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Psychophysiological Biomarkers of Concussion Recovery

Adam Todd Harrison

PSYCHOPHYSIOLOGICAL BIOMARKERS OF CONCUSSION RECOVERY

by

Adam Todd Harrison

Bachelor of Arts
Illinois Wesleyan University, 2012

Master of Science
University of South Carolina, 2015

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Accepted by:

Troy Herter, Major Professor

Robert Davis Moore, Major Professor

Jessica Green, Committee Member

Matthew Pontifex Committee Member

Tracey L. Weldon, Interim Vice Provost and Dean of the Graduate School

DEDICATION

To my family, thank you for you the unconditional love and support you have shown me throughout my life! You have always encouraged me to pursue my own dreams and have supported me at every step of my journey. Without you this milestone would not have been possible.

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ABSTRACT

Each ach year a growing number of individuals report lingering deficits months-years following concussion. Persistent post-concussion symptoms (PPCS) can negatively impact day-today activities and if left untreated may manifest in severe neurological sequelae resulting in long-term cognitive impairment or advanced neurological degeneration (i.e., CTE). Current clinical diagnostic and prognostic assessments (e.g., symptom reports and neurocognitive testing) lack the sensitivity to quantify neurological function. Accordingly, there is a critical need to identify objective biomarkers specific to PPCS to improve an individual's quality of life and prevent severe long-term neurological dysfunction.

Psychophysiological measurements (e.g., EEG derived event-related potentials, heart rate variability, and indices of pupil dynamics) utilize involuntary fluctuations in organ behavior (brain potentials, heart rate, pupil size) in response to environmental events quantify higher-order neurological function. Numerous studies have indicated significant alterations in psychophysiological function in both acute (days-weeks) and chronic (months-years) phases of concussion recovery. These studies demonstrate that psychophysiological measures may possess the necessary sensitivity to serve as reliablemeasures of concussion recovery. However, previous methodological limitations have restricted cross study comparisons and implementation into clinical settings. Specifically, few research studies directly compare currently asymptomatic and symptomatic individuals with a recent history of concussion. This comparison is critical as

previous research has demonstrated neurological deficits months to years following injury. By excluding this comparison analytical interpretations fail to account for neurological adaptations that may underlie typical recovery patterns. Additionally, traditional psychophysiological assessments employ task paradigms that do not fully capture the complexity of real-world engagement. If a task is too simplistic, it may fail to adequately challenge the individual and may not reveal lingering neurological dysfunction when completing tasks in the real-world.

The present series of investigations found demonstrated that symptomatic individuals with a history of concussion report significant symptom burden spanning somatic disruptions, psycho-affective health, and general quality of life. Furthermore, symptomatic individuals demonstrated significant deficits in tasks of cognitive control, executive function, and attention. These deficits were exacerbated by more complex tasks designed to mimic real-world interactions. In addition to behavioral deficits, both symptomatic and asymptomatic individuals tended to demonstrate lingering deficits in psychophysiological function (i.e., pupillometry and ERPs). Unfortunately, ERP measures collected during more dynamic and complex tasks produced muted waveforms making comparisons across groups difficult. Finally, deficits in both cognitive performance and psychophysiological behavior demonstrated significant relationships with reported symptom burden. This supports their use as potential biomarkers of neurological dysfunction following concussion. In conclusion, the present series of studies supports the growing body of literature suggesting slow-to-recovery demonstrate lingering impairments in neurological function. Furthermore, behavioral assessments designed to mimic real-world interactions may more precisely capture day-to-day impairments. However, these

tasks may be too complex and therefore distort neuroelectric recordings of cognitive function

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CHAPTER 1

GENERAL INTRODUCTION

Concussion, sometimes referred to as a mild traumatic brain injury (mTBI), is a neurological injury induced by biomechanical forces directed at the head, neck, or body.[1] This impact, transmits impulses to the brain resulting in a series of neurophysiological disruptions and structural abnormalities.[2] Externally, individuals suffering from a concussion often report a combination of somatic (headache, dizziness), cognitive (difficulty concentrating, poor memory), and psycho-affective (anxiety, depression) symptoms.[3-5] Individuals often report complete symptom resolution within 7-10 days from the initial injury.[6] This has led to concussions to be stereotyped as mild and transient in nature and this mindset has shaped public perception, diminishing their seriousness and severity. However, the last decade has seen a steady increase in evidence suggesting the potential severity and long-term consequences of these injuries.[3, 7-10]

It is estimated that roughly 3.8 million concussions are diagnosed annually within the United States.[11-13] This number has steadily increased over recent years, in part, due to heightened public awareness stemming from increased advocacy from current and retired athletes as well as research reports highlighting the public health impact of these injuries.[14] Most notably, repeated concussive and sub-concussive head impacts have been linked to chronic traumatic encephalopathy (CTE) a debilitating and fatal neurodegenerative disease, first identified in boxers and more recently found in several deceased retired professional football players.[15, 16] Additionally, while most individuals will experience full symptom resolution within a couple weeks, a growing portion of concussed individuals (~40%) develop persistent post-concussive symptoms (PPCS), hallmarked by debilitating and persistent symptoms months after injury.[17, 18] Our understanding of these conditions is

very limited, however, if left unattended they can negatively impact the inflicted individual's mental health and overall quality of life.[19-23]

Although efforts have been made to develop adequate rehabilitation strategies, our ability to gauge their effectiveness is limited by the lack of objective biomarkers of neurophysiological recovery following concussive injuries.[24-26] One major barrier to this search is the limited number of studies directly comparing symptomatic and asymptomatic individuals with a history of concussion. Research has continuously identified a history of concussion as one of the strongest predictors of both incidence of injury and severity of injury outcomes.[27, 28] Additionally, research has detected atypical neurophysiological profiles in asymptomatic individuals months to years after their last concussion.[29-31] Therefore, this additional level of comparison is crucial as it allows us to tease out atypical recovery patterns. An additional barrier lies in the unknown ecological validity of testing paradigms used to assess neurological function following concussion. To generalize function in the real-world, testing protocols should aim to mimic the dynamic and multidimensional activities individuals experience in their everyday life. Furthermore, paradigms designed to simulate real-world task complexity may provide the necessary level of physiological stress to uncover potentially latent deficits in neurological function.[32]

CHAPTER 2

LITERATURE REVIEW

To better understand the critical need for identifying objective biomarkers of neurological damage following concussion, it is important to review the existing literature. First, an overview of concussion including a brief introduction, injury mechanism, underlying pathophysiology, and its relationship to symptom presentation will be presented. Second, the emerging evidence associated with long-term consequences of concussion, specifically persistent post-concussive symptoms (PPCS) and chronic traumatic encephalopathy (CTE) will be presented. Next, will be a description and critique of the current clinical diagnosis and management protocols of concussion. Finally, a detailed evaluation of behavioral and psychophysiological techniques will be presented, that provide non-invasive objective markers of neurological function and recovery following concussion. Specifically, assessments of cognitive control, saccadic eye-movement behavior, pupillometry, and electroencephalography (EEG) will be introduced; highlighting key research that has advanced our ability to quantify neurological function and identify atypical patterns following concussion and other neurological conditions. This review will conclude with a summary highlighting important research gaps and the purposes of the proposed studies.

Historical Perspectives on Concussion

Roughly 3.8 million concussions are diagnosed each year in the United States.[11-13] However, even with the growing incidence rates and public awareness of these injuries, our understanding of recovery following concussion remains limited. This is in large part due to the lack of sensitive and reliable assessments of neurological health during the recovery period.

Mechanistically, a concussive brain injury occurs when a mechanical force is directed and delivered to the head, neck, body.[6] This impact transmits impulses to the brain resulting in damaging acceleration and deceleration movement of the brain within skull causing deformation of underlying tissue.[1, 2] These events initiate a cascade of neurochemical and neuroanatomical disruptions (see Concussion Pathophysiology) resulting in a constellation of symptoms ranging from headache, emotional dysregulation and cognitive deficits, to temporary loss of consciousness (LOC) and post-traumatic amnesia (PTA).[3, 33] However, concussions can occur in a variety of situations (i.e. contact sports, motor vehicle accidents, assault) leading to the heterogenic and non-specific nature of symptom presentation among individuals, making precise clinical diagnoses difficult.

Most early attempts to define concussion were based on criteria attempting to rule out more severe brain injuries. These criteria emphasized transient symptomology, negative findings on standard computed topography (CT) or magnetic resonance imaging (MRI), a Glasgow Coma Scale (GCS) score less than 15, LOC for less than 30 minutes, and PTA lasting less than a day.[34-36] However, it is estimated that LOC and PTA occur in only about 5% and 24% cases of concussion, respectively.[8, 37] Additionally, it has been well established that MRI and CT imaging techniques lack the sensitivity to detect the microstructural damage of concussive injuries, challenging their utility in the diagnosis of concussion.[38, 39]

Since 2001, sport clinicians and top researchers in the field have gathered regularly to establish and update a consensus statement regarding the nature of concussive brain injuries and their management.[40] In their most recent proceedings from the 2017 5th International Conference on Concussion in Sport, the group defined concussion as

"traumatic brain injury induced by biomechanical forces."[6] They further elaborated providing a series of supplemental features to help aid in the clinical diagnosis. These include: 1) may result from a direct blow to the head, neck, or body; 2) typically result in the rapid onset of transient neurological dysfunction that resolve spontaneously, though in some cases may exhibit delayed onset; 3) acute symptoms are largely due to functional abnormalities rather than large scale structural injury; 4) the range of clinical symptoms vary, and may or may not include LOC; and 5) resolution of symptoms typically occurs within 10-14 days post-injury, however in some cases symptoms may persist beyond this window. While this definition is concise and encompassing, without establishing biomarkers through sensitive imagine techniques or objectively quantifiable measures of neurological function a concrete definition (and diagnostic criteria) of concussion will remain impossible.[41]

Concussion Pathophysiology

As mentioned above, traditional imaging techniques fail to detect neural abnormalities following concussions. However, animal models and advanced imaging techniques in humans have allowed scientists to outline the pathophysiological timeline of concussion.[42, 43] Additionally, research has been able to connect these pathophysiological disruptions with symptoms and neural vulnerability to repeated assault.[43]

Recall, concussions are initiated by biomechanical forces directed at the body that then transmit impulses to the brain. These impulses then result in translational and rotational movements of the brain within the skull.[1, 21,2] This neural insult triggers a cascade of events significantly altering cerebral homeostasis. This 'neurometabolic cascade' is

characterized by alterations in membrane integrity, rapid ionic fluctuations, dysfunctional neurotransmitter release, indiscriminate cellular hyperexcitation, diminished cellular metabolism and uncoupled cerebral blood flow (CBF).[43]

At the onset of injury, the permeability of the cellular membrane is greatly increased resulting in a massive ionic influx of calcium (Ca^{2+}) and sodium (Na^{+}) and efflux of potassium (K^{+}).[43] The rapid intercellular increase in Ca^{2+} and Na^{+} concentration initializes depolarization of the cellular membrane potential, further perpetuating the ionic imbalance and non-specific release of excitatory neurotransmitters (i.e. glutamate, N-methyl D-Aspirate).[44] To prevent the cell from entering a state of excitotoxicity, the cell initiates the adenosine triphosphate (ATP) dependent Na^{+}/K^{+} pump to regulate intercellular and extracellular ion concentrations.[44] This increased metabolic demand subsequently necessitates increased glucose delivery via the cerebral vasculature. However, it has been demonstrated that CBF may be reduced by up to 50% following concussion[45] creating a state of hypoglycemia and energy crisis within the cell.[46] In addition to Na^{+}/K^{+} pump overdrive, the central nervous system tries to restore ionic homeostasis and meet the growing energy demand by shuttling intercellular Ca^{2+} and peripheral lactate[47] into the mitochondria. This temporary solution eventually leads to a rise in oxidative stress within the cell and a breakdown in the capacity of the mitochondria to generate ATP via oxidative phosphorylation, furthering the cellular energy crisis.[48]

In response to the increasing cellular damage and oxidative stress, neighboring astrocytes initiate the neuroinflammatory response by releasing inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) into the extracellular space. In addition to the neuroinflammatory response, peripheral inflammatory markers may enter the brain space as the result of the

decreased integrity of the blood-brain barrier, caused by the trauma.[49] Initially, this process signals the regenerative and recovery processes following neural insult. However, chronic exposure may be detrimental leading to cellular dysfunction, cellular degeneration. and/or apoptosis.[44, 50, 51]

While disruptions in metabolic function following concussion are well established, structural alterations also occur. The translational movement of the brain within the skull induces tensile and shearing stress on the axonal fibers. This stress results in axonal swelling, demyelination, and structural degeneration of the neuron.[52] The microlevel damage disrupts the efficiency and effectiveness of neural transmission impacting the overall network communication.[53-57] While not detectable by conventional structural imaging (i.e. MRI and CT) this level of structural damage and disrupted communication has been shown using more sophisticated neuroimaging techniques such as diffuse tensor imaging (DTI), functional MRI (fMRI).and Susceptibility-Weighted Imaging (SWI).[58-62]

Although the concussive impulse widely distributes throughout the brain, specific brain regions and white matter tracts seem to be more susceptible to injury than others. DTI measures the diffusivity of water (directionality of movement) along the neuron and has been shown to be a valuable index of structural integrity and microscopic lesions following concussion.[63] DTI studies have demonstrated atypical diffusivity patterns along the cortical spinal tract (CST), corpus callosum (CC), corona radiata, and the longitudinal fasciculus.[58, 64] These white matter tracts are vital as they link together various cortical regions allowing for efficient communication and integration. Damage to these networks is associated with reports of cognitive impairments following concussions.[56, 65, 66] The link between structural disruption and cognitive impairment is further evidenced by fMRI studies demonstrating

decreases blood flow in key frontal and temporal brain regions involved in executive function and cognitive control.[52, 59] Finally, SWI has been used to investigate microscopic hemorrhaging following concussion, These investigations have found that individuals may experience microbleeds following concussion.[62, 67] Concussed individuals who develop microbleeds have shown to perform worse on cognitive tests compared to concussed individuals without.[68] Structural abnormalities following concussion may be present months or even years after injury,[69] and chronic impairment may contribute to the late life neurodegeneration, cognitive impairment, and mental health issues seen in individuals with a history of concussion.[70]

Long-Term Outcomes

Though initially believed to be a mild injury with transient disruptions in neurological function, a growing body of literature is beginning to identify severe and debilitating long-term conditions associated with concussions; specifically, persistent post-concussive symptoms (PPCS) and chronic traumatic encephalopathy (CTE).[15, 16, 71-73] While studies have identified significant structural and functional abnormalities in individuals suffering persistent symptoms, there is no concise definition or symptom profile for PPCS.[74, 75] Generally, PPCS is characterized as a clustering of non-specific symptoms following a concussion persisting beyond the typical recovery window (>1-3 months) and negatively impacting daily function.[72] Reported symptoms typically fall within one of three categories; somatic disruptions (chronic headache, photosensitivity), emotional imbalance (depression, anxiety), and cognitive impairment (poor concentration, memory issues). PPCS has been linked to an unregulated neuroinflammatory response triggered by concussive injuries. The unrestricted release of pro-inflammatory cytokines

and excitotoxins results in increased neural damage, and lingering symptoms.[76] In addition to patients with PPCS reporting lingering symptoms, these slow to recover individuals have demonstrate persistent deficits in neurological function. (Sicard, unpublished) Impacting approximately 30-40%[18, 77] of concussed individuals, lingering symptoms associated with PPCS negatively impact daily quality of life.[21-23, 78-81]

CTE is a distinct neurodegenerative disease brought on by repeated exposure to concussive and sub-concussive blows over a lifetime.[73] This chronic exposure to head trauma leads to irreversible structural and functional alterations of the brain. The first cases of CTE, termed 'punch-drunk', were used described abnormal behavior in retired boxers.[82, 83] However, recent autopsy reports identifying CTE in retired football players, military veterans, and individuals with a history of non-sport related concussions (motor-vehicle accidents, falls) has expanded the scope of the disease.[19, 84, 85]

It has been hypothesized that the resulting neurochemical hyperexcitability combined with overactivation of the microglial immune response following injury induces a state of "immunoexcitotoxicity."[49, 51] This combination of events may result in significant oxidative stress on the neural mitochondria, further limiting energy production via oxidative phosphorylation, and eventual cell death. Research suggests that repeated injuries may prime the microglial response, exacerbating the release of pro-inflammatory cytokines and excitotoxins on subsequent injuries resulting in further neural degredation.[86] The heightened immune response and neural damage may serve as a mechanistic link between repeated neural trauma and CTE.[20, 87, 88] Mitochondrial dysfunction (calcium influx) and increased concentrations of excitotoxins disrupt the regulation of tau proteins within the brain.[89] Unregulated tau phosphorylation causes the protein to coil producing tau plaques.

These tau plaques are hallmark signs of CTE, and other neurodegenerative diseases.[16, 90, 91] In CTE, the non-specific accumulation of hyperphosphorylated tau-proteins within the cortex (layers II-III) resulting in irregular patterns of cortical (i.e., frontal and temporal cortex) and subcortical (i.e., hippocampus, amygdala, and locus coeruleus) atrophy.[91, 92]

Unfortunately, the current diagnostic criteria for CTE relies on the localization and histological examination of brain tissue found during post-mortem evaluations.[92] However, retroactive reports have linked CTE with several stereotypical clinical manifestations such as declines in mental health (depression, suicidal thoughts, aggression), substance abuse problems, impairments in fine motor skills, and cognitive decline/dementia.[19, 20, 93] Additionally, investigations have begun to test the reliability of advanced neuroimaging to identify early biomarkers of PPCS and CTE.[94-96]

Emerging evidence is starting to highlight the association of repeated sub-concussive head impacts (SCHI) and chronic neurological dysfunction. SCHI are classified as blows to the head that inefficient to produce characteristic symptoms associated with concussion. Numerous studies over the last decade have identified significant alterations in neurological function and increased blood-brain barrier permeability in current and retired athletes of contact sports, who did not experience a concussive event.[97-101] More concerning are the reports of CTE emerging in individuals with repeated (sub-concussive) head trauma, but no history of neurological injury. In a recent investigation, Stern and colleagues[102] collected positron emission tomography (PET) scans from retired professional football players, without a history of traumatic brain injury but reported cognitive and/or mood disruption and age-matched non-athlete control. Compared to the controls, the images of former athletes showed significantly greater traces of tau

aggregation in frontal, parietal, and temporal brain regions, all regions associated with tau deposits found in CTE.[92]

Although little is known about the etiology and progression of both PPCS and CTE, they are both associated with repeated head trauma, with individuals sustaining more head impacts being at greater risk of these long-term conditions.[73, 103-105] In addition to PPCS and CTE, increased exposure to concussive and sub-concussive blows is associated with general long-term cognitive deficits and an early onset of mild cognitive impairment (MCI)/dementia.[8, 106] While not everyone will experience these severe outcomes following concussive injuries, these conditions represent abnormal recovery patterns following injury that significantly impair a person's ability to carry out day to day tasks.[22, 78, 80, 87, 105, 107-109] These findings highlight the importance of accurately tracking concussion recovery and the prescription of specific therapeutic techniques in cases where recovery is lacking.

Current Trends in Clinical Management of Concussion

As previously stated, (see Historical Perspectives on Concussion) the diagnosis of a concussive injury is a significant clinical challenge. Acute symptoms presentation following concussion tends to be the most agreed upon indicator of injury.[110] However, the reliance on self-reported symptoms has been challenged, as their accuracy is inherently dependent on the motivation of the patient. Patients often feel pressure to lie or under report symptoms to return to school, work, or sport activities.[111-113] In these instances, individuals may prematurely return to everyday activities before nervous system is able to accommodate the physical and mental stressors.[32, 114-116] Premature re-introduction may

exacerbate concussion related deficits, prolong concussion recovery, or increase risk of more severe secondary injury.[3, 9, 27, 108]

This has led officials to call for multimodal evaluation protocols that extends beyond symptom reports and include assessments of other domain impacted by concussion[6].[6] In addition to symptom reports, recent clinical tools such as the Sport Concussion Assessment Tool 5th edition (SCAT5) now include assessments of cognition, neurological function, and balance.[117] Computerized neurocognitive tests such as; the Immediate Post-concussion Assessment & Cognitive Testing (ImPACT)[118] and the CogState Brian Injury Test Battery[119] have become widely used clinical and sideline assessments of concussion. These tools quickly generate easy to interpret composite scores that can be used to identify cognitive impairment. Indeed, these tools have been vital in identifying concussive injuries within the acute phase.[120, 121] However, these computerized assessments have received immense scrutiny due to their low reliability and vulnerable to practice effects limiting their utility to be used repeatedly over the recovery period.[122, 123] Research has demonstrated that these computerized tests lose their value after approximately 72-hours post-injury as they are not sensitive enough to detect subtle, but meaningful cognitive deficits.[124] While the addition of computerized assessments of neurocognitive function reduces observer bias and provides a more objective measure of response efficiency and cognitive function their use is limited to the first few days of injury. Furthermore, these measures provide little information regarding the health and integrity of brain failing to provide crucial information needed to determine whether an individual is ready to return to normal activity.

Ophthalmological (i.e., visual processing and oculomotor) dysfunction is very common following brain injuries, including concussion.[125-129] Common symptoms associated with concussion include photosensitivity, erratic eye movements, blurred vision, and vestibulo-ocular deficits.[129] This has led to the incorporation of ophthalmological screenings into the clinical concussion assessment toolbox.[130-132] The Vestibular/Ocular-Motor Screening (VOMS) was developed as a clinical screening tool to assess how combination of head and eye movements (e.g. smooth pursuits, saccades, vestibular ocular reflex, convergence) affect symptoms.[131] One by one practitioners guide the patient through the various assessments, asking the patient to report if executing the given movement exacerbates any symptoms. When administered correctly the VOMS demonstrates a high degree of sensitivity in detecting concussive injuries.[133, 134] However, to get the most out of the test administration, trained practitioners are needed to detect subtle abnormalities in eye movement quality indicative of underlying injury to vestibulo-ocular pathways. Furthermore, reports suggest that approximately 56% of clinical practitioners administering the VOMS lack a true understanding vestibulo-ocular deficits and their implications following concussion.[135]

To overcome some of the shortcomings of the VOMS, the King-Devick test (KD test) of rapid number naming was developed as a quick, and easy to administer sideline tool.[136] When administering the KD test, patients are given three index cards with numbers arranged horizontally left-to-right. Patients are then asked to read the numbers aloud as quickly and accurately as possible. Patients are scored based on the time it takes to complete each card and the total number of errors committed.[137] While quick and easy to administer, even as a sideline assessment in athletes, there are many confounding variables

that hinder its utility as an assessment of concussive injuries. Most notably is its reliance on individualized pre-injury assessments to establish baseline performance levels.[138] This may be practical for some athletic populations but in the general public it simply is not a feasible option. Additionally, relying on change scores from pre-injury baseline data (or normative data) you must establish meaningful cutoff thresholds for injury diagnosis and management of recovery. Finally, while the behavioral outcomes from the KD test seem to be sensitive to concussive injuries in the acute phase of recovery, the assessment lacks the ability to quantify the quality of eye movements. This is crucial because it is possible that as patients progress through the initial recovery phase, acute neural plastic adaptations may set in. These changes may result in compensatory neural activity reducing observable behavioral deficits, obscuring still present neurological dysfunction.

In conclusion, with the increased awareness in concussive injuries over the last decade drastic changes have occurred in clinical management practices. However, identifying complete recovery from injury remains one of the most difficult clinical challenges to date. The importance of proper management is further exacerbated by research repeatedly identifying previous concussion history as one of the strongest predictors of repeat injury, prolonged recovery, and long-term negative outcomes.[3, 8, 10, 73, 139, 140] Findings from neurophysiological research suggest a potential disconnect between symptom recovery and the neurophysiological recovery of neural tissue.[141, 142] These studies both structural[60, 63, 143] and functional[144-148] abnormalities in concussed individuals no longer reporting symptoms or negative indications on computerized tests. This may suggest that individuals may be returning to normal activities prematurely, putting

themselves at risk for further injury or long-term neurological sequalae.[7, 9, 10, 33, 149] Therefore, it is crucial that we identify objective measures of neurological recovery.

Behavioral & Psychophysiological Biomarkers to Index Neural Function

As stated in the previous section, diagnoses and tracking individual recovery profiles remains to be one of the most difficult clinical challenges related to concussive brain injuries. This is largely due to the lack of validated and objective biomarkers that can be used to infer symptom presentation and underlying neurological health. Biomarkers are characteristics of biological systems (e.g., heart rate, oxygen concentration of blood) that can be quantified. Biomarkers are critical to the medical field as they provide objective measurements that can be tracked overtime and provide insight into the health of the overall system.

Concussion assessments of neurological function primarily reliant on performance scores from neurocognitive testing batteries that are insensitive to subtle deficits in cognitive performance. However, evidence suggests that tasks assessing various aspects of cognitive control may prove viable resources in identifying and understanding cognitive dysfunction following concussion.[120, 150, 151] Additionally, psychophysiological measurement techniques can be used to assess natural responses of physiological systems (i.e., brain, heart, eye, skin) to assess function in a variety of situations (e.g., rest, exercise, cognitive demand, emotional processing). These assessments have been utilized to quantify underlying neurological health in a variety of healthy and clinical populations. In this section I will review some promising psychophysiological assessment techniques and how they are well suited for assessing neurological dysfunction following concussion.

Cognitive Control Measures to Index Neural Function

Successful completion of everyday tasks relies on the ability to organize behaviors to achieve a common goal. This is achieved by higher-order neurological processes collectively referred to as cognitive control (or executive control).[152, 153] Effective cognitive control allows us to acquire information from our environment, prioritize what information is relevant, select and coordinate appropriate responses, and evaluate response selection for future performance adaptations.[154] The three tenet components of cognitive control are inhibition (ability to willingly override prepotent/automatic behaviors), working memory (ability to store and manipulate information over a short period of time), and mental flexibility (ability to fluctuate between multiple operating rule sets).[155] Functional neuroimaging and anatomical studies have linked cognitive control processes to regions within the pre-frontal cortex (PFC). The PFC possesses vast projections to cortical and subcortical brain regions enable it to modulate lower-level sensory and motor processing.[156-158]

One key function of cognitive control is to mitigate the degree of conflict within the behavioral processing pipeline, by adapting behavior once conflict arises.[159] Conflict in a general sense, can be interpreted as any disturbance limiting goal-oriented cognitive processing. In the action-selection process, conflict results from interference due to competing and concurrent processing streams such as: response to competition from prepotent reflexive actions; having to choose from multiple and equally probable response choices; or from erroneous action evaluations.[159] The process of conflict monitoring has been localized to regions of the frontal lobe, the anterior cingulate cortex (ACC).[160-162] From here, information is passed on to cognitive control centers to adjust behavior.

To better understand its role in conflict mitigation, cognitive control processes have been subdivided into 'proactive' and 'reactive' components.[154] Proactive control refers to the early processes responsible anticipating and preventing sources of potential conflict. Sustained activation of the dorsal lateral PFC (dlPFC) helps to reduce the conflict by allocating attentional resources and biasing the perceptual system toward task-relevant stimuli in the environment.[156, 163] Conversely, reactive control relies on transient activation throughout the PFC, including the ACC. This activation pattern allows the individual to identify the source of the ongoing conflict and employ immediate corrective measures and/or schematic alterations to subsequent behaviors.[159, 164] Within complex daily activities, individuals rely on a combination of both proactive and reactive control strategies to successfully complete complex, goal-driven tasks of everyday life.[160]

Cognitive Control & Concussion

Due to the delayed maturation and anatomical location of frontal brain regions, a wide variety of cognitive control tasks have been utilized to assess neurological function associated with development and concussion.[165-167] Task paradigms such as the Go/No-Go task are commonly used in research to assess aspects of inhibitory control and behavioral monitoring.[168] Both processes are vital as they allow for the effective voluntary control of behavior, maintenance and adaptation of behavior, and learning.[169, 170] Typically within the Go/No-Go task individuals are presented with one of two stimuli. Within one condition of the task, participants are instructed to respond to an infrequently appearing target stimulus while ignoring the frequently occurring distractor stimulus (GO trials). Following the GO trials, the task instructions are reversed, and the subject is instructed to respond to the previous frequently appearing stimuli, while ignoring the infrequent stimulus (NOGO

trials). Inhibitory control, indexed by the number of committed errors (commission errors), is stressed by asking subjects to inhibit both a previously learned rule set and a prepotent response within the NOGO trials.

One investigation by Moore and colleagues[65] investigated Go/No-Go task performance in a group of previously concussed pre-adolescent children. Participants with a history of concussion were on average, 2.1 years post-injury. When comparing overall task accuracy, they found no significant difference in performance. However, further behavioral analysis revealed that compared to non-injured controls, pre-adolescent children with a history of concussion exhibited poorer inhibitory control indexed by a greater number of commission (false alarm) errors. In a similar Go/No-Go paradigm, Zhao and colleagues[171] found that recently concussed adults (mean 15.8 days post injury) demonstrated significantly poorer task performance on several measures; total targets hit, number of omission errors, and overall reaction time. Both studies highlight the potential utility of the Go/No-Go task in assessing progression of neurological function following concussion.

Eye Tracking & Saccade Behavior

In addition to limb-motor movements, the human ocular system has evolved to meet the complex needs of human goal-driven behavior. The eye contains millions of photoreceptors specialized for visual information processing. There are two types of photoreceptors (i.e., rods and cones), each optimized for specific aspects of visual processing. At the front of the eye, the pupil and lens adjust in to control the amount and shape of light entering the eye. These lens and pupillary adjustments focus the incoming

light onto an area of the retina highly concentrated with cones called the fovea.[172] These photoreceptors are optimized for color discrimination and visual acuity. Therefore, the fovea represents the portion of the eye with the greatest visual acuity (foveal vision).[173, 174] To maximize visual information processing, humans must be able to effectively move the eyes to align the fovea on novel/goal-specific stimuli to allow for adequate analysis. Additionally, we must be able to inhibit eye movements toward irrelevant stimuli to maintain foveal vision (fixation) on a specific object.[175]

The oculomotor system has developed two specific types of eye movements designed to direct the fovea to specific areas within the working environment. Fast, stimulus driven saccades are used to quickly orient the visual system toward a novel/task relevant stimulus.[179] Pursuit eye movements allow the visual system to maintain fixation on moving stimuli for continued processing.[176] The remainder of these section will focus on saccadic eye movements and emerging evidence in their ability to detect neurological impairment.

As mentioned, saccadic eye movements are quick, ballistic rotations of the eye intended to maneuver the fovea throughout the environment. Perceptually we view our current environment in a single glance. However, this is not reality, our working representation of the environment comes from the integration (and estimation) of visual information stemming from numerous visual snapshots captured by saccades.[177] The neural circuitry involved in saccade generation spans many cortical and sub-cortical brain regions. The superior colliculus (SC), a midbrain structure, plays a critical role in the integration of sensory information to guide motor behavior.[178, 179] The SC receives direct input from the retina and utilizes this sensory information to drive saccades and/or maintain fixation.[175]

Additionally, higher order brain centers within the frontal (i.e. frontal eye fields, dorsolateral prefrontal cortex) and parietal lobes (lateral interparietal cortex) synapse directly to the SC and exert influence on saccadic eye-movements.[180, 181] These regions are heavily involved in the attention and vigilance networks,[182, 183] exerting top-down regulatory control over gaze fixation and pre-saccadic processing.[184, 185] Because saccadic eye movements rely on both bottom-up (externally driven) and top-down (internally driven) control, experimental task manipulation can be used to provide valuable insight into underlying cognitive control processes.[186]

One of the most common tasks used to study saccade generation is the anti-/pro-saccade task (APST). This task utilizes two experimental conditions in which participants are instructed to make specific directional eye movements toward (pro-saccade) or away (anti-saccade) in response to appearing stimuli.[187] Pro-saccade trials utilize bottom-up reflexes toward an appearing stimulus, investigating sensory and perceptual awareness. On the other hand, anti-saccades require top-down cognitive control to inhibit a prepotent response (i.e., pro-saccade).[188-190] Traditional implementations of the APST utilize a blocked design, in which each trial in each experimental run is either a pro- or anti- saccade trial. However, some researchers challenge the block framework arguing that the constant response rule set may mitigate cognitive demand.[191] Recent studies have begun incorporating an interleaved design, in which the trial condition is randomly assigned and defined by a specific stimulus feature (i.e., shape, color) of a pre-response fixation target. The interleaving of anti- and pro- saccade trials may more adequately stress the individual's executive system, as it requires the participant to keep two response rule sets in mind (task

switching) and identify the appropriate rule set for each trial (updating working memory) in addition to the suppression of prepotent reflexive responses (response inhibition).[192-194]

Eye Tracking & Concussive Brain Injuries

Eye tracking technology has greatly improved quality and sensitivity of neurological assessments. Eye tracking has been used to investigate cognitive impairments following neurological disorders such as stroke[195, 196200,201], attention deficit hyperactivity disorder (ADHD)[186, 197], post-traumatic stress disorder (PTSD),[198] as well as providing objective measures of individual levels of psychological status such as fatigue[199] and anxiety.[200] Recent research has utilized eye tracking to identify cognitive deficits following concussive brain injuries. In one of the first studies to investigate oculomotor impairments following concussion, Heitger and colleagues[201] compared self-paced and anti-saccade performance between individuals diagnosed with PPCS and healthy matched controls. They identified that individuals suffering from PPCS demonstrated significant impairment in several measurements of eye movement control, predominantly those related to sub-cortically driven saccades. Furthermore, they observed that several saccadic variables were significantly correlated with patient reported symptom scores, suggesting the possible utility of saccadic performance as an indicator of neurological recovery following injury. This relationship was further investigated by Hunfalvay and colleagues,[202] in their study they compared both vertical and horizontal self-paced saccades in a group of individuals suffering TBI (mild, moderate, severe). They observed that individuals suffering from TBI demonstrated poorer control over saccadic eye movements, namely a decrease in the overall number of saccades and a poorer speed-accuracy trade-off. Interestingly, they observed an overall negative effect of group for many of the measures, with individuals in

the severe TBI group demonstrating poorer performance. The results of these two studies highlight the potential for measures of saccadic performance as biomarkers of neural health.

In addition to self-paced saccadic eye movements, research has investigated task-related saccade behavior to study concussion-related dysfunction. In a preliminary investigation, Ting and colleagues[64] had concussed and non-concussed individuals undergo a neurological assessment battery including DTI scans and an anti-saccade task. Similar to previous research they observed that individuals with a history of concussion demonstrated significantly more directional errors and longer saccadic reaction times. More importantly, they found that saccadic reaction time was highly correlated ($r > 0.90$) with DTI measures of neural integrity in which longer reaction times were associated with poorer neural integrity. More recently, Webb and colleagues[208] had a group of concussed athletes complete the anti-saccade task within the first week of injury and again 2 – 3 weeks later when the athlete was cleared to return to sports participation. They found that recently concussed individuals, within the first week of injury, demonstrated increased saccadic reaction time and increased directional errors to anti-saccade targets. When the athletes returned for the follow-up evaluation, athletes no longer exhibited longer reaction times but continued to commit more directional errors compared to matched controls. This is important because while the athletes reported no more concussion-related symptoms at follow-up, assessments of saccadic control were able to detect significant deficits in cognitive function (i.e., response inhibition). These studies highlight the sensitivity of eye tracking technology and the anti-saccade task to detect subtle neurocognitive deficits

typically missed by standard clinical assessments. Furthermore, they demonstrate a significant relationship between saccadic behavior and underlying integrity of the brain.

Pupillometry

In addition to eye movements, pupillary dynamics have become a popular metric in psychophysiological research.[203] The pupil is the clear circular opening in the front of the eye, positioned in the center of the iris (colored portion of the eye) which contain the pupillary musculature. The primary purpose of the pupil muscles are to increase (dilate) or decrease (constrict) the diameter of the pupil modulating the amount of light that entering the interior space of the eyeball and ultimately the photoreceptors of the retina.[204] Constriction and dilation of the pupil are controlled by the intricate interplay between the parasympathetic (constriction) and sympathetic (dilation) branches of the autonomic nervous system (ANS).[205] Tonic parasympathetic activity keeps the pupils in a natural state of constriction.[172] This is controlled the integration of afferent visual information within the parasympathetic preganglionic Edinger-Westphal Nucleus (EWN). The EWN then activates the iris sphincter muscles causing the pupil to constrict.[204, 205] However, in response to environmental stimuli, activation of the sympathetic dilation pathway both directly and indirectly override the tonic pupillary constriction. The hypothalamus and locus coeruleus (LC) are both regions of the brain activated during periods of increased arousal.[206] These brain regions directly influence pupil diameter by innervating the iris dilator muscles. Additionally, during periods of increased mental effort, the hypothalamus, LC, and frontal brain regions inhibit the EWN, indirectly modulating pupil size by blocking parasympathetic activation.[207-210]

By changing the amount of light (visual stimuli) entering the eye, the pupil functions to maximize the trade-off between focused visual acuity (high acuity, small area of focus) and broad visual sensitivity (low acuity, large area of focus).[172] A prime example of this is the pupillary light reflex (PLR) characterized by the automatic dilation and constriction of the pupil in response to changes in ambient lighting.[211] When you turn on a lamp in a dark room, the increased light is detected by the photoreceptors on the retina and transmitted to the EWN initiating pupillary constriction. The narrowing of the pupil aids in focusing the incoming visual information on the cone dense fovea, allowing for increased visual discrimination (i.e., visual acuity) of the objects in the room. On the other hand, if you turn off the light, activation of the hypothalamus and LC cause the pupil to dilate. Increasing the size of the pupil allows the peripheral regions of the retina (highly concentrated with rods) to process the incoming visual information. Unlike cones, rods are maximally tuned to detect movement, subtle changes in light intensity (visual sensitivity) and are therefore well suited for processing visual information in the dark.[173] In addition to being inherent evolutionary advantage, researchers have hypothesized that the PLR also has been maintained to prevent the retinal photoreceptors from becoming desensitized to maintain responsiveness to fluctuations in visual stimuli.[172]

While the PLR is probably the most well-known behavioral response associated with the pupils, modulation of pupil size can be observed in response changes in other situational demands. Recall, higher order frontal brain regions, the LC, and hypothalamus can inhibit the EWN. Therefore, pupillary dilation and constriction can be observed in response to internal fluctuations in arousal, cognitive load, and emotion, termed the psychosensory pupil response (PPR).[172, 199, 212-217] While the circuitry involved in the PPR

is unclear, many point to activation of the LC-noradrenaline pathway by frontal brain regions.[206, 218-220] It is hypothesized that the coordinated release of noradrenaline and activation of downstream brain regions (i.e. SC) act to inhibit EWN projections to the iris sphincter muscles allowing for the pupil to dilate.[221-223] This relationship between pupil dilation and cognitive processing suggests task-related pupil response may serve as a psychophysiological measure of attentional engagement and individualized mental work load. Therefore, tasks designed to manipulate the PPR may be able to identify neurological dysfunction following brain injury.

Video-Oculography: Eye Tracking & Pupillometry

Ophthalmological screening used within the clinical management of concussion are extremely limited by their subjective nature, reliance on observer quantification, and insensitivity of their coarse scoring systems. However, with the emergence of infrared-based pupillography in the 1950s, scientist have been able to accurately record ocular dynamics in real time during various tasks.[205] This discovery has permitted adequate illumination for video cameras to capture a clear image of the eye and more importantly the pupil, without using light within the visible spectrum. When using visible light, the luminance induces noise by eliciting the PLR. Incorporating eye-tracking technology into assessments administrators can quantify ocular kinematics and pupillary dynamics allowing a deeper investigation into the integrity of neurological systems following neurological insult.

As a non-invasive index of transitioning arousal states, pupillometric measures have been utilized in clinical populations as an index of autonomic regulation[143, 224-227] and

fatigue.[199, 215] To date few studies have investigated alterations in pupillary dynamics following concussive brain injuries. The PLR is the most commonly assessed pupillary response studied in the concussion literature.[228] A recent study found that compared to healthy controls, individuals with a recent concussion demonstrated exacerbated PLR responses.[229] Further validating the utility of pupillometric measures as indexes of neurological recovery following concussion.

As mentioned previously, pupillary responses can also be modulated by variations in individual perceptions of cognitive load or an individual's attentional resource allocation to a specific task (the PPR). Hershaw and colleagues[230] manipulated task difficulty of the Fusion n-Back task to compare cognitive load among concussed individuals and health controls. They failed to find any differences in task performance among concussed individuals and healthy controls. However, they observed that concussed individuals demonstrated greater activation of the PPR under the low cognitive load condition of the task. This is significant because it suggests that concussed individuals needed to utilize greater mental effort just to meet the same level of performance at lower levels of cognitive demand. Since pupillary constriction and dilation within the PLR and PPR are tightly controlled by the sympathetic and parasympathetic nervous systems (respectively) the pupillary abnormalities seen following concussion may indicate disruptions in the integrated communication between frontal cortical brain regions and brain stim nuclei governing autonomic nervous system behavior.[231]

Neuroelectric Function

When we carry out any task in our everyday life (i.e., driving, grocery shopping, getting dressed) or in an experimental setting, only the stimulus-response behaviors are observable and therefore quantifiable. However, there is a great deal of simultaneous neural processing occurring to form, select, and generate (or inhibit) behavioral actions. Historically, the only way to observe real time neural activity required the surgical implantation of electrode arrays over large brain regions or embedded in single neurons.[232] In 1924, German scientist Hans Berger was the first to non-invasively record neural activity from EEG electrodes placed on the surface of the scalp.[233, 234] Since its introduction, the utilization of EEG has expanded to include investigations of ongoing cognitive processes during task execution,[235-244] identification of neurological disease,[245-251] functional connectivity patterns,[252-257] and interfacing with computer-based devices.[258-260]

EEG recordings depict graphical representations associated with activity dependent voltage fluctuations of underlying neural populations.[261, 262] The voltage fluctuations are believed to represent the extracellular post-synaptic activity within regional cortical pyramidal cells (layers III & IV) summating at the scalp underneath each EEG sensor.[262] Due to the negligible resistance in the speed of current flow from source to electrode, EEG recordings provide an almost instantaneous measure of ongoing neural activity.[262] This high degree of temporal resolution permits the parcellation of neural activity surrounding a given behavioral event, allowing for the investigation of underlying cognitive processes.[263] By taking advantage of these physiological properties research has been able to utilize EEG to identify disruptions in neurological function following concussion and other brain injuries.

Event-related Potentials (ERP)

Embedded within the continuous raw EEG recording lie neural activations associated with event specific neural processes. By time-locking and averaging recorded EEG data to specific events such as stimulus presentation or behavioral response we can identify event-related potentials (ERPS).[264] ERPs represent coordinated and synchronous activity of large pools (>1000) of cortical neurons serving specific sensory, cognitive, and motor functions.[261] ERP components are typically categorized based on; their positive (P) or negative (N) polarity and the time (latency) in which they occur.[261] By comparing a component's amplitude and latency researchers are able to investigate deviations in cognitive function irrespective of behavioral performance.

Stimulus-locked ERPs

Stimulus-locked ERPs are components elicited by the onset of a stimulus and occur across sensory modalities (i.e., visual, auditory, tactile). These ERPs are dichotomized based on their relative occurrence. Early stimulus-locked components (exogenous components) are hypothesized to represent externally evoked aspects of selective attention relating to stimulus features. Late components (endogenous components) are believed to reflect internally driven aspects of stimulus-related cognitive processing.[265] Stimulus-locked ERPs occur across sensory modalities, however, their interpretations vary slightly based on the how the stimulus is presented (especially early components).[261] Therefore, for the following section, I will focus on definitions and interpretations based on visually presented stimuli.

P1. The P1 component is the first positive going peak occurring after stimulus presentation. This component reflects arousal/attentional allocation to given stimulus features.[266] Given the modulation of P1 amplitude to attended stimuli, it is hypothesized to reflect an enhanced processing of attended (goal-relevant) information and inhibition of distractors.[267] The P1 peak is most prominent over occipito-parietal electrodes peaking approximately 100 – 130ms after stimulus onset. Furthermore, studies have associated the visual P1 component with activation of extrastriatal and fusiform brain regions.[268]

N1. Following the visually evoked P1 is the visual N1. The N1 is the first negative heading deflection peaking 150 – 200ms after stimulus onset. The N1 reflects the initial allocation of attentional focus toward stimulus features, allowing for stimulus discrimination of attended targets.[269] Research has identified several subcomponents of the N1 each occurring maximally in different recording regions along the scalp. The stimulus discrimination subcomponent of the N1 appears predominantly over the occipito-parietal sites, like the P1.

N2. The anterior N2 is a late occurring stimulus-locked component associated with the process of, conflict monitoring.[261] In tasks where multiple actions may be possible (i.e., push or pull a door open), there becomes a competition for response selection. This competition generates conflict detected by the ACC, as it tries to determine the appropriate action given the current task goals.[270] The N2 amplitude has been shown to be positively associated with the amount of perceived conflict within a given trial. Higher degrees of conflict (i.e., tougher response selection) produce a larger N2 amplitude, whereas N2 latency has been linked to response selection and 'conflict resolution'.[271, 272] The N2 peaks approximately 180 – 350ms over fronto-central electrodes. Source localization studies

have indicated frontal brain regions (most likely Anterior Cingulate Cortex) as neural generators of the N2.

P3. The P3 is one of the most studied ERP components. This late occurring stimulus-locked component is characterized by a positive deflection peaking between 300 – 800ms after stimulus onset. Two subcomponents of the P3 have been identified, the fronto-central P3a and the centro-parietal P3b.[264] Both of these components occur in response to infrequently occurring stimuli, in which working memory must be contextually updated to suit the current demand.[273] The frontal P3a is elicited in response to the detection of distractor or novel stimuli,[273] and is believed to index involuntary re-orientation of attentional focus.[274] In tasks of inhibitory control (i.e., Go/No-Go or APST) the P3a is elicited in response to stimuli in which an action must be withheld or inhibited.[272] In contrast, the P3b is generated in response to target stimuli.[261, 275] Therefore, the P3b amplitude is believed to reflect attentional resources allocated during stimulus engagement.[276] As contextual revisions cannot occur without stimulus classification, the latency of the P3b is associated with the speed at which the individual is able to identify and classify stimuli.[261]

Response-Locked ERPs

Continuous EEG data can also be time-locked to behavioral responses (e.g., button press, eye movement, reach) to investigate neural processes underlying response preparation[277, 278] or the cognitive processes behavior monitoring and adaptation.[279, 280]

Bereitschaftspotential. The Bereitschaftspotential (BP) is a gradual slow negative wave beginning approximately 2000ms prior to movement onset over centro-parietal

electrode sites. Recent research has sub-divided the BP into early and late components representing distinct processes of motor preparation. The early component characterizes the slow gradual negative climb of the BP. It peaks maximally at CPz and is thought to reflect generalized motor preparation of the PFC and supplementary motor area (SMA).[281] The late component is represented by an abrupt, steeper increase in negative polarity occurring approximately 600ms prior to movement onset. The late component, sometimes referred to as the lateralized readiness potential (LRP), occurs maximally over central electrode sites contralateral to the movement effector.[260] This asymmetrical distribution may reflect more specific motor preparation of the primary motor cortex (M1).[260] The motor monitoring potential (MMP) has been observed as a persistent climb in negativity continuing until the movement ends.[244, 282] This continued negative ramping has been associated with ongoing motor feedback associated with online activity of the SMA.[283] Collectively, these ERPs have been referred to as movement-related cortical potentials (MRCP)

ERN. The error-related negativity (ERN) is a fronto-central negative deflection peaking 50 – 150ms after an error response.[284] Similar to the N2, the ERN is thought to reflect early conflict that arises when there is disconnect between the intended and actual outcome (i.e., error).[285] It is hypothesized that the ERN acts as an internal error signal to initiate compensatory corrections on future behaviors.[286] The amplitude of the ERN has been associated with the subjective magnitude of the error, with greater perceived errors generating larger ERN amplitudes. Interestingly the ERN will occur whether the individual is consciously aware that an error has been committed or not.[243] Given their involvement in behavioral monitoring, the N2 and ERN have been closely linked to error monitoring

and learning reinforcement learning behavior.[162] Source localization studies have also identified the anterior cingulate cortex as a common source generator for the ERN and N2.[287]

Pe. Most of the time, following the ERN is a slow positive deflection called the error positivity (Pe). The Pe peaks maximally in centro-parietal electrodes 300 – 500ms post error response. Pe amplitude has been linked to post-error compensatory behavior (post-error increases in RT, post-error accuracy).[241] As such, the Pe is believed to reflect conscious awareness of an error being committed.[243, 288]

Stimulus-Locked ERPs & Concussion

ERP techniques have been used to evaluate neurological function following concussion for nearly two decades.[289, 290] Most of the research has focused on comparing sensory and early cognitive processing associated stimulus-locked components. This research has included individuals within the acute, post-acute, and chronic (i.e., PPCS) phases of injury. The findings from these and other neuroimaging studies have helped to elevate the serious nature of concussive brain injuries.

Few studies have investigated the impact of concussion on early sensory components (i.e., P1 and N1). Visual pattern reversal tasks are commonly used to evoke early sensory components and investigate extrastriatal and fusiform gyrus integrity.[291] Moore and colleagues[292] utilized this paradigm in a group of young adults who experienced their last concussion in early adolescents. They found that compared to matched controls, adults with a history of concussion demonstrated significantly reduced P1 amplitudes reflecting a potential inability to attend to task relevant stimuli. Early sensory components

have also demonstrated the capacity to delineate soccer players with a sport-related concussion from those without but experience repetitive sub-concussive blows.[101] Using a visual three-stimulus oddball task, investigators found that compared to non-contact athletes only individuals with a concussion demonstrated reduced N1 amplitudes. Furthermore, N1 amplitudes were sensitive to the number of previous injuries. More recently, Desjardins and colleagues[101] employed a visual search task to probe functional hemispheric asymmetries and their contributions to P1 and N1 morphology in older individuals with concussion. They observed that following concussion older individuals demonstrated a reduction in normal patterns of hemispheric specialization, marked by increased activation of the contralateral hemisphere. The authors pointed out that this pattern is associated with normal aging processes,[293] supporting the hypothesis that concussion induces hyper-maturation of the brain.[99, 294] This highlights that impairments in upper level cognitive processing may be attributed to issues in downstream sensory capture.[292, 295] Additionally, the literature suggests potentially chronic impairment in sensory capture following concussion, even in normally recovered individuals.

Late components stimulus-locked components associated with conflict monitoring and attentional resource allocation are the most widely studied in the concussion literature. The directional flanker task[296] is commonly utilized to induce response conflict (N2) by forcing participants to make directional responses with compatibly oriented flanking distractors or in a more difficult scenario with incompatibly oriented (opposite facing) flanking distractors. Using a child friendly variant of the flanker task, Moore and colleagues[297] found that asymptomatic children with a history of concussion demonstrated increased N2 amplitude during response incompatible trials of the flanker task. This

suggests that these children with a history of concussion experienced greater response conflict when distractors were incongruent to the cuing stimulus. Additionally, across both conditions, previously concussed children demonstrated longer N2 latencies, an index of prolonged conflict resolution. The prolonged N2 latency on incompatible trials was positively associated with omission errors. Indicating that individuals with a history of concussion necessitated longer periods and could not resolve the stimulus-response conflict and select the appropriate response within the allocated response window. Using a similar paradigm, Olson and colleagues[298] found a similar increase in N2 amplitude among asymptomatic recently concussed Division I athletes. They failed to see any significant group differences in N2 latency but noted that N2 latency was significantly correlated with time since injury. These studies suggest that concussion may result in long-term deficits in response conflict monitoring, allocating more attentional resources than non-injured controls.

As mentioned, the P3 is one of the most studied ERP components. Therefore, it is no surprise that several neurophysiological studies of concussion have analyzed this measure of attention. Studies consistently show that P3b amplitude is significantly reduced in individuals with a history of concussion.[150, 297, 299, 300] This pattern is consistent across multiple task paradigms and age at injury. In their study comparing sport-related concussion and sub-concussive blows, Moore and colleagues[101] found that both the sport-related concussion group and sub-concussive blow groups demonstrated significant decreases in P3a and P3b amplitude. This suggests that attentional allocation and orienting processes are sensitive to impacts to the head whether it leads to a concussion or not. A more recent study by Cavanagh and colleagues[301] used an auditory oddball task to

investigate the association among P3a and P3b components and reported symptomology. They evaluated participants within the sub-acute phase (<2 weeks post-injury) and again at a two-month follow-up. Contrary to previous research they failed to observe any difference in P3a or P3b morphology in either the sub-acute or follow-up evaluations. However, they found that greater P3b amplitude at the sub-acute evaluation accurately predicted better improvement in symptom reporting on the Frontal Systems Behavior Scale, a questionnaire used to assess severity of behavioral disturbances.[309] In a recent study Sicard and colleagues[302] investigated neurological function in slow-to-recover and asymptomatic athletes, using a three-stimulus odd-ball task. They found that compared to healthy controls, both slow-to-recover and asymptomatic athletes demonstrated increased latency in P3b. However, only slow-to-recover athletes demonstrated reduced P3b amplitude. These findings further support research that has identified target related attentional deficits following concussion. Additionally, these results demonstrate the utility of neuroelectric measures in identifying individuals who have not fully recovered from their injury.

Response-locked ERPs & Concussion

Response-locked ERPs of behavior monitoring (ERN) and error detection (Pe) have not been as widely used in the concussion literature. One of the first investigations was carried out by Pontifex and colleagues.[144] Utilizing the flanker task in group of adolescent individuals with a history of concussion they found that concussion history was associated with significant decrease in ERN amplitude. Additionally, ERN amplitude was associated with the number of previous injuries, with more injuries correlating with greater reductions in ERN amplitude. These associations were later corroborated by De Beaumont and

colleagues[303] who found reduced ERN amplitude in a group of young adults with a history of concussion. Moore and colleagues[297] found that children with a history of concussion not only demonstrate a reduction in ERN amplitude, but also Pe amplitude. The authors also found that Pe amplitudes were positively correlated with post-error accuracy. With reduced Pe amplitudes within the concussion group, the results suggest that children with a history of concussion may not be able to adequately detect erroneous behaviors therefore unable to effectively moderate behavior. While modulations of Pe have not been observed in other studies, the developing brain of children may be more susceptible to more debilitating injuries.[7] Behavior monitoring and error detection are crucial processes involved in motor learning.[170] A recent study by Beaulieu and colleagues[311] investigated ERN modulation in asymptomatic concussed and non-concussed individuals during repeated blocks of a sequence learning task. They found that in addition to blunted reaction times throughout the task, asymptomatic concussed individuals demonstrated reduced ERN amplitude primarily in the later learning blocks. Supporting the role of error-based motor learning, the authors reported ERN amplitude was positively correlated sequence learning. However, this relationship was not observed in asymptomatic concussed individuals. This finding may indicate the increased reliance on compensatory processes in concussed individuals to maintain performance.

Movement-Related Potentials & Concussion

In addition to cognitive and somatic symptoms, concussive brain injuries are associated with disruptions in motor behavior; impaired coordination, deficits in postural control, and slowed movement speed.[304-306] However, few studies have investigated the impact of concussion on movement-related potentials. Slobounov and colleagues[307]

recorded EEG activity while previously concussed (~17mo since injury) and neurologically healthy controls participants performed a series of sub-maximal isometric finger contractions. They observed that at higher force demands (50% MVC), individuals with a history of concussion demonstrated more difficult maintaining consistent force production. Additionally, individuals with a history of concussion showed attenuated amplitude of all MRP compared to the health controls. Therefore, impaired motor-related brain activity may elicit decreased synchronization of muscle activity resulting in poor postural control and coordination seen following concussion.

In a follow-up study, Slobounov and colleagues[308] investigated static and dynamic postural control in athletes at pre-season baseline and multiple recovery time points (3-days, 10-days, and 30-days) following concussion. When compared to baseline performance recently concussed athletes demonstrated significant deficits in postural control within the first 10 days. These deficits in postural control were characterized by increased postural sway (static balance) and decreased range of control in a self-paced anterior-posterior sway test of dynamic balance. Furthermore, while behavioral indices of postural control by the 30-day assessment, MRPs remained attenuated. These results further suggest lingering neurological dysfunction following concussion, even in the absence of behavioral deficits.

Barriers in Establishing Psychophysiological Biomarkers

As described above, psychophysiological techniques are rapidly advancing our understanding of the neurological sequelae following concussions. Furthermore, these techniques have allowed investigators to identify patterns of abnormal neurological activity

underlying inadequate recovery. Unlike current assessment tools utilized in concussion management, psychophysiological techniques measure automatic and naturally occurring responses of the body. These automatic responses are not under the conscious control of the patient, and therefore cannot be masked or faked. Therefore, they provide consistent and reliable measures of underlying neurological function that can be used as a biomarker to gauge recovery status following injury. However, there are two critical barriers that must be overcome in order to progress forward in establishing psychophysiological biomarkers of concussion.

First, studies in investigating deficits following concussion often either compare symptomatic individuals (HCx-S) to healthy controls with no history of concussion (HC-) or asymptomatic individuals with a history of concussion (HCx-A). These studies have been instrumental in establishing deviations in function in concussion, but by not comparing all three groups (HCx-S, HCx-A, HC-) we are unable to associate deviations in function to abnormal recovery. By comparing Cx-S individuals to HC- we are able to tease out functional abnormalities associated with sustaining a concussion. However, research has consistently identified EEG abnormalities several months after the initial injury in Cx-A individuals.[145, 309, 310] When attempting to establish biomarkers of concussion recovery it is essential to identify functionality profiles associated with atypical recovery. Therefore, it is imperative to include both HC- and HCx-A control groups.

A second barrier in current concussion research is the limited ecological validity, stemming from the experimental paradigms frequently used. Ecological validity reflects the ability of the research findings to predict real-world behaviors. Real-world behaviors often require continuous integration and rapid utilization of sensory, cognitive, and motor

processes. This dynamic and complex behavior is often neglected in the relatively simple and discrete button press tasks used in psychophysiological research. These tasks can be modified to incorporate reaching or continuous behaviors more reflective of real-world activities. Additionally, when assessing individuals, tasks are often completed in a basal/resting state or analyses are computed on data collected within a single timepoint within the experimental protocol. However, physiological function is designed to respond and regulate to systemic stressors to optimize performance and this dynamic response may serve as a valuable indicator an individual's ability to adequately function within the real-world.[311-314] Indeed, several research studies have demonstrated that following concussion, individuals demonstrate a maladaptive response to acute stressors, even with no apparent symptoms at rest.[32, 114, 115, 315, 316] In conclusion, when assessing the recovery of neurological function following brain injury, it is imperative to assess function that reflects behaviors and stressors required for conducting everyday activities.

It must be noted, that to evaluate neurological function in ecologically valid paradigms, several pieces of sophisticated technology need to be integrated to work seamlessly with one another. EEG systems, multidimensional assessment devices (e.g., KINARM lab systems, motion capture environments) and eye-tracking systems are typically developed by individual companies and require a bit of technical expertise to integrate and allow synchronous communication across all systems. Additionally, acquiring all these pieces of equipment can end up being quite expensive. Finally, each system generates a lot of data, reducing and analyzing EEG, eye-tracking, and behavioral kinematic data requires a high level of training and expertise. However, while all the aforementioned factors must be taken into account this pilot and exploratory investigation

will help generate proven and validated assessment paradigms for the evaluation of brain injuries. Once these paradigms have been established, they can be implemented in more portable and automated systems for more simplistic assessments.

Conclusion

Concussive brain injuries are no longer marginalized as transient injuries with no long-term consequences. With the increased public awareness and incidence of concussive brain injuries it is imperative that we develop neurological assessment techniques that are sensitive and reliable enough to readily detect lingering neurological dysfunction, even in the absence of behavioral deficits. Current clinical applications, while suitable for the first few days following injury, lack the robustness necessary to identify proven dysfunction beyond. Psychophysiological assessments using eye tracking and electroencephalography have demonstrated the ability to quantify neurological dysfunction and are tied to brain regions known to be impacted by concussion. These techniques are relatively inexpensive, non-invasive, and can generate objective values that when compared against normative samples can provide quick and easy to understand indications of neurological injury. By incorporating objective measures like these into practice clinicians will have a clearer understanding of the patient's underlying neural function throughout the recovery process. Additionally, by establishing consistent indexes of neurological health and recovery from concussion we can begin to design, test, and implement individualized and evidence-based rehabilitation programs to endure adequate recovery for everyone following concussion.

Statement Of Problem

Establishing sensitive biomarkers associated with neurological health and recovery is crucial for the clinical management of concussive brain injuries. Psychophysiological biomarkers may serve as viable measures of neurological recovery, as they have demonstrated the capacity to detect specific and subtle abnormalities in structure and function. However, current methodological barriers limit the interpretation of current literature and preclude their implementation in clinical practice. Specifically, studies fail to directly compare symptomatic and asymptomatic individuals with a history of concussion. This additional level of comparison is crucial as it allows us to tease out atypical recovery patterns. Additionally, the ecological validity of testing paradigms used to assess neurological function following concussion is limited. To generalize function in the real-world, testing protocols should aim to mimic the dynamic and multidimensional activities individuals experience in their everyday life. The purpose of the proposed study is to overcome these identified barriers and advance the search for objective biomarkers of concussion recovery.

Specific Aims & Hypotheses

General Hypothesis. Compared to HC- individuals, both HCx-S and HCx-A individuals will demonstrate significant alterations in non-invasive, physiological measures of neurological function, with HCx-S individuals demonstrating the greatest deviation in neurological function.

Specific Aim 1. Compare saccadic and pupillometric measures among HCx-A, HCx-S, and HC- individuals during an interleaved Anti-/Pro- Saccade Task (APST).

Premise: The interleaved APST task stresses all three aspects of cognitive control. By comparing task-related saccade behavior as well as pupillometric indices among HC-, HCx-A, and HCx-S individuals we will be able to identify specific neurological profiles underlying persistent symptoms.

Innovation: This is innovative because it is one of the first investigations to saccade behavior and pupillometry in HCx-A and HCx-S individuals.

Hypothesis 1.1. HCx-S individuals will demonstrate more directional errors and increased saccadic reaction time than HCx-A and HC- individuals during anti-saccade trials. There will be no differences in directional errors and reaction times of HCx-A and HC- individuals.

Hypothesis 1.2. HCx-A and HCx-S individuals will demonstrate progressive increases in their PPR compared to HC- individuals.

Significance: This is significant as it will provide crucial steps towards validating prognostic biomarkers of concussion.

SPECIFIC AIM 2 Validate neuroelectric measures of conflict monitoring and attention in HC- individuals during performance of discrete and continuous arm reaching variants of the traditional (button-press) Go/No-Go task.

Premise: Real world tasks require continuous perceptual, cognitive, and motor integration. Current paradigms used to assess cognitive control lack the requisite ecological validity to generalize findings to real-world behavior.

Innovation: By utilizing all three Go/No-Go variants, systematic and stepwise comparisons of collected neuroelectric indices can be made. Establishing referenced N2 and P3 waveforms from the traditional button press variant will allow for the validation of N2 and P3 collected from discrete and continuous reaching variants.

Hypothesis 2.1. Neuroelectric indices of subconscious conflict monitoring (N2) and attentional resource allocation (P3) gathered from discrete and continuous arm reaching variants of the Go/No-Go task will be quantitatively similar in amplitude and latency compared to those collected during a discrete button press variant of the Go/No-Go task.

Significance: This is significant because established N2 and P3 waveforms from more ecologically valid reaching variants of the Go/No-Go task these will allow for more realistic assessments in clinical populations. The increased complexity of these tasks may reveal neurological deficits not previously seen in traditional assessments.

SPECIFIC AIM 3. Compare behavioral performance and neuroelectric measures of conflict monitoring and attentional resource allocation among HCx-S, HCx-A and HC- individuals during discrete and continuous arm reaching variants of the traditional Go/No-Go task.

Premise: Real world tasks require continuous perceptual, cognitive, and motor integration. Current paradigms used to assess cognitive control lack the requisite ecological validity to generalize findings to real-world behavior. These more complex tasks may provide enough cognitive challenge to provide a truer picture of cognitive deficits underlying the persistent symptoms experienced by HCx-S individuals.

Innovation: Assessing both HCx-S and HCx-A using more complex and ecologically valid assessments will allow

Hypothesis 3.1. Compared to HC- individuals, HCx-A and HCx-S individuals will demonstrate progressive increases in commission errors (Go responses on No-Go trials) during discrete and continuous arm reaching variants of the Go/No-Go task.

Hypothesis 3.2. HCx-A and HCx-S individuals will exhibit progressive decreases in amplitude of their N2 and P3 stimulus-locked ERPs compared to HC- individuals.

Hypothesis 3.3. In HCx-S individuals N2 and P3 amplitudes will be negatively correlated with symptom severity reported on the Rivermead Post-Concussion Questionnaire.

Hypothesis 3.4. N2 and P3 amplitudes will demonstrate significant correlations with self-reported scores on the Neuro- Quality of Life questionnaire.

Significance: This is significant as it will provide crucial steps towards validating prognostic biomarkers of concussion.

CHAPTER 3

GENERAL METHODS

Participants.

Male and female (18 – 30 years of age) were invited to participate in the proposed protocol. All interested participants completed a comprehensive demographic questionnaire to identify eligible participants for each aim of the study. In general, to limit the impact of potentially confounding variables, participants were excluded if they indicated any pre-existing history of neurological conditions (e.g., seizures, meningitis), learning disability or learning disorder (i.e., ADHD, LD), psychiatric or mood disorder, or any history of moderate to severe brain injury. Additionally, participants were excluded if they indicated any injury that would prevent them from making repeated reaching arm movements or sitting upright in a chair for an extended period. Eligible participants that indicated a medical diagnosis of a concussion (>3 weeks prior) were dichotomized into the history of concussion group (HCx). HCx individuals were further categorized as either asymptomatic (HCx-A) or symptomatic (HCx-S) based on individual reporting on the Rivermead Post-Concussion Questionnaire. Participants that indicated no history of diagnosed or suspected concussion were included in the healthy control (HC-) group. To prevent the possibility of an individual with an undiagnosed concussion being included in the control group, control participants were asked: "following a blow to the head, neck, or body, have you ever experienced any of the following symptoms: headache, dizziness, confusion, blurred vision, balance problems, sensitivity to light and/or noise, fatigue, drowsiness, difficulty falling asleep, emotional, irritable, sad, or anxious?" Participants who responded "yes" to any symptoms were excluded from the control group. Prior to beginning the testing procedure, informed consent was be obtained from each participant.

All testing procedures have been approved by the University of South Carolina Institutional Review Board.

Procedure.

Upon arrival to the testing site, participants were immediately familiarized with the experimental procedures and informed consent will be obtained. Following the informed consent process, participants completed a series of questionnaires (see *Questionnaires*). After completion of the questionnaires, participants were seated in front of the testing apparatus (see *Apparatus*) and outfitted with an electroencephalography (EEG) cap. Finally, once the EEG cap was adequately situated and the participant is comfortably seated, the participant completed the customized cognitive testing battery (see Figure 3.1). Prior to each task, participants were given oral instructions from a member of the research team. Additionally, for behavioral tasks, participants completed a block of practice trials to ensure adequate understanding.

Questionnaires.

Participants completed a series of questionnaires, these evaluations are all standardized evaluations of neurological injury and will be utilized to assess psycho-affective health and observational behavior during the laboratory assessment.

1. The BDI-II.[317] The BDI-II consists of 21 questions designed to assess the presence and intensity of cognitive, affective, and somatic symptoms of depression. Participants are asked to choose between 4 statements, rated from 0 to 3, which best describes how they have been feeling during the past 2 weeks. Scores range from: 0-21 for cognitive, 0-15 for affective, and 0-27 for somatic sub-dimensions. A total

Figure 3.1. Experimental Protocol. Diagram of experimental cognitive battery consisting of Anti-/Pro-saccade task (APST), continuous reach Go/NoGo task (GNGC), discrete button Go/NoGo task (GNGB), discrete reach Go/NoGo task (GNGR), and resting (REST) assessments

score, ranging from 0 to 63, is obtained by adding the answers to each question, a higher score indicating greater intensity of depressive symptoms.

2. Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[318-320] The RPQ is a list of 16 concussion-related symptoms (i.e., headaches, dizziness, nausea). Participants were asked to indicate the degree/severity in which they are currently experiencing each symptom using a five-point Likert scale 0 (not a problem) to 4 (severe problem). Additionally, participants were asked to answer each question comparing how they feel now, compared to how they previously felt before the injury. Symptoms included within the RPQ have been mapped to DSM-IV diagnostic criteria for PCS.[3215] This criterion was used to dichotomize HCx individuals into symptomatic (HCx-S) and asymptomatic (HCx-A) subgroups.
3. Neurological Quality of Life (Neuro-QoL).[322] Participants were asked to complete several sub-scales selected from the Neuro-QoL NIH Common Data Elements testing toolkit for brain injury. These short form assessments are designed to investigate how neurological injury and disease impact a variety of mental, physical, and social health domains.
4. State Trait Anxiety Inventory (STAI).[323] The STAI is a 40-item survey aimed at assessing both current (20 questions) and general (20 questions) feelings of psychological health. Participants were asked to indicate the level to which they experience each statement on a 4-point scale (1- "Not at all', 4 – "Very much so").

Apparatus.

Robotic assessments were conducted on the BKIN KINARM End-Point robot (BKIN Technologies, Kingston, ON, Canada). The KINARM lab system generates an

augmented-reality environment using an inverted monitor to project stimuli at 60Hz on to a semi-transparent mirror that orients the task into the horizontal plane in front of the participant. Participants were seated in a custom-built chair set on floor mounted tracks and hydraulic lift. A custom chin rest will be used to help stabilize the head and prevent extraneous movement. The KINARM system is also equipped with an EyeLink 1000 Gaze Tracking System (SR Research, Kanata, ON, Canada). This setup allows us to track and monitor eye movements throughout the duration of each task. This system uses a high-resolution camera mounted at the rear of the workspace.

CHAPTER 4

IMPACT OF CONCUSSION ON OCULOMOTOR CONTROL & PUPILLARY DYNAMICS

Harrison, A.T., Green, J., Pontifex, M., Herter, T.M., & Moore, R.D. To be submitted to *Int J Psychophys* (in preparation)

INTRODUCTION

Roughly 3.8 million concussions are diagnosed each year in the United States.[11-13] Concussions represent a form of traumatic brain injury (TBI), and occur from either a direct blow to the head (i.e., helmet to helmet contact) or indirectly from a blow delivered to the neck or body.[6, 41] The subsequent biomechanical impulses initiate a cascade of pathological reactions leading to neurophysiological alterations throughout the brain[43, 49] These changes result in a constellation of immediate or delayed symptoms ranging from headache, emotional dysregulation and cognitive deficits, to temporary loss of consciousness (LOC) and post-traumatic amnesia (PTA)[3, 4]

Despite the growing public awareness of concussions, accurately diagnosing and tracking recovery remains a major barrier in the clinical management of these injuries. Unfortunately, due to the micro level damage associated with concussions, conventional clinical neuroimaging modalities (i.e., magnetic resonance and computed tomography) fail to detect abnormalities in neural structure.[39, 324] Therefore, current trends in clinical practice heavily rely on patient-reported symptom scales,[117, 318] assessments of balance and vestibular-ocular function,[131] as well as computerized tests of neurocognitive function.[118, 119] However, these assessments are limited by the inherent subjective nature of symptom scales[111, 112] and questionable reliability of neurocognitive tests beyond the acute phase of injury.[123]

The effective management of concussive injuries is critical, as individuals who prematurely return to full sport, work, or academic engagement may exacerbate concussion related deficits, prolong recovery, and are at increased risk of developing chronic neurological sequela such as persistent post-concussive symptoms (PPCS).[8, 9, 27, 108] PPCS

is characterized as a clustering of non-specific symptoms following a concussion persisting beyond the typical recovery window (>1-3 months) and negatively impacting daily function.[71, 72] It is estimated that roughly 30 - 40% of individuals will develop PPCS following a concussion.[77] In addition to lingering symptoms, these slow to recover individuals demonstrate persistent deficits in neuroelectric indices of attentional control,[302] and alterations in cortical white matter integrity.[74] If left untreated persistent concussion-related symptoms may negatively impact the individual's social, emotional, and vocational well-being.[22, 23, 28] Therefore, it is crucial to develop and implement sensitive assessments that can objectively quantify function of neurological systems impacted by concussion.

Advances in video-based eye tracking systems have allowed for assessments of psychophysiological function that are easy to administer yet sensitive enough to detect specific deficits following acquired and developed brain injuries.[195, 197, 198, 325] The neural network underlying the oculomotor system relies on complex integrations among distributed cortical[180, 221] and subcortical brain regions.[179, 184, 326] Accordingly, these brain regions work together to coordinate eye-movements (saccades and smooth pursuits) and pupil size to effectively and efficiently gather information from our environment, and guide goal-driven behavior.[327-330] Research has shown saccadic eye-movements tend to be the most sensitive to neurological injury, especially in tasks requiring high levels of cognitive demand.[331-333] Furthermore, impaired oculomotor function following traumatic brain injury has been shown to correlate with injury severity and loss of neural integrity.[52, 64, 201, 334, 335] In addition to deficits in oculomotor control, abnormal task-dependent pupillary modulations have been observed following concussion.[228, 230, 336] These abnormal pupillary

dynamics may serve as psychophysiological biomarkers for impairments in autonomic arousal and cognitive control, commonly seen following concussion.[188, 337]

Incorporating eye-tracking and oculomotor-based tasks into the assessment of concussive brain injuries may allow for more sensitive evaluations of neurological function and recovery from injury. The objective of the present study is to compare saccadic and pupillometric behavior among asymptomatic (HCx-A) and symptomatic (HCx-S) individuals with a history of concussion, as well as non-injured controls (HC-). Compared to HC-, we predict that individuals with a history of concussion (HCx-A and HCx-S) will demonstrate poorer oculomotor performance, with HCx-S individuals demonstrating the worst performance. Similarly, we hypothesize individuals with a history of concussion (HCx-A and HCx-S) will exhibit significant alterations in task-evoked pupillary dynamics (TEPD). Finally, we hypothesize that deficits in oculomotor behavior will be associated with concussion-related symptom burden.

METHODS

Participants. A description of participant sampling procedures, inclusion, and exclusion criteria is provided elsewhere (see Chapter 3: General Methods-Participants). To investigate the impact of concussion recovery on oculomotor control and pupillary dynamics HC-, HCx-A, and HCx-s individuals completed an interleaved variant of the Anti-/Pro-Saccade task.

Procedures. A generalized description and illustration of study procedures can be found elsewhere (see Chapter 3: General Methods-Procedure).

Symptom Reporting Participants were asked to fill out questionnaires to assess various symptom-domains commonly associated with concussion.

5. The BDI-II.[317] The BDI-II consists of 21 questions designed to assess the presence and intensity of cognitive, affective, and somatic symptoms of depression. Participants are asked to choose between 4 statements, rated from 0 to 3, which best describes how they have been feeling during the past 2 weeks. Scores range from: 0-21 for cognitive, 0-15 for affective, and 0-27 for somatic sub-dimensions. A total score, ranging from 0 to 63, is obtained by adding the answers to each question, a higher score indicating greater intensity of depressive symptoms.
6. Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[318-320] The RPQ is a list of 16 concussion-related symptoms (i.e., headaches, dizziness, nausea). Participants were asked to indicate the degree/severity in which they are currently experiencing each symptom using a five-point Likert scale 0 (not a problem) to 4 (severe problem). Additionally, participants were asked to answer each question comparing how they feel now, compared to how they previously felt before the injury. Symptoms included within the RPQ have been mapped to DSM-IV diagnostic criteria for PCS.[3215] This criterion was used to dichotomize HCx individuals into symptomatic (HCx-S) and asymptomatic (HCx-A) subgroups.
7. Neurological Quality of Life (Neuro-QoL).[322] Participants were asked to complete several sub-scales selected from the Neuro-QoL NIH Common Data Elements testing toolkit for brain injury. These short form assessments are designed to investigate how neurological injury and disease impact a variety of mental, physical, and social health domains.

8. State Trait Anxiety Inventory (STAI).[323] The STAI is a 40-item survey aimed at assessing both current (20 questions) and general (20 questions) feelings of psychological health. Participants were asked to indicate the level to which they experience each statement on a 4-point scale (1- "Not at all', 4 – "Very much so").

Anti-/ Pro-saccade Task. Participants were asked to complete 80 trials of an interleaved variant of the Anti-saccade/Pro-saccade task.[338] Each trial began with the presentation of a colored (blue/yellow) central fixation target (CF_T; diameter 0.5°, 140 lum). The trial condition was defined by the color of the CF_T (e.g., pro-saccade, blue CF; anti-saccade, yellow CF_T. Colors of the CF_T were matched for luminance). After 1000ms, the CF_T disappeared for 200ms (gap) prior to the appearance of the peripheral target (P_T, diameter 0.5°, 140 lum) to the left or right of CF_T location (10° eccentricity on the horizontal axis). In pro-saccade trials, participants were asked to make directed eye movements in the direction of the P_T as soon as it appears. In anti-saccade trials, participants were asked to make directed eye movements in the opposite direction of the P_T as soon as it appears (Figure 4.1). Trial condition (pro-saccade or anti-saccade) and P_T location (left or right) were randomly distributed throughout the task. Additionally, color mapping to trial condition (i.e., pro-saccade, blue or pro-saccade, yellow) was randomly assigned and counterbalanced among participants. Prior to beginning the task, participants were given oral instructions outlining the task objectives as well as informing the participant of the appropriate color mapping. Additionally, participants were given 16 practice trials to ensure familiarization with the task.

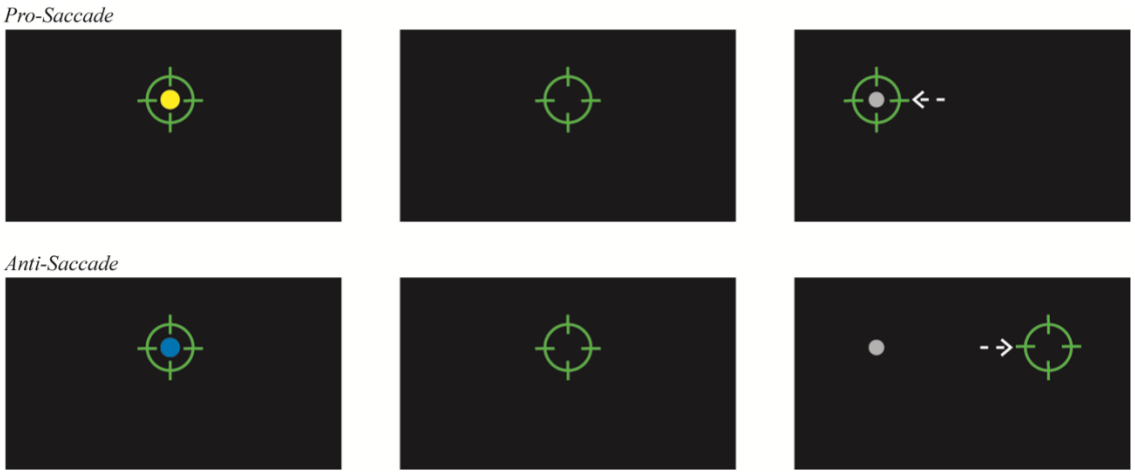

Figure 4.1. Anti-/Pro-Saccade Task

Oculomotor Control. Gaze position was recorded using EyeLink 1000 (SR Research Ltd. Ottawa, Canada). This system is a monocular system with a maximum sampling frequency of 500 Hz, accuracy of 0.5°, and microsaccade resolution of 0.25°. Recorded gaze data was processed and classified incorporating previously validated and published methods within our KINARM environment.[65] This involves data reduction steps to remove any blink artifacts, one sample spike artifacts due to temporary loss of corneal detection, and outliers that occur when gaze position moves outside of the workspace. Once data has been cleaned, the Cartesian (X, Y) coordinates recorded by the gaze tracking system is converted into rotational kinematics to assist in the classification of saccade onset. Saccade onset was defined as >30°/s and >8000°/s^2 for >30ms.[193] Trials with excessive artifacts (e.g., blink or loss of corneal lock) occurring within the gaze fixation or saccade onset windows will be thrown out and excluded from further analyses. Trial accuracy was determined based on gaze positioning following the first saccade initiated after P_T onset. Similarly, saccadic reaction time (SRT) was calculated as the temporal delay from P_T onset to the first saccade away from CF_T. Like previous eye-tracking research utilizing gap periods, any SRT < 100ms was labeled an express saccade and excluded from analyses.

Statistical Analysis. All statistical analyses were computed in MATLAB 2020b (Mathworks, Natick, MA) using functions within the Statistics and Machine Learning toolbox, with an a priori alpha level of $p < 0.05$. Parametric and non-parametric tests of group comparisons were used to analyze continuous and categorical, respectively, to identify potential demographic differences among groups. APST performance and pupil behavioral data were examined via a series of analysis of variance (ANOVA) models with group (HC-, HCx-A, and HCx-S) as the between-subjects variable. Continuous outcome

variables were assessed for normality via Kolmogorov-Smirnov tests. Post-hoc comparisons were used to evaluate interaction and main effects with Bonferroni corrections for multiple comparisons. Eta squared (η^2) measures of effect size were calculated for each ANOVA (η^2: < 0.05 = small; (η^2: 0.06 – 0.13 = medium; η^2: > 0.14 = large). To investigate potential associations among task performance, neuroelectric measures, and symptom burden Pearson correlation coefficients were calculated among all individuals with a history of concussion.

RESULTS

Participant Characteristics. Thirty-nine participants were included in our analyses. Participants were identified as either non-brain injured healthy control (HC-, n = 11), history of concussion – asymptomatic (HCx-A; n = 9), or history of concussion – symptomatic (HCx-S; n = 19) based on self-reported medical history and symptoms. Parametric and non-parametric group comparisons failed to reveal any demographic differences among groups (p's > 0.05). Demographic information is provided in Table 4.1.

Symptom Reporting. Table 4.2 presents means and standard deviations for self-reported outcome measures of concussion-related symptom burden for each group. Compared to HC- and HCx-A, HCx-S individuals reported significantly greater RPQ symptoms (p's < 0.001, η^2's > 0.31), feelings of depression (p's < 0.01, η^2's > 0.15), and state anxiety (p = 0.002, η^2 = 0.20). Additionally, HCx-S individuals reported significantly worse outcomes on several sub-scales within the Neuro-QoL (p's < 0.001, η^2's > 0.23). There were no significant differences among HC- and HCx-A individuals. This suggests that individuals within the HCx-S group fit the defined criteria for PPCS.

Table 4.1. Participant Demographics & Injury Characteristics.

	HC- (n=11)		HCx-A (n=9)		HCx-S (n=19)	
Demographics						
	Mean	*±SD*	*Mean*	*±SD*	*Mean*	*±SD*
Age (yrs)	20.9	1.7	21.5	2.5	21.4	3.2
Sex [#M /#F]	4/7	-	5/4	-	4/15	-
BMI	26.2	4.9	24.4	3.4	24.7	4.1
Injury Characteristics						
Prev Cx (n)			1.4	0.7	2.2	1.2
Days Since Cx			1430	973.9	743	797.5

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, SD: Standard Deviation, yrs: years, M: male, F: female, BMI: body mass index, Prec Cx: previous concussioons.

Table 4.2. Self-Reported Concussion Symptom Burden.

	HC- (n=11)		HCx-A (n=9)		HCx-S (n=19)		GRP Stat
	Mean	*±SEM*	*Mean*	*±SEM*	*Mean*	*±SEM*	η^2
Symptoms							
RPQ16	2.4	0.4	5.3	1.1	20.5*‡	2.1	0.63
RPQCog	0.7	0.2	0.9	0.4	4.4*‡	0.4	0.63
RPQEmo	0.6	0.2	0.2	0.2	3.5*‡	0.5	0.52
RPQSom	0.8	0.3	1.9	0.4	6.7*‡	0.8	0.57
Depression							
BDItotal	2.2	0.9	1.8	0.7	15.1*‡	1.8	0.57
BDIcog	1.1	0.4	0.7	0.4	2.7*‡	0.5	0.21
BDIncog	0.8	0.3	1.9	0.4	5.1*‡	0.6	0.57
Anxiety							
SAI	23.0	1.0	26.2	1.7	34.7*‡	2.2	0.35
TAI	52.0	0.5	51.8	0.7	50.3	0.6	0.13
Neuro-Quality of Life							
Fatigue	39.7	1.8	40.7	1.1	51.0*‡	1.3	0.53
Cog Func	53.5	1.2	52.5	1.2	40.2*‡	1.4	0.65
EmoDsy	39.1	1.1	37.2	1.1	50.3*‡	1.4	0.61
AffW-B	56.1	0.8	56.7	1.0	51.7*‡	1.2	0.24
Sleep	43.7	0.9	41.0	1,9	56.6*‡	1.9	0.58
PSR	48.1	0.9	49.3	0.6	43.4*‡	0.6	0.56
SSR	48.5	0.5	50.9	0.4	45.2*‡	0.8	0.46

Note: Data are presented as mean ± standard error (SEM), p-value, and effect size (η^2).

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog

Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities
* Comparison to HC- $p < 0.05$
‡ Comparison to HCx-A $p < 0.05$

APST Task Performance. Table 4.3 presents means and standard deviations for task performance measures on the APST. Figure 4.2 illustrates significant group differences. Group comparisons revealed trends for group differences for measures of total accuracy ($p = 0.25$), Pro- errors ($p = 0.11$), or Anti- errors ($p = 0 .18$).

Analysis of pro-saccade reaction times revealed a significant group effect ($F[2,36] = 24.9$, $p < 0.001$, $\eta^2 = 0.58$; Figure 4.3). Bonferroni corrected multiple comparisons revealed that HCx-A ($m = 276.4$ms $\pm$ 24.3) demonstrated significantly longer reaction times to pro-saccade targets compared to HC- ($m = 208.0$ms $\pm$ 15.3); $p < 0.001$) and HCx -S ($m = 221.4$ms $\pm$ 24.3; $p < 0.001$). Similarly, analysis of the pro-saccade CVRT revealed a significant group effect ($F[2,36] = 6.4$, $p < 0.001$, $\eta^2 = 0.18$). Bonferroni corrected multiple comparisons revealed that HCx-A ($m = 28.1 \pm 5.3$) demonstrated significantly greater reaction time variability to pro-saccade targets compared to HC- ($m = 19.8 \pm 2.6$; $p = 0.003$). No other group differences were found.

Analysis of anti-saccade reaction times revealed a significant group effect ($F[2,36] = 9.6$, $p < 0.001$, $\eta^2 = 0.17$). Bonferroni corrected multiple comparisons revealed that both HCx-A ($m = 314.1$ms $\pm$ 24.6) and HCx-S ($m = 301.8 \pm 21.8$) demonstrated significantly longer reaction times to anti-saccade targets compared to HC- ($m = 274.0$ms $\pm$ 18.0) (p's < 0.001). No other group differences were found.

Within participants with a history of concussion, several associations were found between measures of APST task performance and self-reported symptom burden (see Table 4.4). Task accuracy was negatively associated total BDI score ($r = -0.48$) and the cognitive subscale of the BDI ($r = -0.54$). Anti-saccade errors were positively associated with BDI

Table 4.3. Anti-/Pro-Saccade Task Performance & Pupil Dynamics

	HC- (n=11)		HCx-A (n=9)		HCx-S (n=19)		GRP Stat
	Mean	*±SEM*	*Mean*	*±SEM*	*Mean*	*±SEM*	η^2
Acc (%)	88.0	1.51	91.0	1.86	85.2	2.47	0.07
Pro-Saccade							
Errors (%)	1.8	0.36	1.9	0.60	3.9	0.92	0.11
RT (ms)	208.0	4.61	276.4*	8.1	227.1	5.57	0.58
CRVT	19.8	0.78	28.1*	1.77	23.1	1.38	0.18
MaxConst	-0.35	0.05	-0.49	0.11	-0.46	0.05	0.06
TEPD	0.10	0.03	0.15	0.04	0.10	0.02	0.07
Anti-Saccade							
Errors (%)	18.5	2.3	13.6	2.80	24.5	4.40	0.09
RT (ms)	274.0	5.4	314.1*	8.20	301.8*	5.00	0.17
CRVT	16.8	0.81	15.4	1.30	18.1	1.08	0.07
MaxConst	-0.46	0.07	-0.51	0.08	-0.56	0.05	0.04
TEPD	0.22	0.03	0.16	0.04	0.16	0.02	0.08

Note: Data are presented as mean ± standard error (SEM), p-value, and effect size (η^2).

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, Acc: Task Accuracy, RT: Reaction Time, CVRT: Coefficient of Variation Reaction Time, Max Const: Max Constriction, TEPD: Task-evoked Pupil Dynamics.
* Comparison to HC- $p < 0.05$
‡ Comparison to HCx-A $p < 0.05$

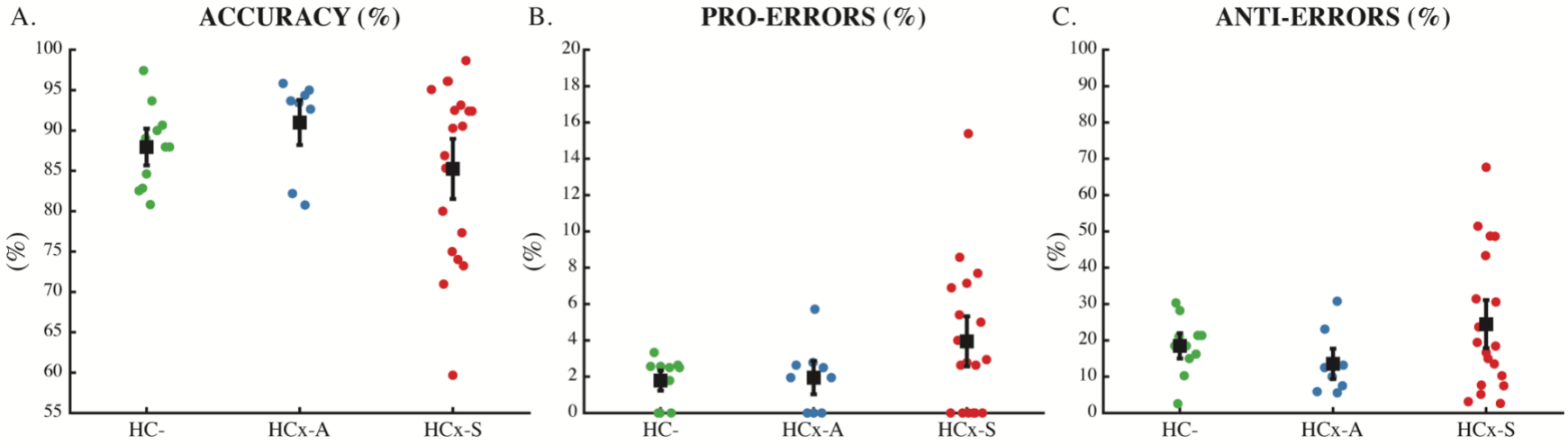

Figure 4.2. APST Task Performance. Individual performance and group averages for APST measures of task accuracy (A), Pro-Saccade errors (B), and Anti-saccade errors (C). Dots represent HC- (green), HCx-A (blue), and HCx-S (red). Black squares and whiskers represent group means and standard errors.

Table 4.4. Correlation Coefficients: APST Task Performance and Symptom Burden

	APST ACC	Pro- Errors	Anti- Errors
RPQ16	-	-	-
RPQCog	-	-	-
RPQEmo	-	-	-
RPQSom	-	-	-
BDItotal	-0.48	-	0.49
BDIcog	-0.54	-	0.56
BDIncog	-	-	-
SAI	-	-	0.39
TAI	0.43	-	-0.47
Fatigue	-	-	-
Cog Func	-	-	-
Emot Dsy	-	-	0.42
AffW-B	-	-	-
Sleep	-	-	-
PSR	-	-	-
SSR	-	-0.42	-

APST ACC: Anti-/Pro-saccade accuracy, Pro- Errors: Pro-saccade errors, Anti- Errors: Anti-saccade errors, RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities
- Correlation $p > 0.05$

score (r = 0.49), BDI cognitive sub-scale (r = 0.56), state anxiety (r = 0.39) and emotional dysregulation scale of the Neuro-QoL (r = 0.42).

Task Evoked Pupillary Dynamics. Table 4.3 presents mean and standard deviation data for computed measured of pupil dynamics. Figure 4.4 depicts average changes in pupil size throughout pro-saccade (Figure 2.3A) and anti-saccade (Figure 2.3B) trials for each group. Statistical analysis failed to reveal significant differences in task evoked pupil dynamics.

Within participants with a history of concussion, associations between metrics of task-evoked pupillary dynamics and self-reported measures of concussion burden failed to reach statistical significance. However, several relationships demonstrated strong trends towards significance. Anti-saccade TEPD was inversely associated with overall RPQ symptom burden (r = -0.28; p = 0.15), the emotional RPQ subscale (r = -0.26; p = 0.19), and the cognitive BDI subscale (r = -0.27; p = 0.17).

DISCUSSION

The present study set out to investigate the impact of concussion recovery on oculomotor performance and task-evoked pupil dynamics. We achieved this by comparing saccade behavior and pupil fluctuations during an interleaved APST among symptomatic (HCx-S) and asymptomatic (HCx-A) individuals with a history of concussion (>4 weeks post injury), and non-injured controls (HC-). Symptomatic individuals with a history of concussion tended to demonstrate poorer performance on the APST compared to both asymptomatic and non-injured controls (HCx-S: 85%; HCx-A: 91%; HC-: 88%). This was accompanied by more errors made in both the pro-saccade (HCx-S: 3.9%; HCx-A: 1.9%; HC-: 1.8%) and anti-saccade (HCx-S: 24.5%; HCx-A: 13.6%; HC-: 18.5%) trials.

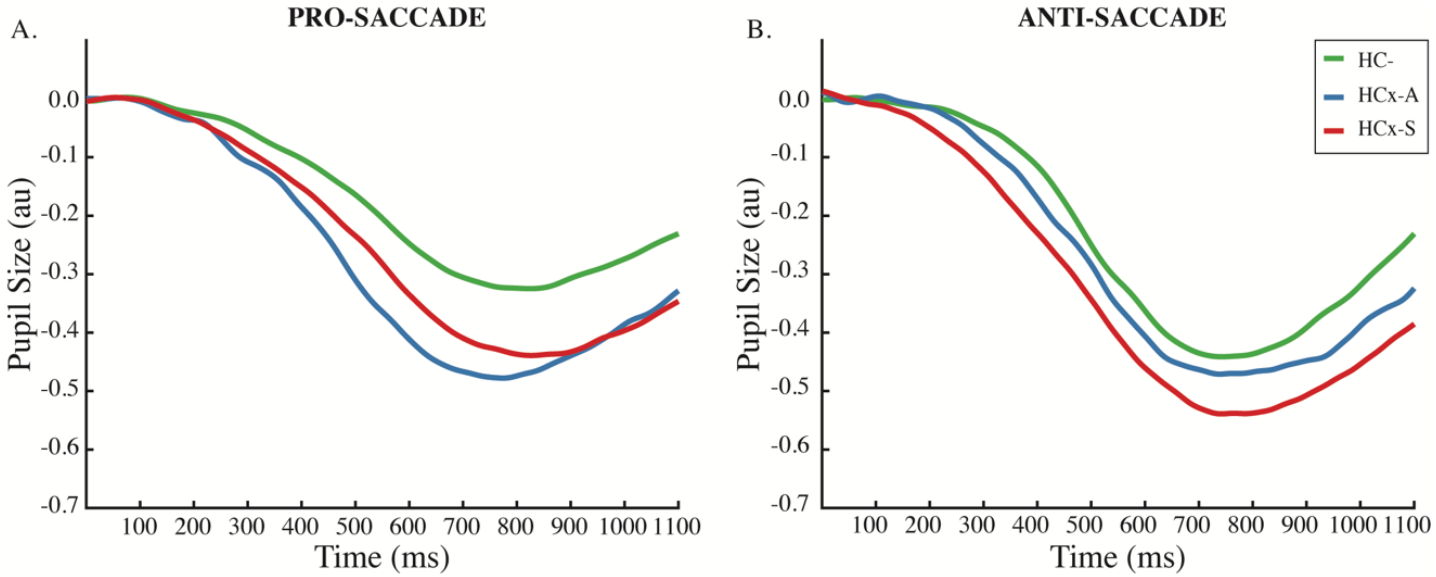

Figure 4.4. Task Evoked Pupil Dynamics. Average changes in pupil size during Pro-Saccade (A) and Anti-Saccade trials. Solid lines represent HC- (green), HCx-A (blue), and HCx-S (red) groups.

Additionally, both HCx-A and HCx-S groups demonstrated slower saccadic reaction times. Surprisingly, HCx-A individuals exhibited significantly longer saccadic reaction times compared to both HC- and HCx-S individuals. These finding support previous research that concussive brain injuries negatively impact oculomotor control.[52, 202, 339]

Additionally, the present study observed concussive brain injuries may alter typical task-evoked pupillary responses. Compared to HC-, both HCx-A and HCx-S groups tended to demonstrate larger degrees of pupillary constriction in both the pro-saccade and anti-saccade trials, leading to an overall reduction in pupillary dilation (TEPD) during the anti-saccade trial fixation periods. This is contradictory to previous findings demonstrating larger pupillary dilation during anti-saccade fixation periods.[336] Pupillary dynamics are tightly regulated by inputs from the autonomic nervous system.[210, 340] Research has demonstrated that during periods of increased cognitive load, parasympathetic inhibition over the pupillary dilator muscles withdraws resulting in increased pupil size.[221] This task-evoked pupil dilation is therefore thought to index arousal and cognitive load.[213, 341] Given the results of the both the current investigation and previous studies, atypical task-evoked pupil dynamics may both indicate autonomic dysfunction. In the present study, the observed pattern of increased pupillary constriction followed by smaller degrees of pupillary dilation during anti-saccade trials may indicate failure of the autonomic nervous system to adequately adapt to situational demands.

The present study also observed associations within individuals with a history of concussion (HCx-A + HCx-S) between task performance and self-reported measures of concussion burden. Worse task accuracy and an increased anti-saccade error rate were associated with worse emotional symptom reports (BDI and Emotional Dysregulation

Neuro-QoL). We also observed several associations among pupil dynamics, overall self-reported symptom burden (RPQ16) and emotional dysregulation (BDI) that trended toward significance. The possible relationships among pupillary dynamics and emotional dysregulation are not surprising as the branches of the autonomic nervous system have been linked to pupillary control[212, 225] and emotional regulation.[342-347] These relationships with symptom burden provide support for the utility of oculomotor and pupillary assessment of recovery following concussion. Further research is needed to further investigate these relationships.

Limitations.

While informative, the present study is not without its limitations. First, the present study utilized a small sample size. The small sample size possibly limited our ability to detect significant group differences. Future studies should aim to recruit more participants to ensure it is sufficiently powered to detect meaningful differences. Additionally, while not significantly different, averages days since injury within the HCx-A group is almost double the HCx-S group. There was no association between days since injury and any of our measures of task performance or pupil dynamics. However, future studies should aim to better match on this variable to reduce the potential confounding influence.

Conclusion.

The present study demonstrated that concussive brain injuries negatively impact gaze behavior and task dependent pupillary responses. Furthermore, these measures demonstrated meaningful associations to self-reported symptom burden. This provides

support that eye-tracking and pupillometric measures may serve as viable biomarkers for concussion recovery.

CHAPTER 5

VALIDATION OF EVENT-RELATED POTENTIALS DURING CONTINUOUS TASK PERFORMANCE

Harrison, A.T., Green, J., Pontifex, M., Herter, T.M., & Moore, R.D. To be submitted to *Frontiers in Human Neuroscience* (in preparation)

INTRODUCTION

When humans interact with their environment they are confronted with a vast number of competing stimuli. We must continuously filter through distractions in search for task-informative sources, synthesize and integrate incoming data, then select and execute our chosen action.[328, 348] For decades, scientists across all domains of neuroscience have tried to understand the neural mechanisms and information flow that make up efficient and effective human behavior and decision making.[180, 349-352] In the field of cognitive neuroscience, research has focused on understanding the neural processes that dwell between the stimulus presentation and behavioral execution. These processes of attention and cognitive control allow us to acquire information from our environment, prioritize what information is relevant, select and coordinate appropriate responses, and evaluate response selection for future performance adaptations.[152-154] Better understanding these processes, and the neural networks involved are crucial to both normal and abnormal behavior.

Functional neuroimaging techniques such as electroencephalography (EEG) have been vital for the study of cognitive processing and human behavior.[161, 262, 263, 265, 267, 276, 353] Unlike other functional imaging techniques, magnetic resonance imaging (MRI) and near-infrared spectroscopy (NIRS) that indirectly quantify neural activity from alterations in cerebral blood flow, EEG utilize the instantaneous electrical activity generated by active neurons. This allows for an extremely high level of temporal precision, with accuracy down to the millisecond. Furthermore, by time-locking the recorded neural series data to specific task-related events and analyzing the amplitude (i.e., magnitude) and latency of specific waveform components can quantify specific cognitive processes.[261, 264, 354] These event-

related potentials (ERPs) represent coordinated and synchronous activity of large pools (>1000) of cortical neurons serving specific sensory, cognitive, and motor functions.

Stimulus-locked analyses represents one ERP event-locking technique that allows for the quantification of processes serving conflict monitoring (i.e., N2) and stimulus evaluation (i.e., P300). The N2 ERP component is associated with the process of conflict monitoring.[261] In tasks where multiple actions may be possible (i.e., push or pull a door open), there becomes a competition for response selection. Higher degrees of conflict (i.e., tougher response selection) produce a larger N2 amplitude, whereas N2 latency has been linked to response selection and 'conflict resolution'.[271, 272] The P300 component occurs in response to infrequently occurring stimuli, in which working memory must be contextually updated to suit the current demand.[279] Depending on the specific task, the P300 is believed to index attentional resource allocation to processes serving response inhibition (P3a) or stimulus engagement (P3b).[273-276, 355]

Over the last several decades these well-established waveforms have helped shape our understanding of human cognition. However, traditional paradigms rely on simple and discrete button press tasks. This level of response mapping fails to fully encompass the complex and continuous nature of real-world interactions. This limits the generalizability of the current literature findings. Additionally, these methods have even been utilized to identify cognitive deficits in neurological conditions (i.e., ADHD, PTSD, autism spectrum disorder),[248, 356, 357] and acquired brain injury (i.e., stroke, concussion).[297, 299, 302, 358, 359] Relying on tasks that are too simple may fail to fully capture or even completely miss ongoing deficits. Previous research has demonstrated that assessing psychophysiological function of recently concussed individuals under periods of acute cognitive and physical

stress exacerbates deficits not seen at rest or low stress loads.[32, 114] Therefore, to advance the utility of EEG and ERP techniques, traditional recording methods need to be applied to more complex and real-world task paradigms.

Accordingly, the aim to the present study is to validate neuroelectric measures of conflict monitoring and stimulus evaluation while participants perform discrete and continuous arm reaching variants of the traditional Go/No-Go task. We hypothesize that neuroelectric indices of subconscious conflict monitoring (N2) and stimulus evaluation (P300) gathered from discrete and continuous arm reaching variants of the Go/NoGo task will be quantitatively similar in amplitude and latency compared to those collected during a discrete button press variant of the Go/NoGo task.

METHODS

Participants. A description of participant sampling procedures, inclusion, and exclusion criteria is provided elsewhere (see Chapter 3: General Methods-Participants). To validate ERP measures during continuous task performance data from HC- participants were analyzed.

Procedures. A generalized description and illustration of study procedures can be found elsewhere (see Chapter 3: General Methods-Procedure).

Cognitive Task. Following setup and preparation of the EEG cap, participants were comfortably seated in front of the KINARM. Within the KINARM environment, participants completed three variants (discrete button, discrete reach, and continuous reach) of a modified Go/NoGo task (see Figure 5.1). For each variant, participants completed two separate conditions. The response infrequent condition in which participants were

instructed to respond quickly and accurately to the appearance of a grey diamond (25% of trials) and inhibit responses to a grey square (75% of trials). Conversely, in the response frequent condition participants were instructed to respond to the appearance of a grey square (75% of trials) and inhibit responses to a grey diamond (25% of trials). Within each variant, participants completed two blocks of the response infrequent condition followed by three blocks of the response frequent condition. Each block consisted of 120 trials. Prior to beginning the task, participants were given oral instructions outlining the task objectives as well as informing the participant of the appropriate target shape. Additionally, participants received a set of 20 practice trials to ensure familiarization with the task.

Within each variant, the method in which the participant is asked to respond changed. For the discrete button (BUTTON) variant, participants grasped a custom two-button digital trigger box (Figure 5.1A). The participant instructed to make responses by pressing the button corresponding with their dominant hand. When the task began, an object (square or diamond) appeared in the center of the KINARM workspace. Targets were presented for 200ms followed by a 1500ms response window.

For the discrete reach (REACH) variant, participants grasped one of the KINARM robotic arms with their dominant hand (Figure 5.1B). The participant's hand position in the workspace is represented within the workspace as a white dot and movement of the robotic arm produced equivalent movement of the white dot. To begin the task, participants were instructed to move the dot into a yellow circle to indicate they are ready. This position served as the "waiting position" for every trial. Once the participant moved the dot into the waiting position, and their hand was still (hand velocity < 5mm/s for 200ms), an object (square or diamond) appeared in one of five potential object locations positioned

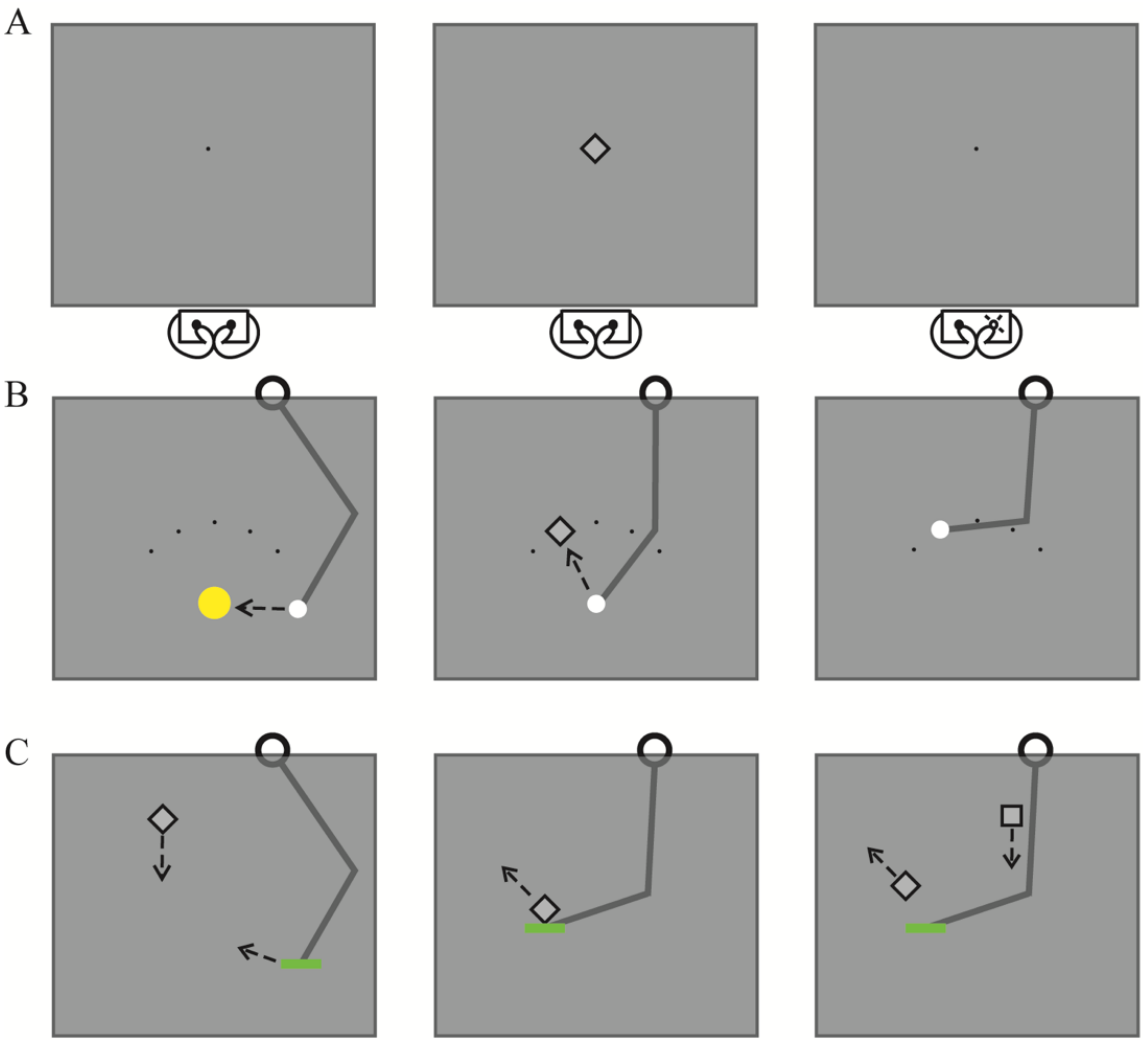

Figure 5.1. Go/NoGo Task Variants. Visualization of discrete button (A), discrete reach (B), and continuous reach (C) Go/NoGo task variants.

equidistant over the "waiting position." Objects were presented for 200ms followed by a 1500ms response window. Participants were instructed to make a response, they needed to reach to the location where the target appeared then return their hand to the "waiting position" to initiate the next trial.

For the continuous reaching (CTR) variant, participants again grasped one of the KINARM robotic arm with their dominant hand (Figure 5.1C). The participant's hand position within the workspace was represented by a green rectangular paddle. Participants could freely maneuver the green paddle within the workspace by moving the robotic arm. Participants were instructed, once the task begins, to maneuver the paddle to intercept and hit away the target objects (square or diamond) as they fall from the top of the workspace toward the bottom. Objects fell one at a time so that only one object is present in the workspace and fall at a constant speed of 30cm/s. If a participant made contact with an object, a reciprocal perturbation was applied to the robotic handle and the object ricocheted away from the paddle to simulate contact with a real weighted object.

Behavioral Measures.

To calculate behavioral measures for each variant of the Go/NoGo task, all blocks within a given condition were combined. Primary behavioral measures of response accuracy (ACC, %), commission errors (CE, n), and omission errors (OE, n) were calculated for each task variant. Additionally, signal detection metrics were calculated to assess an individual's discrimination sensitivity (dPrime) within each variant.[360]

Neuroelectric Data: Acquisition & Reduction.

Electroencephalography (EEG) data was concurrently recorded from 64 high impedance, active electrodes (AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, FP1/2, AF1/2/4/8, F7/5/3/1/2/4/6/8, FT9/7/8/10, FC5/3/1/2/4/6, T7/8, C5/3/1/2/4/6, TP9/7/8/10, CP5/3/1/2/4/6, P7/5/3/1/2/4/6/8, PO7/3/4/8, O1/2) arranged according to the International 10-10 system[335] using actiCAP (EASYCAP Gmbh, Herrsching, Germany). Recordings were referenced online to FCz, with FPz serving as the ground electrode. Additional electrodes were also placed above and below the left orbit and to the left and right outer canthus to monitor vertical and horizontal electrooculographic (EOG) activity, respectively. Impedances were kept below 25kΩ for all electrodes. Continuous recordings were and amplified using actiChamp amplifier (Brain Products GmbH, Gilching, Germany) digitized at 1000Hz. Finally, an online bandpass filter 0.01 – 100 Hz was applied to each recording. Digital event codes sent from the KINARM and were received via 8-bit (0-256 possible events) input into the back of the electrophysiological system. All EEG activity was recording using Brain Vision Recorder (v1.21, Brain Products GmbH, Gilching, Germany).

Reduction of continuous EEG data was conducted offline in MATLAB 2020b (Mathworks, Natick, MA) using custom scripts and plugins from the EEGLAB and ERPLAB toolboxes.[361, 362] First, event codes and latencies recorded from the KINARM were synced with the continuous EEG data. Data will then be filtered using a 1.0 – 50.0Hz bandpass windowed sinc finite impulse response filter. Prior to independent component analysis (ICA) decomposition, artifact subspace reconstruction (ASR) was used to identify and remove any noise related artifacts.[363] Once the data has been cleaned, an Infomax

independent component analysis (ICA) algorithm was used to characterize individual independent components (ICs) within the data. ICs were then classified using the iclabel() plugin function, and ICs labeled as non-neural (i.e., ocular, muscle) sources were subsequently removed and the data reconstructed. To account for excessive noise, average signal recorded from peripheral channels (i.e., F7/8, CP5/6, Pz/7/5/3/1/8/6/4/2, POz/7/3/8/4, Oz/1/2) were averaged to characterize signal noise. The channels were removed from the data and the characterized noise was subtracted from the remaining channels. Artifact free data was re-referenced to a whole head average and FCz (online reference) was added back in

Stimulus-locked epochs were created from -100 – 1000ms epochs created around the stimulus presentation for correct trials and baseline corrected using the 100ms pre-stimulus period. Incorrect trials and trials containing EEG activity exceeding ±75μV were removed. Finally, remaining trials were manually inspected for remaining artifacts and removed. The N2 component was identified as the mean amplitude within a 30ms window surrounding the largest negative-going peak 150 – 350ms post stimulus onset, at fronto-central sites. The P300 component was obtained by identifying as the mean amplitude within a 50ms time window surrounding the largest positive-going peak within the interval 300 – 800ms post stimulus onset at centro-parietal sites. Within the central-parietal electrode array, local hotspots were generated by locating the electrode with the largest peak and taking an average of neighboring electrodes. Peak amplitude was measured as the difference between pre-stimulus baseline and mean peak-interval amplitude. Peak latency was defined as the time point associated with the maximum deflection within the defined temporal window.

Statistical Analysis. All statistical analyses were computed in MATLAB 2020b (Mathworks, Natick, MA) using functions within the Statistics and Machine Learning toolbox, with an a priori alpha level of $p < 0.05$. Behavioral performance data (accuracy, commission errors, and omission errors) and neuroelectric measures (N2 peak amplitude, N2 peak latency, P300 peak amplitude, and P300 peak latency) were examined via a series of 3 (variant: BUTTON, REACH, CTR) × 2 (condition: response infrequent, response frequent) mixed model ANOVA. Partial eta squared (η_p^2) measures of effect size were calculated for each ANOVA (η_p^2: < 0.05 = small; (η_p^2: 0.06 – 0.13 = medium; η_p^2: > 0.14 = large).

RESULTS

Participant Characteristics. Twenty-three participants without a history of brain injury (or suspected brain injury) were included in our analyses. Demographic information is provided in Table 5.1.

Go/NoGo Task Performance. Statistical analysis of task accuracy revealed a significant variant x condition interaction ($F[2,20] = 9.3$; $p < 0.001$; $\eta_p^2 = 0.06$). Simple main effects of condition were observed for all three task variants; BUTTON ($t[22] = 8.6$; $p < 0.001$), REACH ($t[22], = 9.3$; $p < 0.001$), and CTR ($t[22] = 2.17$; $p = 0.04$). In each variant participants performed significantly worse in the response frequent condition (BUTTONm = 95.6 ± 2.2, REACHm = 92.2 ± 3.7, CTRm = 89.8 ± 4.7) compared to the response infrequent condition (BUTTONm = 99.4 ± 0.6, REACHm = 99.2 ± 0.6, CTRm = 91.3 ± 4.1). Additionally, a significant simple main effect of variant was observed ($F[2,20] = 60.9$; $p < 0.001$; $\eta_p^2 = 0.37$). Bonferroni corrected multiple comparisons revealed irrespective of

Table 5.1. Participant Demographics

	HC- (n=23)	
Demographics		
	Mean	*±SD*
Age (yrs)	22.1	2.8
Sex [#M /#F]	8/15	-
BMI	25.0	3.8

HC-: non-injured control, M: male, F: female, BMI: body mass index

condition, participants performed significantly worse on the CTR variant (est. m = 90.6 ± 0.5) compared to the BUTTON (est. m = 97.5 ± 0.5; $p < 0.001$) and REACH (est. m = 95.5 ± 0.5; $p < 0.001$). Participants also performed significantly worse on the REACH variant compared to the BUTTON ($p = 0.02$).

Statistical analysis of commission errors reveled a significant variant x condition interaction ($F[2,20] = 8.1$; $p < 0.001$; $\eta_p^2 = 0.05$). Simple main effects of condition were observed for all three task variants; BUTTON ($t[22] = -8.7$; $p < 0.001$), REACH ($t[22], = -9.5$; $p < 0.001$), and CTR ($t[22] = -7.1$; $p = 0.04$). In each variant participants committed significantly more errors of commission in the response frequent condition (BUTTONm = 14.0 ± 7.3, REACHm = 21.4 ± 10.5, CTRm = 18.4 ± 8.7) compared to the GO condition (BUTTONm = 0.3 ± 0.6, REACHm = 0.5 ± 1.0, CTRm = 9.7 ± 7.2). Additionally, a significant simple main effect of variant was observed ($F[2,20] = 10.5$; $p < 0.001$; $\eta_p^2 = 0.06$). Bonferroni corrected multiple comparisons revealed irrespective of condition, participants committed significantly more errors of commission on the CTR variant (est. m = 14.0 ± 1.0; $p < 0.001$) and REACH (est. m = 11.3 ± 1.0; $p = 0.02$) compared to the BUTTON (est. m = 7.4 ±1.0).

Statistical analysis of dprime revealed a significant variant x condition interaction ($F[2,20] = 12.6$; $p < 0.001$; $\eta_p^2 = 0.06$). Simple main effects of condition were observed for both the BUTTON ($t[22] = 9.7$; $p < 0.001$) and REACH ($t[22], = 8.9$; $p < 0.001$) variants. In both variants, participants exhibited lower dprime metrics in the response frequent condition (BUTTONm = 3.6 ± 0.5; REACHm = 3.3 ± 0.4) compared to the response infrequent condition (BUTTONm = 4.7 ± 0.3; REACHm = 4.4 ± 0.7) indicating greater

difficulty distinguishing targets from distractors. Additionally, a significant simple main effect of variant was observed ($F[2,20] = 101.3$; $p < 0.001$; $\eta_p^2 = 0.47$). Bonferroni corrected multiple comparisons revealed irrespective of condition, participants exhibited lower dprime metrics on the CTR variant (est. $m = 2.6 \pm 0.8$) compared to the BUTTON (est. $m = 4.2 \pm 0.8$; $p < 0.001$) and REACH (est. $m = 3.8 \pm 0.8$; $p < 0.001$). Participants also exhibited lower dprime metrics on the REACH variant compared to the BUTTON ($p = 0.009$).

Statistical analysis failed to reveal a significant interaction for omission errors. However, a significant main effect of variant was observed ($F[2,20] = 104.7$; $p < 0.001$; $\eta_p^2 = 0.57$). Bonferroni corrected multiple comparisons revealed irrespective of condition, participants committed significantly more errors of omission on the CTR variant (est. $m = 13.9 \pm 0.7$) compared to the BUTTON (est. $m = 1.2 \pm 0.7$; $p < 0.001$) and REACH (est. $m = 1.6 \pm 0.7$; $p < 0.001$). No significant differences were observed between the REACH and BUTTON variants.

Neuroelectric Measures. Figure 3.1 depicts average neuroelectric waveforms for response infrequent (Figure 3.1A) and response frequent (Figure 3.1B) conditions during all three task variants.

Statistical analysis of peak N2 latency revealed significant variant x condition interaction ($F[2,15] = 7.6$; $p < 0.001$; $\eta_p^2 = 0.12$). Simple main effects of condition were observed for all three task variants; BUTTON ($t[17] = -8.7$; $p < 0.001$), REACH ($t[17], = -9.5$; $p < 0.001$), and CTR ($t[17] = -7.1$; $p = 0.04$). In both the BUTTON and CTR variants participants exhibited significantly shorter N2 latencies in the response frequent condition

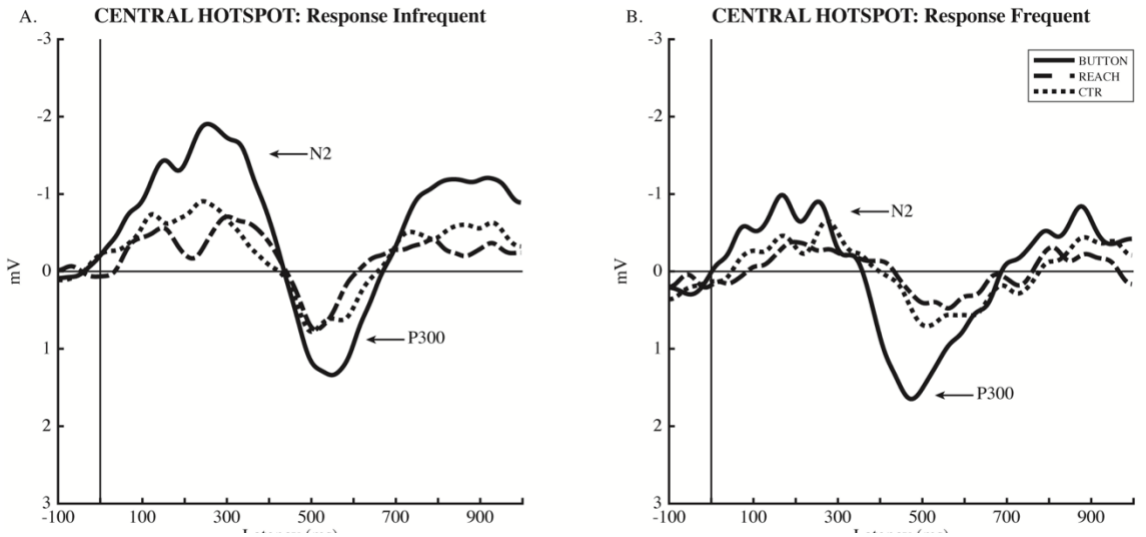

Figure 5.2. Average ERP Waveforms. Average ERP waveforms recorded during the response infrequent (A) and response frequent (B) of each Go/NoGo task variant; BUTTON (solid line), REACH (dashed line), and CTR (dotted line).

(BUTTONm = 212.7ms ± 65.7; CTRm = 226.2ms ± 77.8) compared to the response infrequent condition (BUTTONm = 268.4ms ± 55.7; CTRm = 295.3ms ± 60.0). Conversely, in the REACH condition participants exhibited significantly longer N2 latencies in the response frequent condition (REACHm = 276.2ms ± 61.3) compared to the response infrequent condition (REACHm = 240.7 ± 45.1). Analyses failed to detect a significant simple main effect for variant.

Statistical analysis of P300 latency revealed significant variant x condition interaction ($F[2,15] = 7.2$; $p = 0.001$; $\eta_p^2 = 0.12$). Simple main effects of condition were observed for the BUTTON ($t[17] = 4.8$; $p < 0.001$) variant. In the BUTTON variant participants exhibited significantly longer P300 latencies in the response infrequent condition (m = 542.7ms ± 38.9) compared to the response frequent condition (m = 487.8ms ± 43.1; $p < 0.001$). Analyses failed to detect a significant simple main effect for variant.

No interaction effect was observed for peak N2 amplitude. However, a main effect for variant was detected ($F[2,15] = 20.9$; $p < 0.001$; $\eta_p^2 = 0.28$). Bonferroni corrected multiple comparisons revealed irrespective of condition, participants exhibited participants exhibited significantly smaller peak N2 amplitudes in both the CTR variant (est. m = -0.89 ± 0.09; $p < 0.001$) and REACH variant (est. m = -1.1 ± 0.09; $p < 0.001$) compared to BUTTON (est. m = -1.7 ± 0.09). No significant differences were observed between the CTR and REACH variants.

No interaction effect was observed for peak P300 amplitude. However, a main effect for variant was detected ($F[2,15] = 37.4$; $p < 0.001$; $\eta_p^2 = 0.41$). Bonferroni corrected multiple comparisons revealed irrespective of condition, participants exhibited

significantly smaller peak P300 amplitudes in both the CTR variant (est. m = 1.2 ± 0.1; p < 0.001) and REACH variant (est. m = 1.5 ± 0.01; p < 0.001) compared to BUTTON (est. m = 2.3± 0.01). No significant differences were observed between the CTR and REACH variants.

DISCUSSION

The present study set out to compare N2 and P300 waveforms collected from both discrete continuous variants of a traditional Go/NoGo. Previous research has demonstrated the ability to collect ERP-like waveforms during arm movement and continuous tasks.[237, 364] However, to our knowledge, the present study is the first to systematically compare ERP waveforms collected during discrete and continuous arm reaching task variants to a standard button press task. By comparing ERPs collected across the three variants we sought to characterize differences in the waveforms.

These results demonstrated that N2 and P300 latencies did not differ across the three task variants. However, peak amplitudes for both ERPs were significantly smaller in both the discrete and continuous reach task variants. These reduction in ERP amplitudes may reflect the computationally more complex motor planning necessary for arm movements compared to button press actions.[365] While the more dynamic and complex reaching tasks elicited similar These differences in ERP characteristics further highlights the importance of factoring in task parameters when comparing ERPs recorded under differing conditions.

In the present study, ERPs collected from the discrete button press variant produced better overall waveforms. However, future studies should look to improve experimental

setups and ERP data reduction pipelines to allow for the investigation of psychological performance under continuous task paradigms. There are several advantages to using more complex task paradigms like the continuous and discrete reach variants in the present study. First, these types of tasks more closely resemble real-world behaviors and therefore the results will be more generalizable and potentially more ecologically valid. The field of brain-computer interfacing (BCI) utilizes real-time EEG and ERP recordings to allow for individuals to use brain activity to interact with various forms of technology.[366] Advances in this field have been applied to neural prosthetics giving individuals suffering from spinal cord injuries and amputees increased functionality and independence.[367] Collecting meaningful EEG and ERP data during continuous task paradigms will be crucial to further help these individuals independently function in their day-to-day lives.

Additionally, more dynamic and complex tasks generate more cognitively demanding environments in which behavior and physiological parameters can easily be observed. Assessing physiological performance during periods of increased task complexity is crucial in the study of neurological conditions such as concussion. Individuals recovering from concussion experience a series of often transient somatic, emotional, and cognitive symptoms.[33] While the established recovery window for adults is 10-14 days, the true timeline of recovery is controversial.[6] This is supported by research showing that individual's reporting to be symptom free at rest report exacerbated symptoms following exercise or bouts of increased mental workload.[32, 114, 316] Therefore, using more complex cognitive tasks in the assessment of concussion (or other neurological disorders) may elicit neurological deficits not seen at rest or under low load situations. Finally, one limitation of cognitive assessment batteries in clinical settings is the time

requirements to collect a necessary number of trials to allow for meaningful comparisons. Using continuous stimulus presentation and response, reduces the time needed to collect data.

Limitations

While informative, the present study is not without its limitations. First, EEG data is very sensitive to biological artifacts such as muscle activity. The present study aimed to reduce the influence of muscle activity by utilizing a chin rest mounted in front of the presentation device, eliminating electrode site closest to muscle insertions on the skull and utilizing an IC classification algorithm with stereotyped components corresponding to muscle activation. Further studies should aim to further investigate this issue by more securely stabilizing the head or develop more sophisticated reduction algorithms. Finally, in stimulus-locked ERP analyses it is vital to have accurate time stamps corresponding to stimulus appearance. In a continuous task where objects are continuously appearing and moving stimulus "appearance" estimates become difficult. The present study aimed to minimize this issue by only having one object on the screen at a time. Future studies can potentially circumvent this issue with integrated eye tracking systems.

Conclusion.

The present study demonstrated the utility of recording and computing similar ERP waveforms during continuous arm reaching tasks, compared to traditional discrete button tasks. However, the increased task complexity and cognitive load resulted in significantly smaller N2 and P300 amplitudes, making comparisons across tasks more difficult. Future studies should aim to improve on the present results by modifying experimental setups and

task parameters to reduce possible sources of noise. To help advance the field of cognitive neuroscience and These findings will help advance the field of cognitive neuroscience by allowing for the evaluation of cognitive processes during tasks aimed to more closely mirror real-world tasks.

CHAPTER 6

COGNITIVE PERFORMANCE AMONG SYMPTOMATIC AND ASYMPTOMATIC INDIVIDUALS WITH A HISTORY OF CONCUSSION: COMPARISON WITHIN DISCRETE AND CONTINUOUS TASK PARADIGMS

Harrison, A.T., Green, J., Pontifex, M., Herter, T.M., & Moore, R.D. To be submitted to *Scientific Reports* (in preparation)

INTRODUCTION

Concussive brain injuries result from rapid acceleration and deceleration of brain tissue brought on by biomechanical impulses transmitted to the brain.[6] The ensuing neuronal disfigurement and neurochemical cascade lead to significant neurophysiological dysfunction.[49] Individuals who suffer a concussion often experience a myriad of immediate and/or delayed symptoms; ranging from headache, fatigue, emotional dysregulation and cognitive deficits, to temporary loss of consciousness (LOC) and post-traumatic amnesia (PTA).[3, 4] Individuals typically report complete symptom resolution within the first two weeks of injury. This has resulted in the common public perception that concussions represent a transient and minor brain injury. However, there is a growing body of literature suggesting concussions can manifest into debilitating chronic conditions.[71, 74]

Persistent post-concussive symptoms (PPCS) are a clustering of non-specific symptoms following a concussion persisting beyond the typical recovery window (>1-3 months) and negatively impacting daily function.[727] It is currently estimated that roughly 40% of individuals will meet the criteria for PPCS following a concussion.[77] PPCS represents a potentially debilitating condition with many individuals reporting a significant impact on their psychoaffective and social well-being,[93, 302] as well as their academic and vocational attainment.[21, 78, 109] Furthermore, slow-to-recover individuals with PPCS may be at greater risk of late life cognitive impairment or chronic traumatic encephalopathy (CTE).[8, 73, 105] Given the impact of PPCS and the potential long-term neurological sequelae, it is imperative that these individuals be identified early in the concussion management process.

Current clinical practice relies on a multidimensional assessment battery typically consisting of self-reported symptom checklists,[117, 318] manual assessments of vestibular and ocular function,[131, 136] and computerized tests of cognitive function.[119, 121] These assessments have greatly improved the diagnostic accuracy of acute concussive brain injuries. However, the effectiveness of these assessments is limited by the subjective nature of symptom checklists and poor sensitivity of computerized tests beyond the acute stage of recovery[122-124, 368, 369] Additionally, these tests do not provide measurable insight into the neurophysiological function and recovery of the brain. Research suggests that neurophysiological recovery extends beyond the traditional window of recovery, and that premature return to full school or sport engagement before this neurophysiological recovery predisposes individuals to subsequent injury and chronic concussion-related deficits.[6, 60, 142, 300] Accordingly, it is crucial to utilize sensitive and objective measures of neurological function to effectively and more accurately track recovery following a concussion.

Electroencephalography (EEG) is well suited to track the neurophysiological recovery following concussion. EEG provides a non-invasive manner in which to measure fluctuations in electrical activity produced given off by cortical neurons. This allows for extremely reliable quantification of neuronal activity down to the millisecond.[262, 354] Utilizing this high level of temporal resolution, we are able to quantify task-related neural activity. Event-related potentials (ERPs) represent coordinated and synchronous activity of large pools of cortical neurons serving specific sensory, cognitive, and motor functions.[261, 264] EEG and ERP recordings have been used in numerous clinical populations to identify abnormal cognitive processing[247-249, 370-372] Decisional conflict monitoring (N2) and

attention allocation (P300) are two domains of cognitive control commonly studied in concussion using ERPs.[264] Individuals with a history of concussion often demonstrate alterations in both the N2 and P300 amplitude and latency.[142, 297-299] These findings suggest that individuals with a history of concussion exhibit abnormal neural function related to processes of cognitive control.

While informative, due to methodological barriers these findings are limited in their clinical utility. First, most studies rely on a two-group design comparing either symptomatic or asymptomatic individuals to non-injured controls. To disentangle what is a typical recovery pattern compared to an abnormal pattern associated with PPCS, it is necessary to compare all three groups. A recent study utilizing this three-group design demonstrated that individuals with a history of concussion exhibited increased P300 latency while performing an auditory odd-ball task. However, symptomatic individuals also demonstrated reduced P300 amplitude, indicating separate neurophysiological profiles among asymptomatic and symptomatic individuals.[30210] A second limitation to current research is the utilization of simple and discrete button press tasks to assess cognitive function. To effectively interact within the real-world requires complex and continuous integration among perceptual, cognitive, and motor neural systems.[180, 373-375] Indeed, research suggests incorporating physiological stressors or increasing cognitive complexity may expose underlying deficits that originally go unnoticed.[32, 114, 376]

Therefore, the aim of the current study is to investigate behavioral performance and neuroelectric measures within asymptomatic (HCx-A) and symptomatic (HCx-S) individuals with a history of concussion (>4 weeks post-injury), compared to non-injured controls (HC-). We will collect behavioral and neuroelectric performance while they

complete discrete and continuous arm reaching variants of the traditional Go/NoGo task. We predict that compared to HC- individuals, HCx-A and HCx-S individuals will demonstrate progressive increases in commission errors (Go responses on NoGo trials) during discrete and continuous arm reaching variants of the Go/NoGo task. Furthermore, HCx-A and HCx-S individuals will exhibit progressive decreases in amplitude and latency of their N2 and P300 stimulus-locked ERPs compared to HC- individuals. Finally, we hypothesize that deficits in neuroelectric and behavioral performance will be related concussion-related symptom burden.

METHODS

Participants. A description of participant sampling procedures, inclusion, and exclusion criteria is provided elsewhere (see Chapter 3: General Methods-Participants). To investigate the impact of concussion recovery on cognitive performance HC-, HCx-A, and HCx-s individuals completed three variants of the traditional Go/NoGo task.

Procedures. A generalized description and illustration of study procedures can be found elsewhere (see Chapter 3: General Methods-Procedure).

Cognitive Task. Following setup and preparation of the EEG cap, participants were comfortably seated in front of the KINARM. Within the KINARM environment, participants completed three variants (discrete button, discrete reach, and continuous reach) of a modified Go/NoGo task (see Figure 5.1). For each variant, participants completed two separate conditions. The response infrequent condition in which participants were instructed to respond quickly and accurately to the appearance of a grey diamond (25% of trials) and inhibit responses to a grey square (75% of trials). Conversely, in the response

frequent condition participants were instructed to respond to the appearance of a grey square (75% of trials) and inhibit responses to a grey diamond (25% of trials). Within each variant, participants completed two blocks of the response infrequent condition followed by three blocks of the response frequent condition. Each block consisted of 120 trials. Prior to beginning the task, participants were given oral instructions outlining the task objectives as well as informing the participant of the appropriate target shape.

Within each variant, the method in which the participant is asked to respond changed. For the discrete button (BUTTON) variant, participants grasped a custom two-button digital trigger box (Figure 6.1A). The participant instructed to make responses by pressing the button corresponding with their dominant hand. When the task began, an object (square or diamond) appeared in the center of the KINARM workspace. Targets were presented for 200ms followed by a 1500ms response window.

For the discrete reach (REACH) variant, participants grasped one of the KINARM robotic arms with their dominant hand (Figure 6.1B). The participant's hand position in the workspace is represented within the workspace as a white dot and movement of the robotic arm produced equivalent movement of the white dot. To begin the task, participants were instructed to move the dot into a yellow circle to indicate they are ready. This position served as the "waiting position" for every trial. Once the participant moved the dot into the waiting position, and their hand was still (hand velocity < 5mm/s for 200ms), an object (square or diamond) appeared in one of five potential object locations positioned equidistant over the "waiting position." Objects were presented for 200ms followed by a 1500ms response window. Participants were instructed to make a response, they needed to

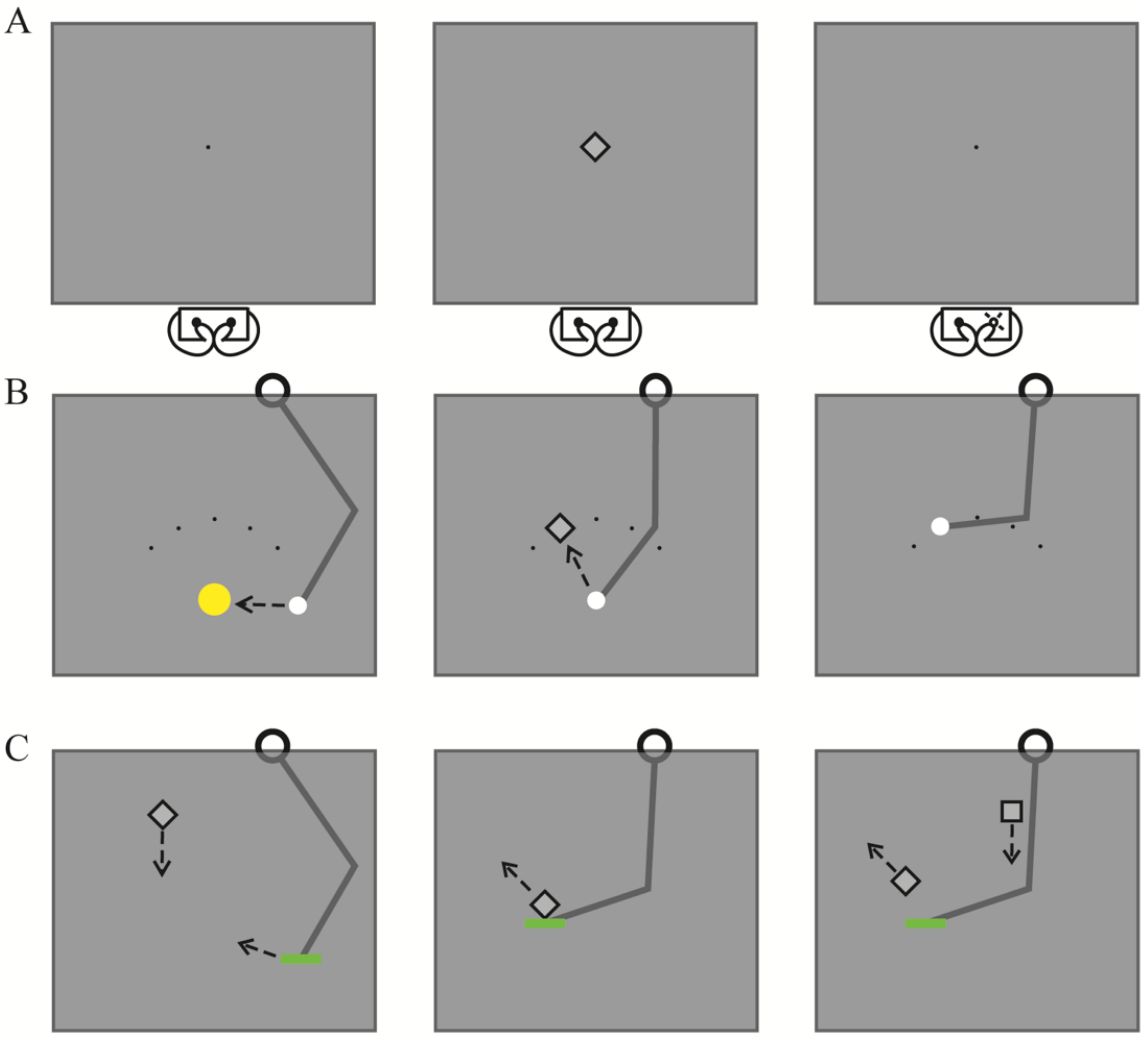

Figure 6.1. Go/NoGo Task Variants. Visualization of discrete button (A), discrete reach (B), and continuous reach (C) Go/NoGo task variants.

reach to the location where the target appeared then return their hand to the "waiting position" to initiate the next trial.

For the continuous reaching (CTR) variant, participants again grasped one of the KINARM robotic arm with their dominant hand (Figure 6.1C). The participant's hand position within the workspace was represented by a green rectangular paddle. Participants could freely maneuver the green paddle within the workspace by moving the robotic arm. Participants were instructed, once the task begins, to maneuver the paddle to intercept and hit away the target objects (square or diamond) as they fall from the top of the workspace toward the bottom. Objects fell one at a time so that only one object is present in the workspace and fall at a constant speed of 30cm/s. If a participant made contact with an object, a reciprocal perturbation was applied to the robotic handle and the object ricocheted away from the paddle to simulate contact with a real weighted object.

Behavioral Measures.

To calculate behavioral measures for each variant of the Go/NoGo task, all blocks within a given condition were combined. Primary behavioral measures of response accuracy (ACC, %), commission errors (CE, n), and omission errors (OE, n) were calculated for each task variant. Additionally, signal detection metrics were calculated to assess an individual's discrimination sensitivity (dPrime) within each variant.[360]

Neuroelectric Data: Acquisition & Reduction.

Electroencephalography (EEG) data was concurrently recorded from 64 high impedance, active electrodes (AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, FP1/2, AF1/2/4/8, F7/5/3/1/2/4/6/8, FT9/7/8/10, FC5/3/1/2/4/6, T7/8, C5/3/1/2/4/6, TP9/7/8/10,

CP5/3/1/2/4/6, P7/5/3/1/2/4/6/8, PO7/3/4/8, O1/2) arranged according to the International 10-10 system[335] using actiCAP (EASYCAP Gmbh, Herrsching, Germany). Recordings were referenced online to FCz, with FPz serving as the ground electrode. Additional electrodes were also placed above and below the left orbit and to the left and right outer canthus to monitor vertical and horizontal electrooculographic (EOG) activity, respectively. Impedances were kept below 25kΩ for all electrodes. Continuous recordings were and amplified using actiChamp amplifier (Brain Products GmbH, Gilching, Germany) digitized at 1000Hz. Finally, an online bandpass filter 0.01 – 100 Hz was applied to each recording. Digital event codes sent from the KINARM and were received via 8-bit (0-256 possible events) input into the back of the electrophysiological system. All EEG activity was recording using Brain Vision Recorder (v1.21, Brain Products GmbH, Gilching, Germany).

Reduction of continuous EEG data was conducted offline in MATLAB 2020b (Mathworks, Natick, MA) using custom scripts and plugins from the EEGLAB and ERPLAB toolboxes.[361, 362] First, event codes and latencies recorded from the KINARM were synced with the continuous EEG data. Data will then be filtered using a 1.0 – 50.0Hz bandpass windowed sinc finite impulse response filter. Prior to independent component analysis (ICA) decomposition, artifact subspace reconstruction (ASR) was used to identify and remove any noise related artifacts.[363] Once the data has been cleaned, an Infomax independent component analysis (ICA) algorithm was used to characterize individual independent components (ICs) within the data. ICs were then classified using the iclabel() plugin function, and ICs labeled as non-neural (i.e., ocular, muscle) sources were subsequently removed and the data reconstructed. To account for excessive noise, average

signal recorded from peripheral channels (i.e., F7/8, CP5/6, Pz/7/5/3/1/8/6/4/2, POz/7/3/8/4, Oz/1/2) were averaged to characterize signal noise. The channels were removed from the data and the characterized noise was subtracted from the remaining channels. Artifact free data was re-referenced to a whole head average and FCz (online reference) was added back in

Stimulus-locked epochs were created from -100 – 1000ms epochs created around the stimulus presentation for correct trials and baseline corrected using the 100ms pre-stimulus period. Incorrect trials and trials containing EEG activity exceeding ±75μV were removed. Finally, remaining trials were manually inspected for remaining artifacts and removed. The N2 component was identified as the mean amplitude within a 30ms window surrounding the largest negative-going peak 150 – 350ms post stimulus onset, at fronto-central sites. The P300 component was obtained by identifying as the mean amplitude within a 50ms time window surrounding the largest positive-going peak within the interval 300 – 800ms post stimulus onset at centro-parietal sites. Within the central-parietal electrode array, local hotspots were generated by locating the electrode with the largest peak and taking an average of neighboring electrodes. Peak amplitude was measured as the difference between pre-stimulus baseline and mean peak-interval amplitude. Peak latency was defined as the time point associated with the maximum deflection within the defined temporal window.

Statistical Analysis. All statistical analyses were computed in MATLAB 2020b (Mathworks, Natick, MA) using functions within the Statistics and Machine Learning toolbox, with an a priori alpha level of $p < 0.05$. Parametric and non-parametric tests of group comparisons were used to analyze continuous and categorical, respectively, to

identify potential demographic differences among groups. Behavioral performance data (accuracy, commission errors, and omission errors, dPrime) and neuroelectric measures (N2 peak amplitude, N2 peak latency, P300 peak amplitude, and P300 peak latency) were examined via a series of 3 (group: HC-, HCx-A, HCx-S) × 2 (condition: response infrequent, response frequent) mixed model ANOVA. Partial eta squared (η_p^2) measures of effect size were calculated for each ANOVA (η_p^2: < 0.05 = small; (η_p^2: 0.06 – 0.13 = medium; η_p^2: > 0.14 = large). To investigate potential associations among task performance, neuroelectric measures, and symptom burden Pearson correlation coefficients were calculated among all individuals with a history of concussion.

RESULTS

Participant Characteristics. Sixty-one participants were included in our analyses. Participants were identified as either non-brain injured healthy control (HC-, n = 23), history of concussion – asymptomatic (HCx-A; n = 16), or history of concussion – symptomatic (HCx-S; n = 22) based on self-reported medical history and symptoms. Chi Square analysis revealed significant differences in the distribution between male and females within each group. Accordingly, biological sex will be included as a covariate in subsequent behavioral and neuroelectric analyses. Demographic information is provided in Table 6.1.

Table 6.1. Participant Demographics & Injury Characteristics.

	HC- (n=23)		HCx-A (n=16)		HCx-S (n=22)	
Demographics						
	Mean	*±SD*	*Mean*	*±SD*	*Mean*	*±SD*
Age (yrs)	22.1	2.8	21.4	2.3	21.1	2.7
Sex [#M /#F]	8/15	-	9/7	-	5/17	-
BMI	25.0	3.8	24.4	3.4	25.2	5.1
Injury Characteristics						
Prev Cx (n)			1.6	0.9	2.1	1.1
Days Since Cx			1232.9	961.5	694.4	749.1

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, M: male, F: female, BMI: body mass index, Prec Cx: previous concussioons.

Go/NoGo Task Performance.

Discrete Button Performance.

Table 6.2 provides group means and standard deviations for measures of task performance. Figure 6.2 depicts observed significant group differences. Group wide analyses failed to detect any interaction effects for outcome measures of task performance. A main effect of Group was observed for task accuracy ($F[2,58] = 4.2$, $p = 0.02$, $\eta_p^2 = 0.04$). Bonferroni corrected multiple comparisons revealed HCx-S individuals performed significantly worse (est. $m = 95.9 \pm 0.4$) compared to HC- (est. $m = 97.5 \pm 0.4$; $p = 0.01$). A main effect of Group was also observed for omission errors ($F[2,58] = 5.7$, $p = 0.004$, $\eta_p^2 = 0.08$). Bonferroni corrected multiple comparisons revealed HCx-S individuals performed significantly more omission errors (est. $m = 4.3 \pm 0.8$) compared to both HC- (est. $m = 1.3 \pm 0.7$; $p = 0.02$) and HCx-A (est. $m = 0.9 \pm 0.9$; $p = 0.01$). Finally, a main effect for dprime was observed ($F[2,58] = 3.7$, $p = 0.03$, $\eta_p^2 = 0.03$). Bonferroni corrected multiple comparisons revealed HCx-S individuals demonstrated significantly more difficulty discriminating targets from distractors (est. $m = 3.9 \pm 0.1$) compared to HC- (est. $m = 4.1 \pm 0.1$; $p = 0.03$).

No significant associations were identified the BUTTON task performance variables and self-reported measures of symptom burden.

Table 6.2. Go/NoGo Task Performance (Discrete Button).

	HC- (n=23)		HCx-A (n=16)		HCx-S (n=22)		GRP	CND	INT
	Mean	*±SEM*	*Mean*	*±SEM*	*Mean*	*±SEM*	η^2	η^2	η^2
Inf ACC	99.4	0.1	99.4	0.2	98.7*‡	0.5	0.04	0.43	0.01
Frq ACC	95.6	0.5	94.5	0.7	93.2*‡	0.9			
Inf OE	0.3	0.1	0.4	0.2	2.7*‡	1.2	0.09	0.04	0.01
Frq OE	2.3	0.5	1.3	0.4	6.0*‡	2.1			
Inf CE	0.8	0.1	0.9	0.2	0.5	0.1	0.01	0.60	0.01
Frq CE	14.0	1.5	17.3	2.0	18.5	2.3			
Inf D’	4.7	0.1	4.7	0.1	4.6	0.1	0.03	0.53	0.01
Frq D’	3.6	0.1	3.4	0.1	3.1	0.2			

Note: Data are presented as mean ± standard error (SEM), p-value, and effect size (η^2).

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, Inf: Infrequent Response Condition, Frq: Frequent Response Condition, ACC: Accuracy, OE: Omission Errors, CE: Commission Errors, D’: dprime, n: number, GRP: Group Effects, CND: Condition Effect, INT: Interaction Effect

* Comparison to HC- $p < 0.05$

‡ Comparison to HCx-A $p < 0.05$

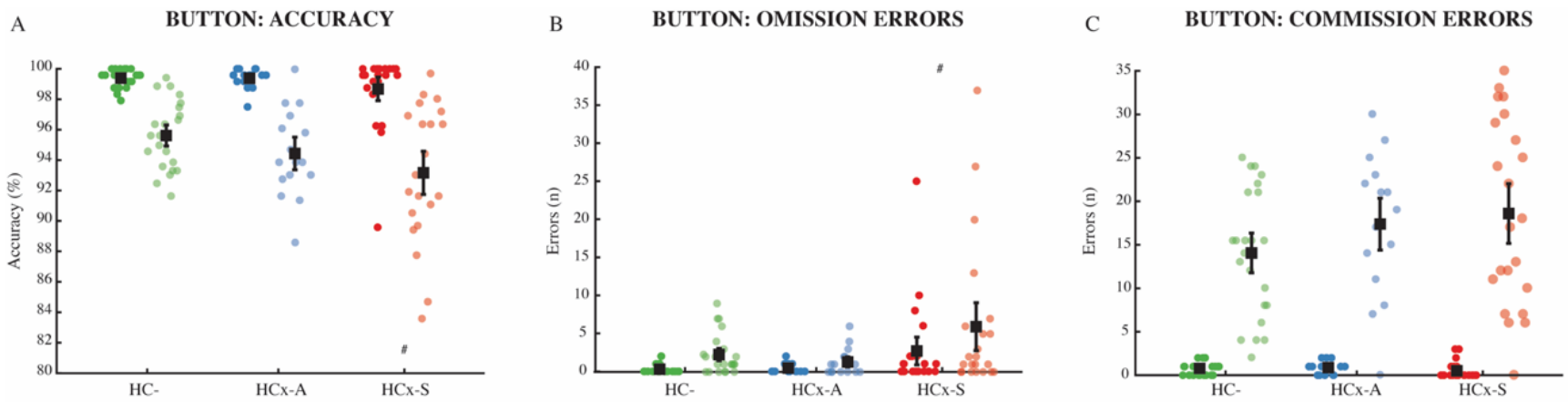

Figure 6.2. Go/NoGo Button Task Performance. Individual and group averages for task accuracy (A), omission errors (B), and commission errors (C). Individual dots represent HC- (green), HCx-A (blue), and HCx-S (red) groups within the response infrequent (solid) and response frequent (faded) conditions. Black squares and whiskers represent group means and standard error.

Discrete Reach Performance.

Table 6.3 provides group means and standard deviations for measures of task performance. Statistical analysis failed to reveal significant differences in in task performance within the REACH variant.

No significant associations were identified for REACH response infrequent task performance variables and self-reported measures of symptom burden. Table 6.4 reports correlation coefficients for REACH response frequent performance and self-reported measures of symptom burden. REACH response frequent commission errors were positively associated with total BDI score (r = 0.39), BDI cognitive sub-scale (r = 0.38), BDI non-cognitive sub-scale (r = 0.33), and Neuro-QoL sleep disturbance scale (r = 0.35). These indicate that individuals that committed more commission errors also reported worse outcomes on these scales. Additionally, task accuracy was negatively associated with BDI cognitive sub-scale (r = -0.37) indicating individuals that performed worse on the task, reported worse outcomes.

Continuous Reach Performance.

Table 6.5 provides group means and standard deviations for measures of task performance. Figure 6.3 depicts observed significant group differences. Group wide analyses failed to detect any interaction effects for outcome measures of task performance. Group wide analyses failed to detect any interaction effects for outcome measures of task performance. A main effect of Group was observed for task accuracy ($F[2,58] = 5.0$, $p = 0.008$, $\eta_p^2 = 0.08$). Bonferroni corrected multiple comparisons revealed HCx-S individuals performed significantly worse (est. m = 85.4 ± 1.2) compared to HC- (est. m = 90.6 ± 1.1;

Table 6.3. Go/NoGo Task Performance (Discrete Reach).

	HC- (n=23)		HCx-A (n=16)		HCx-S (n=22)		GRP	CND	INT
	Mean	*±SEM*	*Mean*	*±SEM*	*Mean*	*±SEM*	η^2	η^2	η^2
Inf ACC	98.6	0.1	98.6	0.2	98.4	0.4	0.01	0.40	< 0.01
Frq ACC	92.2	0.8	93.0	0.2	91.5	1.5			
Inf OE	0.5	0.2	1.1	0.4	1.0	0.5	0.02	0.07	0.02
Frq OE	2.7	0.5	2.3	0.9	5.3	2.1			
Inf CE	1.2	0.2	1.6	0.4	2.7	0.8	0.01	0.48	0.01
Frq CE	21.5	2.2	18.3	2.5	25.2	3.9			
Inf D’	4.4	0.1	4.3	0.3	4.3	0.1	0.01	0.68	0.01
Frq D’	3.3	0.1	2.9	0.1	3.0	0.2			

Note: Data are presented as mean ± standard error (SEM), p-value, and effect size (η^2).

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, Inf: Infrequent Response Condition, Frq: Frequent Response Condition, ACC: Accuracy, OE: Omission Errors, CE: Commission Errors, D’: d prime, n: number, GRP: Group Effects, CND: Condition Effect, INT: Interaction Effect

* Comparison to HC- $p < 0.05$

‡ Comparison to HCx-A $p < 0.05$

Table 6.4. Correlation Coefficients: Go/NoGo REACH performance and Symptom Burden.

	ACC Inf	ACC Frq	OE Inf	OE Frq	CE Inf	CE Frq	D' Inf	D' Frq
RPQ16	-	-	-	-	-	-	-	-
RPQCog	-	-	-	-	-	-	-	-
RPQEmo	-	-	-	-	-	-	-	-
RPQSom	-	-	-	-	-	-	-	-
BDItotal	-	-	-	-	-	0.39	-	-
BDIcog	-	-0.37	-	-0.40	-	0.38	-	-
BDIncog	-	-	-	-	-	0.33	-	-
State Anx	-	-	-	-	-	-	-	-
Trait Anx	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-	-
Cog Func	-	-	-	-	-	-	-	-
Emot Dsyf	-	-	-	-	-	-	-	-
AffW-B	-	-	-	-	-	-	-	-
Sleep	-	-	-	-	-	-	-	-
PSR	-	-	-	-	-	-	-	-
SSR	-	-	-	-	-	-	-	-

RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities, ACC: Accuracy, OE: Omission Errors, CE: Commission Errors, D': dprime, Inf: Infrequent Response Condition, Frq: Frequent Response Condition.
- Correlation $p > 0.05$

Table 6.5. Go/NoGo Task Performance (Continuous Reach).

	HC- (n=23)		HCx-A (n=16)		HCx-S (n=22)		GRP	CND	INT
	Mean	*±SEM*	*Mean*	*±SEM*	*Mean*	*±SEM*	η^2	η^2	η^2
Inf ACC	91.3	0.9	88.6	0.1	86.4*	2.3	0.08	0.01	< 0.01
Frq ACC	89.8	1.0	88.2	1.6	84.3*	2.0			
Inf OE	11.0	1.0	13.3	2.1	17.1*	2.6	0.07	0.09	0.01
Frq OE	16.7	2.0	23.1	3.9	30.4*	5.5			
Inf CE	9.7	1.5	11.3	2.8	15.5*	3.2	0.05	0.12	< 0.01
Frq CE	18.4	1.8	19.3	3.6	26.1*	3.3			
Inf D’	2.7	0.1	2.4	0.2	1.9*	0.2	0.15	< 0.01	< 0.01
Frq D’	2.6	0.1	2.3	0.2	1.8*	0.2			

Note: Data are presented as mean ± standard error (SEM), p-value, and effect size (η^2).

HC-: non-injured control, HCx-A: History of Concussion-Asymptomatic, HCx-S: History of Concussion-Symptomatic, Inf: Infrequent Response Condition, Frq: Frequent Response Condition, ACC: Accuracy, OE: Omission Errors, CE: Commission Errors, D’: d prime, n: number, GRP: Group Effects, CND: Condition Effect, INT: Interaction Effect

* Comparison to HC- $p < 0.05$

‡ Comparison to HCx-A $p < 0.05$

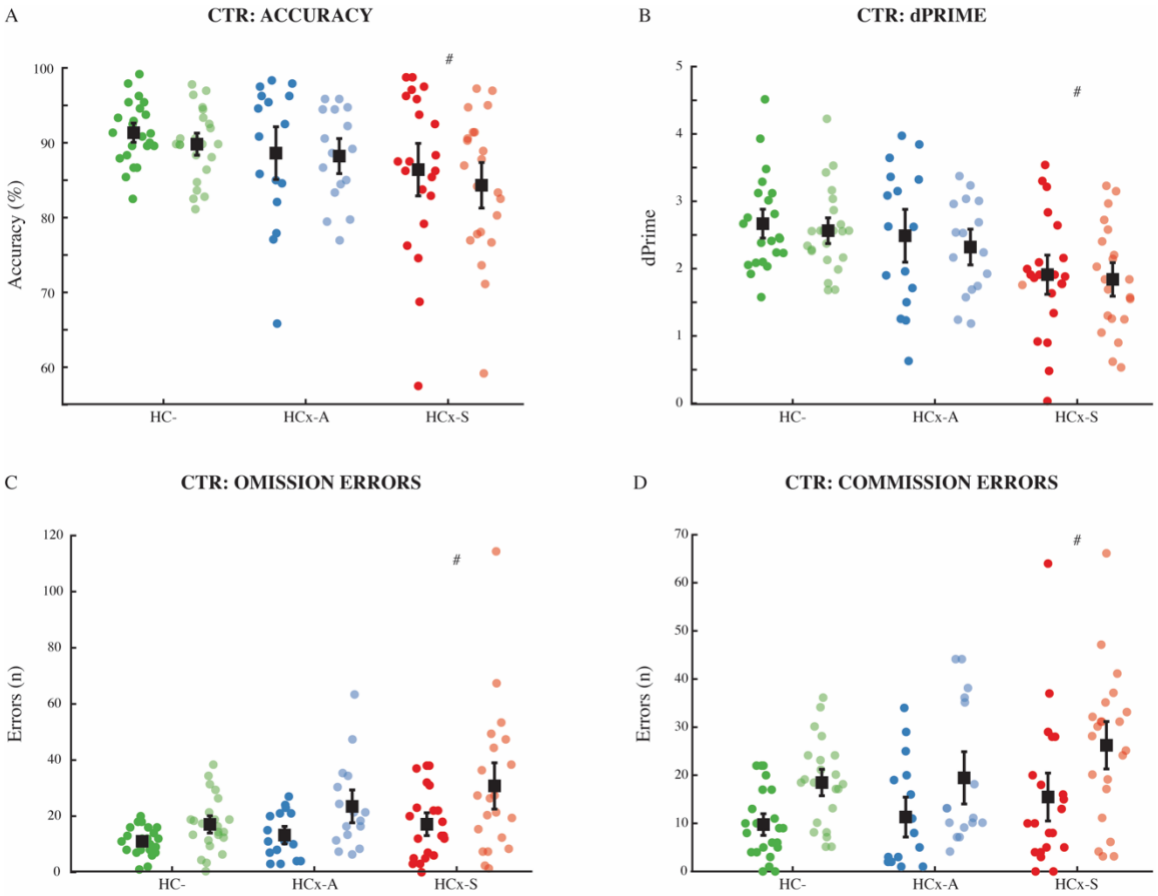

Figure 6.3. Go/NoGo CTR Task Performance. Individual and group averages for task accuracy (A), dPrime (B), omission errors (C), and commission errors (D). Individual dots represent HC- (green), HCx-A (blue), and HCx-S (red) groups within the response infrequent (solid) and response frequent (faded) conditions. Black squares and whiskers represent group means and standard error.

Significant difference from HC- ($p < 0.05$).

p = 0.006). A main effect of Group was also observed for omission errors (F[2,58] = 5.1, p = 0.007, η_p^2 = 0.02). Bonferroni corrected multiple comparisons revealed HCx-S individuals committed significantly more omission errors (est. m = 23.8 ± 2.2) compared to HC- (est. m = 13.9 ± 2.1; p = 0.005). A main effect of Group was also observed for commission errors (F[2,58] = 3.6, p = 0.03, η_p^2 = 0.03). Finally, a main effect for d' was observed (F[2,58] = 10.3, p < 001, η_p^2 = 0.15). Bonferroni corrected multiple comparisons revealed HCx-S individuals demonstrated significantly more difficulty discriminating targets from distractors (est. m = 1.9 ± 0.1) compared to HC- (est. m = 2.6 ± 0.1; p < 0.001) and HCx-A (est. m = 2.4 ± 0.1; p = 0.01).

Associations with several self-reported measures of symptom burden were observed with both CTR response infrequent and response frequent (Table 6.6) Go/NoGo BUTTON performance.

Neuroelectric Behavior. Figure 6.4 depicts group average stimulus-locked ERP waveforms computed for each Go/NoGo task variant.

Discrete Button.

No significant interactions were identified for either peak N2 amplitude or latency. A significant main effect for variant was observed for N2 latency (F[2,43] = 5.0; p = 0.009; η_p^2 = 0.09). Bonferroni corrected multiple comparisons revealed HCx-S individuals demonstrated a significantly delayed N2 peak (est. m = 286.5ms ± 11.1) compared to HC- (est. m = 240ms ± 0.1; p < 0.009) indicating greater difficulty in conflict resolution across task conditions.

Table 6.6. Correlation Coefficients: Go/NoGo CTR performance and Symptom Burden.

	ACC Inf	ACC Frq	OE Inf	OE Frq	CE Inf	CE Frq	D' Inf	D' Frq
RPQ16	-0.36	-0.34	-0.34	-	0.45	0.39	-0.42	-0.40
RPQCog	-	-	-	-	-	-	-	-
RPQEmo	-0.37	-0.35	-0.42	-	0.40	0.35	-0.41	-0.39
RPQSom	-	-	-	-	0.39	-	-0.35	-
BDItotal	-0.55	-0.52	-0.52	-0.38	0.46	0.49	-0.50	-0.66
BDIcog	-0.55	-0.52	-0.50	-0.38	0.54	0.49	-0.49	-0.63
BDIncog	-0.46	-0.43	-0.43	-	0.33	0.40	-0.42	-0.56
State Anx	-0.41	-0.47	-0.38	-0.36	0.49	0.42	-0.39	-0.48
Trait Anx	-	0.50	0.36	0.40	-0.39	-0.43	-	0.55
Fatigue	-	-	-0.33	-0.33	-	-	-	-0.42
Cog Func	-	-	-	-	-	-	-	-
Emot Dsyf	-	-0.40	-0.34	-	-	0.40	-	-0.48
AffW-B	0.42	0.40	0.46	-	-0.39	-0.46	-0.39	0.47
Sleep	-0.36	-0.43	-0.37	-0.46	-	0.35	-	-0.55
PSR	-	-	-	-	-	-	-	0.37
SSR	-	-	-	-	-	-	-	0.39

RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities, ACC: Accuracy, OE: Omission Errors, CE: Commission Errors, D': dprime, Inf: Infrequent Response Condition, Frq: Frequent Response Condition.
- Correlation $p > 0.05$

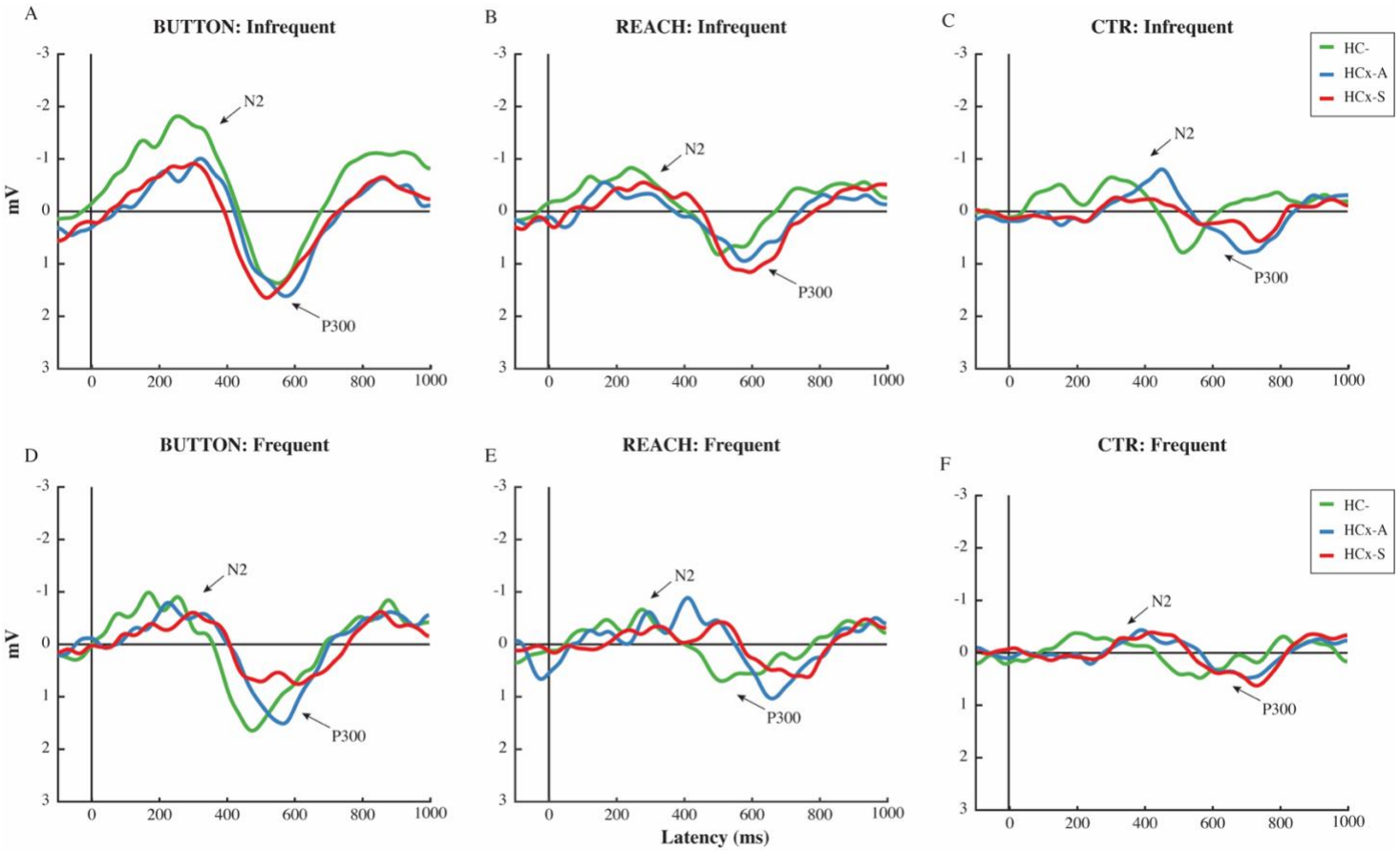

Figure 6.4. Group Average ERP Waveforms. Average ERP waveforms computed for BUTTON (A,D), REACH, and CTR (C,F) task variants. Waveforms are presented for HC- (green), HCx-A (blue), and HCx-S (red) for both response infrequent (top) and response frequent (bottom) within each task variant.

Analysis of peak P300 amplitude revealed a significant interaction ($F[2,43] = 4.5$; $p = 0.01$; $\eta_p^2 = 0.08$). A simple main effect for task condition was found within the HCx-S group ($t[14] = 5.34$; $p < 0.001$). HCx-S individuals demonstrated significantly smaller peak P300 amplitude in the response frequent condition ($m = 1.2mV \pm 0.5$) compared to the response infrequent condition ($m = 2.2mV \pm 0.6$). A simple main effect for group was also observed ($F[2,43] = 7.2$; $p = 0.001$; $\eta_p^2 = 0.12$). Bonferroni corrected multiple comparisons revealed HCx-S individuals demonstrated a significantly smaller P300 peak (est. $m = 1.7mV \pm 0.1$) compared to HC- (est. $m = 2.3 \pm 0.1$; $p = 0.001$). Additionally, analyses revealed a significant interaction for P300 latency ($F[2,43] = 7.23$; $p = 0.001$; $\eta_p^2 = 0.13$). A simple main effect for task condition was found within the HC- group ($t[17] = 4.8$; $p < 0.001$). HC- individuals demonstrated significantly delayed P300 latency within response infrequent condition ($m = 542.7ms \pm 38.9$) compared to the response frequent condition ($m = 487.8ms \pm 43.1$). A trend for a significant simple main effect for task was alsoobserved for HCx-S individuals ($t[14] = 2.1$; $p = 0.05$). HCx-S individuals demonstrated shorter P300 latency within the response infrequent condition ($m = 513.3ms \pm 84.4$) compared to the response frequent condition ($m = 563.7ms \pm 74.6$). A simple main effect for group was also observed ($F[2,43] = 7.0$; $p = 0.001$; $\eta_p^2 = 0.12$). Bonferroni corrected multiple comparisons revealed that across task conditions HCx-A individuals demonstrated a significantly delayed P300 latency (est. $m = 569.1ms \pm 11.0$) compared to HC- (est. $m = 515.2ms \pm 9.3$; $p = 0.001$).

Associations with several self-reported measures of symptom burden were observed with BUTTON indices of neuroelectric function (Table 6.7).

Table 6.7. Correlation Coefficients: Go/NoGo Neuroelectric Function (BUTTON) and Symptom Burden.

	Inf N2peak	Frq N2peak	Inf N2latn	Frq N2latn	Inf P3peak	Frq P3peak	Inf P3latn	Frq P3latn
RPQ16	-	0.39	-	-	-	-0.50	-	-
RPQCog	-	-	-	-	-	-0.41	-0.48	-
RPQEmo	-	-	-	-	-	-0.48	-0.41	-
RPQSom	-	0.45	-	-	-	-0.61	-	-
BDItotal	-	-	-	-	-	-	-	-
BDIcog	-	0.46	-	-	-	-0.52	-	-
BDIncog	-	-	-	-	0.39	-	-	-
State Anx	-	-	-	-	-	-	-	-
Trait Anx	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-	-
Cog Func	-	-	-	-	-	0.48	0.42	-
Emot Dsyf	-	-	-	-	-	-	-	-
AffW-B	-	-	-	-	-	-	-	-
Sleep	-	-	-	-	-	-	-0.42	-
PSR	-	-	-	-	-	-	0.55	-
SSR	-	-	-	-	-	-	-	-

RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities, N2latn: N2 peak latency, N2peak: N2 peak amplitude, P3latn: P300 peak latency, P3peak: P300 peak amplitude, Inf: Infrequent Response Condition, Frq: Frequent Response Condition.
- Correlation $p > 0.05$

Discrete Reach.

Analysis of N2 latency revealed a significant interaction ($F[2,42] = 3.4$; $p = 0.04$; $\eta_p^2 = 0.07$). A significant simple main effect for task condition was observed for HC- individuals ($t[17] = -2.2$; $p = 0.04$). HC- individuals demonstrated significantly longer N2 latencies within the response frequent condition (m = 276.2ms ± 45.5) compared to the response infrequent conditions (m = 240.7ms ± 61.3). Additionally, a simple main effect for task condition was observed for the HCx-A group ($t[12] = -2.9$; $p = 0.01$). HCx-A individuals demonstrated significantly longer N2 latencies within the response frequent condition (m = 315.4ms ± 104.9) compared to the response infrequent conditions (m = 223.4ms ± 79.6). No simple main effect of group was observed.

Analysis of P300 amplitude revealed a significant interaction ($F[2,42] = 3.5$; $p = 0.03$; $\eta_p^2 = 0.07$). A significant simple main effect for task condition was observed for HCx-S individuals ($t[13] = 3.7$; $p = 0.003$). HCx-S individuals demonstrated significantly smaller P300 peak amplitude in the response frequent condition (m = 1.0mV ± 0.3) compared to the response infrequent condition. No simple main effect of group was observed.

Analysis of P300 latency revealed a significant interaction ($F[2,42] = 5.5$; $p = 0.006$; $\eta_p^2 = 0.05$). A simple main effect for task condition was observed for HCx-A individuals ($t[12] = -2.9$; $p = 0.01$). HCx-A individuals demonstrated significantly longer P300 latencies in the NOGO condition (m = 624.6 ± 62.2) compared to the response infrequent condition (m = 537.5ms ± 99.3).Similarly, a simple main effect for task condition was observed for HCx-S individuals ($t[13] = -8.37$; $p < 0.001$). HCx-S

individuals demonstrated significantly longer P300 latencies in the response frequent condition (m = 730.3 ± 54.4) compared to the response infrequent condition (m = 590.3ms ± 48.6). A simple main effect for group was also observed ($F[2,42] = 37.4$; $p < 0.001$; $\eta_p^2 = 0.36$). Bonferroni corrected multiple comparisons revealed that across task conditions HCx-S individuals demonstrated significantly delayed P300 latencies (est. m = 660.3ms ± 12.4) compared to both HC- (est. m = 517.7ms ± 10.9; $p < 0.001$) and HCx-A (est. m = 581.1ms ± 12.8; $p < 0.001$). Additionally, across task conditions, HCx-A individuals demonstrated significantly delayed P300 latencies compared to HC- ($p < 0.001$).

Associations with several self-reported measures of symptom burden were observed with REACH response frequent indices of neuroelectric function (Table 6.8). No associations were observed with indices of REACH response infrequent neuroelectric function.

Continuous Reach.

Analysis of N2 latency revealed a significant interaction ($F[2,45] = 3.2$; $p = 0.04$; $\eta_p^2 = 0.05$). A significant simple main effect for task condition was observed for HC- individuals ($t[17] = 3.04$; $p = 0.008$). HC- individuals demonstrated significantly longer N2 latencies within the GO condition (m = 295.3ms ± 60.0) compared to the GO conditions (m = 226.2ms ± 77.8). A simple main effect for group was also observed ($F[2,45] = 10.5$; $p < 0.001$; $\eta_p^2 = 0.18$). Bonferroni corrected multiple comparisons revealed that across task conditions HCx-S individuals demonstrated significantly delayed N2 latencies (est. m = 314.1ms ± 12.0) compared to HC- (est. m = 260.8ms ± 11.3; $p = 0.005$). Additionally, HCx-A individuals demonstrated significantly delayed N2 latencies (est. m = 336.5ms ±

Table 6.8. Correlation Coefficients: Go/NoGo Neuroelectric Function (REACH) and Symptom Burden.

	Inf N2peak	Frq N2peak	Inf N2latn	Frq N2latn	Inf P3peak	Frq P3peak	Inf P3latn	Frq P3latn
RPQ16	-	0.41	-	-	-	-0.41	-	0.46
RPQCog	-	0.46	-	-	-	-0.43	-	-
RPQEmo	-	-	-	-	-	-	-	-
RPQSom	-	-	-	-	-	-	-	0.52
BDItotal	-	-	-	-	-	-	-	-
BDIcog	-	-	-	-	-	-	-	-
BDIncog	-	-	-	-	-	-	-	-
State Anx	-	-	-	-	-	-	-	-
Trait Anx	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-	0.51
Cog Func	-	-0.40	-	-	-	0.39	-	-0.62
Emot Dsyf	-	-	-	-	-	-	-	-
AffW-B	-	-	-	-	-	-	-	-
Sleep	-	-	-	-	-	-	-	-
PSR	-	-	-	-	-	-	-	-
SSR	-	-	-	-	-	-	-	-

RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities, N2latn: N2 peak latency, N2peak: N2 peak amplitude, P3latn: P300 peak latency, P3peak: P300 peak amplitude, Inf: Infrequent Response Condition, Frq: Frequent Response Condition.
- Correlation $p > 0.05$

13.3) compared to HC- ($p < 0.001$). No differences were observed between HCx-S and HCx-A groups.

Analysis of P300 latency failed to reveal any significant interactions. However, a main effect for group was observed ($F[2,45] = 49.5$; $p < 0.001$; $\eta_p^2 = 0.52$). Bonferroni corrected multiple comparisons revealed that across task conditions HCx-S individuals demonstrated significantly longer P300 latencies (est. m = 695.8ms ± 13.7) compared to HC- (est. m = 522.2ms ± 12.9; $p < 0.001$). Similarly, HCx-A individuals demonstrated significantly longer P300 latencies (est. m = 672.5ms ± 15.2) compared to HC- ($p < 0.001$). No differences were observed between HCx-S and HCx-A groups.

Associations with several self-reported measures of symptom burden were observed with CTR indices of neuroelectric function (Table 6.9).

DISCUSSION

The present study set out to compare behavioral performance and indices of neuroelectric function within three different response variants of a Go/NoGo task (discrete button press, discrete reach, and continuous reach) among HCx-A and HCx-S individuals, compared to HC-. The results of the current study demonstrate that HCx-S individuals consistently demonstrate behavioral deficits in all three task variants, regardless of task condition. Similarly, these behavioral deficits are accompanied by neurological dysfunction indexed by both N2 and P300 ERP components. While HCx-A individuals did not demonstrate any significant behavioral deficits compared to HC-, they demonstrated significant alterations in neuroelectric function.

Table 6.9. Correlation Coefficients: Neuroelectric Function (CTR) and Symptom Burden.

	Inf N2peak	Frq N2peak	Inf N2latn	Frq N2latn	Inf P3peak	Frq P3peak	Inf P3latn	Frq P3latn
RPQ16	-	-	-	-	-	-	-	-
RPQCog	-	-	-	-	-0.37	-	-	-
RPQEmo	-	-	-	-	-	-	-	-
RPQSom	-	-	-	-	-	-	-	-
BDItotal	-	-	-	-	-	-	-	-
BDIcog	-	-	-	-	-	-	-	-
BDIncog	-	-	-	-	-	-	-	-
State Anx	-	-	-	-	-	-	-	-
Trait Anx	-	-	-	-	-	-	-	-
Fatigue	-	-	-0.41	-	-	-	-	-
Cog Func	-	-	-	-	0.46	-	-	-0.41
Emot Dsyf	-	-	-	-	-	-	-	-
AffW-B	-	-	-	-	-	-	-	-
Sleep	-	-	-0.41	-	-	-	-	-
PSR	-	-	-	-	-	-	-	-
SSR	-	-	0.47	-	-	-	-	-

RPQ: Rivermead Post-Concussion Questionnaire, RPQCog: Rivermead Post-Concussion Questionnaire – Cognitive domain, RPQEmo: Rivermead Post-Concussion Questionnaire – Emotional subscale, RPQSom: Rivermead Post-Concussion Questionnaire – Somatic subscale, BDI: Beck's Depression Index II, SAI: State Anxiety, TAI: Trait Anxiety, Cog Func: Cognitive Function, EmoDys: Emotional Dysregulation, AffW-B: Affect & Well-Being, PSR: Participation in Social Roles & Activities, SSR: Satisfaction with Social Roles & Activities, N2latn: N2 peak latency, N2peak: N2 peak amplitude, P3latn: P300 peak latency, P3peak: P300 peak amplitude, Inf: Infrequent Response Condition, Frq: Frequent Response Condition.
- Correlation $p > 0.05$

Previous research has demonstrated that individuals with a history of concussion experience persistent deficits in cognitive control and attention.[7, 65, 66, 120, 144, 377, 378] These deficits have been characterized as decrements in task performance,[54, 66, 297, 310] lapses in attentions (i.e., increased omission errors),[171, 379, 380] and difficulties in impulse control.[381, 382] The current study further supports these findings and demonstrates that in tasks of higher cognitive load and complexity behavioral deficits are exacerbated. The latter further highlights the importance of assessing concussed individuals under periods of acute mental and physical stress when determining readiness to return to sport or full vocational participation.

Previous research has also demonstrated persistent deficits in neuroelectric function following concussive injuries.[7, 101, 114, 292, 297-299, 309, 383] The N2 ERP waveform indexes conflict arising from choice decision making. Whereas the P300 ERP waveform represents attentional resource allocation associated with stimulus evaluation. The results of the present study further support the aforementioned findings as both HCx-A and HCx-S individuals demonstrated abnormal N2 and P300 component profiles. Furthermore, HCx-A and HCx-S groups demonstrated distinct neuroelectric deficits, which were most pronounced in the CTR variant. This finding replicates results reported by Sicard and colleagues,[302] which suggested that slow-to-recover athletes (i.e., symptomatic) and asymptomatic athletes with a history of concussion demonstrated significant deficits in P300 peak latency compared to non-injured controls. They similarly found that slow-to-recovery athletes also demonstrated significant reductions in P300 peak amplitude. Together with the findings of the present study suggest atypical recovery in neurological function may underlie persistent symptoms and deficits following concussions.

The present study observed significant relationships between cognitive dysfunction and self-reported measures of symptom burden. Few, meaningful associations were observed in either the BUTTON or REACH variants of the task. However, in the CTR variant, variant with the greatest cognitive load, we observed several significant associations. Generally, individuals with greater cognitive deficits reported worse symptom burden on the RPQ, greater feelings of depression, and worse outcomes on the Neuro-QoL. This supports the premise of utilizing more ecologically valid tasks, as these more readily simulate the difficulties individuals have in their everyday lives.

Limitations

The present study is not without its limitations. First, the present study utilized a small sample size. The small sample size possibly limited our ability to detect significant group differences. Second, the sample consisted of predominately female participants. We attempted to account for this discrepancy by including biological sex as a covariate in all statistical models. Future studies should aim to incorporate more balanced samples to account for possible sex differences. Additionally, while not significantly different, averages days since injury within the HCx-A group is almost double the HCx-S group. There was no association between days since injury and any of our measures of task performance or neuroelectric indices. Future studies should aim to better match on this variable to reduce the potential confounding influence. Finally, in stimulus-locked ERP analyses it is vital to have accurate time stamps corresponding to stimulus appearance. In a continuous task where objects are continuously appearing and moving stimulus "appearance" estimates become difficult. The present study aimed to minimize this issue

by only having one object on the screen at a time. Future studies can potentially circumvent this issue with integrated eye tracking systems.

Conclusion.

In summary, the present study further demonstrates that individuals with a history of concussion exhibit persistent deficits in neurological function. Furthermore, symptomatic individuals exhibited worse deficits in neurological function accompanied by significant deficits in cognitive performance in all variants of the Go/NoGo task. Importantly, these deficits were more pronounced in the CTR task variant. Additionally, performance deficits in the CTR task more strongly related to self-reported symptoms and concussion burden. Findings from this study highlight that chronic concussion-related symptomology reflects abnormal recovery of neurological function. It also suggests that behavioral measures of cognitive function collected during more ecologically valid tasks may serve as reliable biomarkers of recovery following concussive injuries. By establishing reliable and objective biomarkers of neurological recovery, we can begin to effectively test and implement rehabilitative interventions aimed at alleviating specific deficits.

CHAPTER 7

GENERAL DISCUSSION

Concussive brain injuries represent a growing public health crisis. As we begin to understand the long-term impact of these injuries on neurological function, we see these are not the mild and transient injuries they were once thought to be. However, our understanding of the neurophysiological recovery patterns following injury is limited. This restricts our ability to accurately diagnose concussions and our ability to accurately track recovery. With the rising prevalence of PPCS and other long-term conditions such as CTE, there is a critical need for diagnostic and prognostic biomarkers of injury.[77, 384]

One of the biggest barriers in the clinical management of concussion is the lack of a direct measurement of neurological function. By relying on biased and insensitive assessments that indirectly estimate neurological function, we may fail to identify subtle indicators of neurological dysfunction.[122-124, 369] These place patients at an increased risk for subsequent injuries and the development of long-term deficits.[8, 103, 104, 294] The inclusion of psychophysiological assessment techniques in the clinical assessment of concussion may help overcome some of these pitfalls. Psychophysiological techniques such as EEG or pupillometry allow for the quantification of neurological function by taking advantage of the relationship between fluctuations in physiological signals (i.e., pupil size, neuroelectric activity) and psychological behavior. Additionally, these techniques can be monitored in real time allowing for the detection of abnormal patterns at rest or during task execution. The objective of the current investigation was to implement pupillometric and EEG techniques to identify neurological deficits associated with PPCS.

In the first aim of the experiment, we investigated the impact of concussion recovery on gaze behavior and task-evoked pupil dynamics in an interleaved variant of the Anti-/Pro-saccade task. Comparing all three groups, we observed non-significant trends indicating that symptomatic individuals may exhibit issues in oculomotor control. Eye movements are controlled by interactions among subcortical brain regions , and areas within the frontal and parietal cortex.[180, 348] Coincidentally, these brain regions are commonly impacted by concussions.[59, 70, 385] Furthermore,

we observed non-significant trends in task-evoked pupil dynamics. The observed patterns suggest that individuals with a history of concussion exhibited heightened levels of pupillary constriction following the appearance of the central fixation cue. This increased pupil constriction resulted to smaller degrees of stimulus evoked pupil dilation, which has been linked to task-based arousal. Pupillary dynamics are tightly controlled by interactions between the sympathetic (dilation) and parasympathetic (constriction) nervous systems. They also receive modulatory input from higher order brain regions within the frontal cortex.[314, 386] These brain regions work together to prime the body to adapt to dynamically changing environments.[312, 387, 388] The observed pattern of deficits within symptomatic individuals may indicate difficulty regulating neurological systems to meet situational demand.

In the second and third aim of the experiment, we wanted to observe the impact of concussion recovery on cognitive performance during a continuous task paradigm. First, in the second aim, we needed to validate ERPs of situational conflict monitoring (N2) and attention (P300) during continuous task performance in healthy controls. We found that compared to a traditional discrete button press task, discrete reach and continuous reach variants resulted in N2 and P300 with smaller peak amplitudes but no difference in peak latencies. Reaching movements require significantly greater levels of motor planning and coordination.[389] The need to re-distribute cognitive resources to other cognitive processes necessary for reaching compared to thumb press actions may explain the observed reductions in ERP amplitudes. These results suggest that discrete tasks may be best suited for investigations of specific cognitive processes using ERP analyses.

In the third aim, we set out to investigate the impact of concussion recovery on cognitive performance using the task paradigms established in aim 2. We observed that in all three task variants (BUTTON, REACH, CTR) symptomatic individuals demonstrated significant deficits in task performance. Furthermore, compared to non-injured controls these deficits were most pronounced in the more dynamic and complex CTR task variant. This in line with previous research

that has shown increased physical and cognitive demand elicits latent symptoms and deficits in neurological function.[32, 316, 390] When analyzing neuroelectric activity, we similarly observed consistent deficits in task related indices of stimulus-response conflict (N2) and allocation of attentional resources (P300) among individuals with a history of concussion. Based on the results of experiment two we are unable to compare across task variants. However, within each variant individuals with a history of concussion demonstrated increased peak P300 latency, suggesting delayed stimulus classification. Interestingly, in the BUTTON variant while both history of concussion groups demonstrated increased P300 latency only symptomatic individuals exhibited reduced P300 peak amplitude. These results further suggests that concussion results in lingering deficits in neuroelectric function.[142, 144, 378, 383, 391] However, slow-to-recover individuals with PPCS demonstrate unique patterns possibly indicative of impeded recovery.[302, 385]

Overall, we observed that persistent deficits associated with PPCS are indicative of atypical patterns of neurological recovery following injury. It is important to identify these slow-to-recover individuals before their condition progresses into a chronic issue or more severe neurological degeneration. Psychophysiological assessments directly quantify specific deficits in neurological function and appear sensitive enough to detect lingering deficits. Additionally, incorporating dynamic and complex tasks mimicking real-world behaviors exacerbates behavioral performance deficits. Finally, neuroelectric indices and continuous task performance measures were correlated with generalized self-reported symptom burden suggesting these measures may serve as more objective indicators of concussion-related deficits. Future research is needed to further investigate these relationships. However, this research helps emphasize the need for objective biomarkers that can be used to quantify concussion recovery status and provides supports the use of psychophysiological measures to accomplish this.

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