after self-reported concussion. *Journal of the International Neuropsychological Society*, 8(05), 673-682.
- Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *J Clin Exp Neuropsychol*, 19(3), 421-431. doi:10.1080/01688639708403870
- Chen, J.-K., Johnston, K. M., Collie, A., McCrory, P., & Ptito, A. (2007). A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(11), 1231-1238.
- Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage*, 22(1), 68-82. doi:10.1016/j.neuroimage.2003.12.032

- Duncan, C. C., Summers, A. C., Perla, E. J., Coburn, K. L., & Mirsky, A. F. (2011). Evaluation of traumatic brain injury: Brain potentials in diagnosis, function, and prognosis. *International Journal of Psychophysiology*, 82(1), 24-40.
doi:<http://dx.doi.org/10.1016/j.ijpsycho.2011.02.013>
- Eldar, E., Cohen, J. D., & Niv, Y. (2013). The effects of neural gain on attention and learning. *Nature neuroscience*, 16(8), 1146-1153.
- Frencham, K. A., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *J Clin Exp Neuropsychol*, 27(3), 334-351.
- Gasquoine, P. G. (2000). Postconcussional symptoms in chronic back pain. *Applied Neuropsychology*, 7(2), 83-89.
- Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269.
- Gosselin, N., Bottari, C., Chen, J.-K., Petrides, M., Tinawi, S., de Guise, E., & Ptito, A. (2011). Electrophysiology and functional MRI in post-acute mild traumatic brain injury. *Journal of neurotrauma*, 28(3), 329-341.
- Howells, F. M., Stein, D. J., & Russell, V. A. (2012). Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance. *Metabolic brain disease*, 27(3), 267-274.

- Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Current opinion in psychiatry*, 18(3), 301-317.
- Iverson, G. L. (2006). Misdiagnosis of the persistent postconcussion syndrome in patients with depression. *Archives of Clinical Neuropsychology*, 21(4), 303-310.
doi:<http://dx.doi.org/10.1016/j.acn.2005.12.008>
- Iverson, G. L., & McCracken, L. M. (1997). 'Postconcussive' symptoms in persons with chronic pain. *Brain Injury*, 11(11), 783-790.
- Karr, J. E., Areshenkoff, C. N., & Garcia-Barrera, M. A. (2014). The neuropsychological outcomes of concussion: A systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*, 28(3), 321.
- Lavie, N. (2010). Attention, distraction, and cognitive control under load. *Current Directions in Psychological Science*, 19(3), 143-148.
- Marquez de la Plata, C. D., Garcés, J., Shokri Kojori, E., Grinnan, J., Krishnan, K., Pidikiti, R., . . . Diaz-Arrastia, R. (2011). Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Arch Neurol*, 68(1), 74-84. doi:10.1001/archneurol.2010.342
- Mayer, A. R., Mannell, M. V., Ling, J., Gasparovic, C., & Yeo, R. A. (2011). Functional connectivity in mild traumatic brain injury. *Human brain mapping*, 32(11), 1825-1835.

- McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., . . . Yanofsky, N. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. *Neurology*, 53(6), 1300-1308.
- McCrea, M. (2008). *Mild traumatic brain injury and postconcussion syndrome: The new evidence base for diagnosis and treatment*: Oxford University Press, USA.
- Schretlen, D. J., & Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry*, 15(4), 341-349.
- Segalowitz, S. J., Bernstein, D. M., & Lawson, S. (2001). P300 event-related potential decrements in well-functioning university students with mild head injury. *Brain and Cognition*, 45(3), 342-356.
- Silver, J. M., McAllister, T. W., & Arciniegas, D. B. (2009). Depression and cognitive complaints following mild traumatic brain injury. *American Journal of Psychiatry*, 166(6), 653-661.
- Suhr, J. A., & Gunstad, J. (2002). Postconcussive symptom report: The relative influence of head injury and depression. *Journal of Clinical and Experimental Neuropsychology*, 24(8), 981-993.

APPENDIX

A power analysis for a repeated measures ANOVA was conducted in G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) to determine the minimum effect size required to detect significant differences in the proposed study using an alpha of 0.05, a power of 0.80, a total sample size of 30, two groups, three measures, and a correlation of 0.7 among repeated measures. The calculated minimum effect size to detect interactions was 0.185. This is considered a small-to-moderate effect size and is comparable (and in many instances smaller than) to effect sizes typically observed in ERP and cognitive pupillometry studies (Gao & Raine, 2009; Karl, Malta, & Maercker, 2006; Laeng, Ørbo, Holmlund, & Miozzo, 2011).