The persistent effects of concussion on neuroelectic indices of attention

Steven P. Broglio, PhD, ATC
Mathew B. Pontifex
Philip O'Connor
Charles H. Hillman, PhD

University of Illinois at Urbana-Champaign
Department of Kinesiology and Community Health

Corresponding Author
Steven P. Broglio, PhD, ATC
906 S Goodwin Ave
Urbana, IL 61801
217.244.1830 - office
217.244.7322 - fax
broglio@illinois.edu

ABSTRACT

Mild traumatic brain injuries (mTBI) that result from participation in sports are a major public health issue affecting 1.6 to 3.8 million individuals annually. The injury has been postulated as transient and void of long term consequences when rapidly diagnosed and properly managed. Emerging evidence however, has suggested an increased risk for late life cognitive dysfunction in those with previous injuries. The purpose of this investigation was to evaluate young adults with and without a history of concussion using a standard clinical assessment and highly sensitive electrophysiological measures for persistent changes in cognitive functioning. Ninety participants (19.7+1.3 yrs: 44 without mTBI and 46 with previous mTBI) were evaluated using the ImPACT and event-related brain potentials (ERPs) that were recorded during a three stimulus oddball task. Those with a history of concussion reported an average of 3.4 years post-injury. No significant differences were found between groups on the ImPACT. Significant decrements in the N2 and P3b amplitudes of the stimulus-locked ERP were noted for those with a history relative to those without a history of concussion. Although the previously concussed participants performed equal to those without injury on the clinical cognitive assessment, these findings support the notion that sport mTBI can no longer be thought of as a transient injury resulting in short-lived neurological impairment. It is not clear if these persistent deficits will manifest into clinical pathologies later in life.

Key Words: mild traumatic brain injury, electroencephalogram (EEG), event-related potentials (ERP), P3, N2, novelty oddball

INTRODUCTION

Mild traumatic brain injury (mTBI), or concussion, has been defined as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces(Aubry M et al, 2002)." In the acute stage of injury, decrements in cognitive functioning, postural control, and increases in concussion-related symptoms are clearly evident(Broglio SP and Puetz TW, 2008). In most individuals, these impairments resolve spontaneously within seven to ten days of injury(Aubry M et al, 2002;Delaney JS et al, 2002;McCrea et al, 2003). The athletic environment offers the unique advantage for evaluating mTBI because it affords the opportunity to collect pre-injury evaluation (i.e., a baseline) information on a group with a known injury rate. In most instances, several measures of post-concussion injury rapidly return to normal operative levels in the post-morbid state, with concussed individuals returning to the pre-morbid level of functioning within a few days of the injury. For instance, 95% of concussed colligate-level soccer and football athletes no longer report concussion-related symptoms within seven days of injury(Delaney JS et al, 2002). Similarly, McCrea et al. (McCrea et al, 2003) reported a return to baseline levels of postural control and cognitive functioning in a comparable cohort within five and seven days of concussion diagnosis, respectively.

Despite the rapid resolution from concussion on functional performance measures, the potential for persistent effects has yet to be fully elucidated. In young adults reporting zero, one, two, or two or more previous injuries, a pencil and paper evaluation of cognitive functioning indicated no difference between those with and without an injury history. (Guskiewicz KM et al, 2002). Furthermore, computer-based assessments of cognitive functioning have demonstrated no measurable differences in

previously concussed and non-concussed high school and university athletes reporting one or two previous concussions(Iverson GL et al, 2006b). Similarly, Australian rules football players with up to four injuries demonstrated no measurable deficits in cognition(Collie A et al, 2006). These findings may be limited by the testing instruments, which might lack the necessary sensitivity to detect subtle cognitive decrements in the post-acute stage of injury (Broglio SP et al, 2006). Further, concussion-related cognitive dysfunction may occur on a covert level relative to overt behavioral measures (i.e., RT, response accuracy), or may not be apparent until later in life.

A recent investigation evaluated the persistent effects of concussion in a group of retired athletes reporting multiple injuries across their careers. In a sample of former professional football athletes, those reporting at least three concussions during their athletic career displayed a five-fold increase in diagnosed mild cognitive impairment and a three-fold increase in self-reported memory problems compared to a subset of non-concussed former athletes(Guskiewicz et al, 2005). These findings suggest a disconnect between the apparent transient nature of concussive injuries in young adults and the presence of cognitive dysfunction in later life.

Accordingly, implementing sensitive instrumentation with the ability to detect subtle, covert changes in cognitive functioning may clarify this apparent discrepancy. Specifically, electroencephalograms (EEG) have been extensively used to examine electrical activity associated with brain function; however, their use to investigate the impact of concussion on cognition has been limited. One particular aspect of EEG, known as event-related brain potentials (ERPs), has been useful in providing insight into

the underlying neural processes involved in cognitive function beyond that of overt behavioral measures. ERPs reflect patterns of voltage change in ongoing neuroelectric activity that occurs in response to, or in preparation for, a stimulus or response.

The P3 component of a stimulus-locked ERP has been especially well studied with regard to alterations in cognitive function related to development(Ridderinkhof KR and van der Stelt O, 2000), aging (Polich J, 1996), health behaviors (e.g., (Hillman CH et al, 2005)), and clinical pathology(Knight RT, 1984). The P3 is a large positive-going component that appears approximately 300 to 800 ms following stimulus onset and reflects attentional processes, which are indexed by the P3a and P3b subcomponents, each of which has a unique scalp distribution. These components represent related but distinct neuroelectric processes that are distinguished based upon the context in which they occur. That is, different stimulus environments elicit activation of the P3a and P3b leading to modulation of the component amplitude. The P3a is typically elicited by an infrequent and uninstructed novel stimulus. This component is characterized by a fronto-central topographic maximum and relatively short latency. Alternatively, an instructed yet infrequently presented target stimulus elicits the P3b component that is reflected by topographic maximum amplitude over the parietal cortex(Donchin E et al.,1986;Johnson R, 1993).

Accordingly, the cognitive functions required to process the various stimuli provide a basis for inferring the meaning of the appearance and modulation of the various subcomponents. Specifically, the P3a is thought to reflect the selection of stimulus information associated with attentional orienting to a change in the environment (Knight RT, 1984;Kok A, 2001), such that this component reflects the disengagement of

attentional focus from one aspect of the stimulus environment and the reengagement toward another aspect of the environment(Squires NK et al, 1975). As such, P3a amplitude is thought to represent attentional orienting with larger amplitude indicative of greater focal attention(Polich J, 2007). Alternatively, the P3b is theorized to index processes associated with the allocation of attentional resources during cognitive operations involved in the updating of working memory(Donchin E, 1981;Donchin E and Coles MGH, 1988). Thus, P3b amplitude is sensitive to the amount of attentional resources allocated toward a stimulus(Polich J, 1987;Polich J and Heine MRD, 1996). P3b latency is sensitive to stimulus classification speed (Duncan-Johnson CC, 1981;Kutas M et al, 1977). Accordingly, P3b latency is thought to reflect stimulus detection and evaluation time (Ilan AB and Polich J, 1999;Magliero A et al, 1984), independent of response selection and behavioral action (Verleger R, 1997).

Emerging just prior to the P3 is a smaller negative-going component known as the N2. Relative to P3, the meaning of this component is somewhat tenuous, as multiple N2 components have been identified in the literature (see (Folstein JR and Van Petten C, 2008) for review), some of which have unique topographies and others of which overlap in their topography. With regard to the P3, a discernable N2 with a fronto-central maximum occurs just prior to the P3a, and a disparate N2 with a parietal maximum precedes a P3b. In response to uninstructed, novel stimuli, the fronto-central N2 has been linked to deviance or mismatch of a stimulus from a mental template, or an increase in cognitive control over response inhibition (Folstein JR and Van Petten C, 2008). In response to infrequent, target stimuli the parietally occurring N2 has been associated with

the amount of attention required to process stimuli in the visual cortex (during visual tasks).

Changes in the neuroelectric system have been documented in the acute and immediate post-acute stages of mTBI. For example, following a sport-related concussion diagnosis, deficits in P3 (i.e., P3b) amplitude were noted in symptomatic (1.7 months post-injury) athletes when compared to asymptomatic (9.75 months post-injury) and a non-concussed group (Dupuis F et al, 2000). Others have reported a delayed P3 response in both symptomatic and asymptomatic athletes when compared to control participants despite all groups performing normally on a clinical cognitive evaluation (Gosselin N et al, 2006). Further, Gaetz and colleagues (Gaetz M et al, 2000) reported a linear relationship between the number of concussions sustained (up to three) and P3 latency approximately one year post-injury. Taken together, these investigations provide evidence indicating that mTBI sustained from athletic endeavors may have a persistent effect on cognitive functioning up to one year post-injury. The persistence of these deficits beyond one year is not clear.

As such, we hypothesize that young adults reporting a history of concussion would demonstrate persistent changes in cognitive functioning detectable through highly sensitive measures of brain functioning such as ERPs, but not on standard clinical measures of functional cognitive performance. Specifically, we predicted a decrease in the amplitude and an increase in the latency of the P3a and P3b components, indicating prolonged deficits in the orienting of focal attention, the allocation of attentional resources, and cognitive processing speed, respectively. We further predicted that N2 amplitude would be sensitive to concussion history, with decreased amplitude of N2

indicating prolonged deficits in the attentional system. Given the intended design of the ImPACT to assess acute deficits in concussion-induced cognition, we predicted no such differences based on concussion history.

METHODS

Male and female young adults aged 18 to 25 years participating in organized ice hockey, rugby, soccer, judo, and track participated in the study. Each subject provided written informed consent prior to testing. Testing consisted of a single three hour session in which the participant completed the following evaluations: health history and demographics screening indicating no neurological disorders, cardiovascular disease, or any medications that influence central nervous system function. All participants had normal or corrected vision based on the minimal 20/20 standard. Each participant completed the Edinburgh Handedness Inventory (Oldfield RC, 1971) and had their body mass index calculated from their height and weight measured using a stadiometer and a Tanita BWB-600 digital scale, respectively. The Kaufman Brief Intelligence Test (K-BIT; (Kaufman AS et al.,1990)) was then administered to estimate intelligence quotient. Functional cognitive performance was evaluated using the ImPACT inventory. The participant was then fitted with a 64-channel Quik-cap (Compumedics Neuroscan, El Paso, TX), provided instructions for completing the novelty oddball task and given 20 practice trials. Upon completion of the task, participants were informed of the purpose of the experiment and received $30 remuneration for their participation.

ImPACT: The ImPACT (ImPACT Applications, Pittsburgh, PA, version 5.6.724) consists of two segments. The first is a brief demographic questionnaire and symptom report, which is followed by six modules that evaluate functional cognitive performance

indexed by scores of verbal memory, visual memory, processing speed, and reaction time. The test has been widely applied in a number of sports settings to evaluate for cognitive dysfunction following mTBI (Iverson GL et al, 2006a;Lovell et al, 2003;McClincy MP et al, 2006;Pellman EJ et al, 2006). The verbal memory score is the average percent correct for a word recognition task, a symbol-number matching task, and a letter recall task. The visual memory score is the average percent correct scores for two tasks; an abstract line drawings memory task and a memory task requiring the identification of a series of Xs and/or Os after an interference task (counting down from 25 to 1 on random grid). The reaction time score is the average response time (in milliseconds) on a choice reaction time task, a go/no-go task, and the symbol-number matching task. The processing speed composite represents the weighted average of three interference tasks for the memory paradigms.

Novelty Oddball Task: A visual three-stimulus oddball task had participants respond as quickly and accurately as possible with a right hand thumb press only to a randomly occurring, infrequent target stimulus while ignoring all other stimuli(Knight RT, 1997). Target stimuli were 5 cm tall white triangles that occurred with a probability of 0.12, and non-target stimuli were 5 cm tall inverted white triangles that occurred with a probability of 0.76. In addition to the target and non-target stimuli, novel stimuli (e.g., dog, airplane, coffee mug) comprised of simple white line drawings were also presented with a probability of 0.12. Three counterbalanced blocks of 300 trials were presented focally on a computer monitor at a distance of 1m. All stimuli were presented on a black background for a 100 ms duration, with a 1000 ms response window and a 2000 ms inter-trial interval.

ERP Recording

Data Collection: Electroencephalographic (EEG) activity was recorded from 64 electrode sites (FPz, Fz, FCz, Cz, CPz, Pz, POz, Oz, FP1/2, F7/5/3/1/2/4/6/8, FT7/8, FC3/1/2/4, T7/8, C5/3/1/2/4/6, M1/2, TP7/8, CB1/2, P7/5/3/1/2/4/6/8, PO7/5/3/4/6/8, O1/2) of the International 10-20 system(Jasper HH, 1958), using a Neuroscan Quik-cap, referenced to averaged mastoids (M1, M2), with AFz serving as the ground electrode, and impedance < 10kΩ. Additional electrodes were placed above and below the left orbit and on the outer canthus of each eye to monitor electro-oculographic (EOG) activity with a bipolar recording. Cognizant that eye movement artifacts may confound interpretation of the data, our analyses yielded an average of 68.6 (SE = 6.4) blinks per task in the concussion history group and 73.8 (SE = 8.25) blinks per task in the non-concussed group [$t(64) = 4.23$, $p = .423$]. The finding of no difference between group eye movements led us to conclude this variable did not skew data interpretation.

Continuous data were digitized at a sampling rate of 500 Hz, amplified 500 times with a DC to 70 Hz filter, and a 60 Hz notch filter using a Neuroscan Synamps 2 amplifier(2003).

Data Reduction: Reduction of the EEG data was completed with Neuroscan Edit software(2003). Averaged mastoid-referenced continuous data were corrected for eye movement artifacts using spatial filtering. Epochs from 100 ms pre-stimulus to 1000 ms post-stimulus were created and baseline corrected using the 100 ms pre-stimulus period. Data were filtered using a 30 Hz (24 dB/octave) low-pass filter and artifact detection excluded trials containing amplitude excursions of ±75 μV. The N2 component was defined as the largest negative-going peak occurring between 150-300 ms. The P3

components were defined as the largest positive-going peaks occurring within 300-700 ms. Amplitude was measured as the difference between the mean pre-stimulus baseline and maximum peak amplitude; peak latency was defined as the time point corresponding to the maximum amplitude. Trials were then averaged for each participant based on task condition. Each participant's condition-averaged data was outputted in ASCII format for statistical analysis.

Statistical Analysis: All statistical analyses were completed using SPSS version 14.0 (SPSS, Inc, Chicago, IL) and statistical significance was noted when $p < 0.05$. Between group differences in demographic variables (e.g. age, IQ, and years of education) were evaluated using independent samples t-tests.

ImPACT: Output variables (verbal memory, visual memory, processing speed, and reaction time) were generated through automated algorithms embedded within the program. Box's test was implemented to evaluate violations to the assumption of covariance matrix homogeneity. Group performance differences in cognitive variables were then evaluated using a multivariate analysis of variance (MANOVA). This statistical technique was selected as the ImPACT output variables are thought to collectively represent cognitive functioning(Broglio SP et al, 2006). An independent samples t-test was conducted to evaluate differences in the total number of symptoms endorsed by the participants.

ERPs: Statistical analyses were performed using 4 midline electrode sites (Fz, Cz, Pz, Oz). ERP component values (i.e., amplitude, latency) for each participant were submitted to a 2 (Group: concussed and non-concussed) × 4 (Site: Fz, Cz, Pz, Oz) repeated measures MANOVA for each condition (i.e., target, novel). RT and response

accuracy data were analyzed using independent t-tests for group. Post hoc comparisons were conducted using Tukey's honestly significant difference (HSD) tests.

RESULTS

A total of 90 young adults (65 male, 25 female: 19.71±1.27yrs, 26.1±3.6 BMI) free from injury at the time of testing completed this investigation. Participants were separated into groups (0 and 1+) based on their self-report of physician diagnosed concussions.

ImPACT Assessment

Group demographics and ImPACT scores are provided in Table 1. Non-significant differences were noted between groups for demographic measures ($p>0.05$), with the exception of age ($t(88) = 2.43$, $p = .02$), as those with a history of concussion were slightly older than those without previous injury. This single demographic difference was deemed negligible in our homogenous, young adult population and was therefore not considered further. Analysis of the ImPACT scores indicated homogeneity of the covariance matrix ($M=13.82$, $F(10, 36850.86) = 1.31$, $p = 0.22$) and no difference in functional cognitive performance between groups ($\Lambda=.994$, $F(4,85)=.118$, $p = 0.976$). No significant differences were found between the number of symptoms reported ($t(88)=0.59$, $p =0.56$).

Novelty Oddball

Task Performance

Table 2 presents the RT and response accuracy data for the novelty oddball task based on concussion history. Results indicated non-significant group differences for either RT, t's $(88) < .08$, $p \geq .94$, or response accuracy, t's $(88) < 1.8$, $p \geq .08$, indicating

that behavioral indices of cognitive performance on this task was not influenced by concussion history.

N2 Amplitude

The omnibus analysis for N2 amplitude during the novel condition indicated significant main effects of Group, $F(1, 88) = 4.2$, $p < .05$; $\varepsilon = .05$, and Site, $F(3, 86) = 32.1$, $p < .001$; $\varepsilon = .53$, which were superseded by a Group × Site interaction, $F(3, 86) = 3.4$, $p = .02$; $\varepsilon = .11$. Decomposition of this interaction indicated larger N2 amplitude for the group without a history of concussion relative to the group with a history of concussion at the Fz (Concussion group: -4.7 ± 4.0 μV; Non-concussion group: -7.5 ± 4.4 μV) and Cz (Concussion group: -4.5 ± 4.9 μV; Non-concussion group: -7.0 ± 5.4 μV) electrode sites, *t*'s (88) ≥ 2.2, $p \leq .03$ (see Figure 1). No such effect was evident at the Pz or Oz electrode sites ($p > .6$). Analyses of the target condition indicated only a Site effect with the N2 maxima occurring over the Fz site, with significantly smaller amplitude at the Pz and Oz sites, t's (90) ≥ 2.5, $p \leq .01$.

N2 Latency

Omnibus analyses for the novel and target conditiond revealed non-significant group differences. The only significant effect was for electrode site during the target condition, $F(3, 86) = 9.2$, $p < .001$; $\varepsilon = .24$, with follow up analyses indicating significantly longer latency at the Fz site relative to the Cz, Pz, and Oz sites, and at the Cz site relative to the Pz site, t's (89) ≥ 2.5, $p \leq .01$.

P3 Amplitude

P3a amplitude analyses for the novel condition indicated a main effect of Site, $F(3, 86) = 61.5$, $p < .001$; $\varepsilon = .68$, which was superseded by a Group × Site interaction, F

(3, 86) = 3.3, $p < .025$; $\varepsilon = .10$. However, decomposition of this interaction did not reveal any significant group differences, t's (88) $\leq$ 1.2, $p \geq .24$. Analyses of the target condition (i.e., P3b) also yielded a main effect of Site, F (3, 86) = 192.7, $p < .001$; $\varepsilon = .87$, which was superseded by a Group × Site interaction, F (3, 86) = 4.5, $p < .01$; $\varepsilon = .13$. Decomposition of the interaction revealed significantly larger P3b amplitude at the Pz electrode site for the group without a history of concussion (20.4 ± .96 μV) relative to the group with a history of concussion (17.6 ± 1.1 μV), t (88) = 2.0, $p < .05$ (see Figure 1).

P3 Latency

Analyses for P3 latency revealed no significant group effects. Site effects were observed for both the novel and target conditions, F's (3, 86) = 5.1, $p < .005$; $\varepsilon = .15$, with follow up analyses indicating short P3 latency at the Oz site relative to the Cz and Pz sites for the novel condition, t's (89) $\geq$ 2.2, $p \leq .03$, and shorter latency at the Fz and Oz sites relative to the Cz and Pz sites for the target condition, t's (89) $\geq$ 2.1, $p \leq .04$.

DISCUSSION

Our findings fail to support the supposition that concussion is a transient injury, void of long term consequences(Aubry M et al, 2002). We found that persistent deficits in the neuroelectric system are present following concussion in young adults three years post-injury, despite normal cognitive performance on a standard clinical assessment. The neuroelectric deficits were noted in the P3b and N2 components during the target and novelty conditions of the three-stimulus oddball task, respectfully. These findings indicate that specific deficits in component cognitive processes occurring between stimulus engagement and response execution in the information processing stream persist following trauma.

Specifically, the P3b is thought to correspond with the allocation of attentional resources in the service of working memory operations once a stimulus has been presented(Donchin E, 1981;Polich J, 2007). P3b amplitude is modulated by target stimuli that are expected, but presented infrequently(Polich J, 2007). The suppressed P3b amplitude in the concussed group may therefore reflect a decreased capacity to allocate attentional resources(Polich J, 1987) compared to the non-concussed group. Recent research by Polich (Polich J, 2007) has theorized that P3 generation might reflect neural inhibition. That is, the amplitude of this component indexes the suppression of extraneous neuronal activity, which is relevant to the engagement of focal attention (P3a) and the allocation of attentional resources towards working memory (P3b). Accordingly, the differential P3b amplitude exhibited by the concussion history group would suggest a failure to inhibit extraneous neural activity in the service of attentional resource allocation necessary for processing the target stimulus. Given that group differences were not evident for the P3a component, the current findings suggest that prolonged deficits in the attentional system are selective to attentional processing. Specifically, reductions in attentional orienting were not observed for the concussion history group, as measured via P3a amplitude, suggesting that not all attentional systems exhibit long-term deficits.

However, deficits in the neuroelectric system were noted during conditions requiring attentional orienting, as N2 amplitude was smaller in the concussion history group. Based on contemporary theories of the N2 during novel conditions requiring attentional orienting, the current findings suggest that the reduced N2 component for the concussion history group might reflect a deficit in a general alerting system or the mismatch of a novel stimulus with the mental template (based on task instructions). It is

366 also possible that the decreased N2 for the concussion history group reflects a decrease in
367 cognitive control over response inhibition. That is, the N2 during certain tasks (i.e.,
368 Go/NoGo and flanker tasks) has been linked to the inhibition of a prepotent response. In
369 the novelty condition of the three stimulus task implemented here, the N2 may reflect
370 motor inhibition, which has traditionally been considered a component of the orienting
371 response to ongoing environmental changes(Ohman A et al.,2000). Based on this
372 interpretation, the current findings indicate prolonged deficits in the cognitive control of
373 motor inhibition. Clearly, future research will need to elucidate whether any of these
374 inferences regarding concussion history and novelty N2 are most probable. Lastly, the N2
375 to target stimuli has been previously linked to visual processing. Given that group
376 differences were not observed during the target condition, the findings suggest no
377 prolong deficits in visual processing following concussion.

378 Other investigations have also reported suppressed neuroelectric activation using
379 shorter intervals following mTBI. For example, persistent deficits were demonstrated in
380 concussed athletes who were asymptomatic 15 weeks post-injury and symptomatic
381 athletes 5 weeks post-injury relative to non-concussed control athletes during
382 performance of a stimulus discrimination task. Specifically, both concussed groups
383 exhibited increased P3b latency compared to controls, suggesting that concussion
384 resulted in delays in cognitive processing speed regardless of the presence of post-
385 concussion symptoms and normal performance on standard clinical measures of cognitive
386 functioning(Gosselin N et al, 2006). Other research has corroborated these findings as
387 longer P3b latency to a stimulus discrimination task was observed in individuals a
388 minimum of six months post-injury who have sustained up to three concussions (394.5

ms) relative to those that had never been injured (354.3 ms) (Gaetz M et al, 2000). The relationship between increased latency and concussion history appears linear as those that had sustained one (375.8 ms) or two (375.5 ms) concussions exhibited P3b latencies that fell between those with three concussions and those that had never been concussed. In combination with our results, these findings highlight the sensitivity of ERP measurement to persistent concussion-induced changes in cognition and the inadequacy of standard clinical evaluations to detect subtle changes in cognitive functioning beyond the acute phase of injury.

Our lack of significant findings of chronic functional deficits is not unprecedented and may be related to the clinical test we employed. The sensitivity of the computer based assessment employed here and in other investigations (Broglio SP et al, 2006;Collie A et al, 2006;Iverson GL et al, 2006b) does not seem adequate to detect chronic cognitive deficits. In part, these tests were not developed to detect subtle persistent changes, but rather to be sensitive to the gross changes in cognition that are present immediately following mTBI. We speculate that other cognitive measures may provide greater sensitivity to persistent decrements associated with mTBI. For example, Ellemburg (Ellemberg D et al, 2007) reported prolonged cognitive decrements in concussed soccer athletes six to eight months post-injury on the Stroop Color Word Test and the Tower of London DX, whereas Collins (Collins MW et al, 1999) reported deficits in previously concussed collegiate athletes on the Trail Making Test - Part B. Each of these pencil and paper tests are well established evaluative measures of various aspects of executive function that are not indexed by the ImPACT battery used here.

411 Whether or not the suppressed neuroelectric profile reported here and elsewhere is
412 related to increased reports of mild cognitive impairment and depression(Guskiewicz et
413 al, 2005) is not clear. The underlying mechanism of those impairments cannot be fully
414 elucidated by this investigation, although similarly suppressed P3 amplitude and scalp
415 distribution has been tied to non-pathological aging (Polich J, 1997). Consequently, we
416 speculate that the reported late life clinical pathologies reported in retired athletes might
417 reflect some form of accelerated aging resulting from mTBI. Abated pyramidal cell
418 structure is a well known effect associated with aging(Peters A, 2002) and cellular death
419 in the CA3 region of the hippocampus has been reported in mice 72 hours following
420 mTBI (Tashlykov V et al, 2007). Similarly, TBI has been linked to pyramidal neuron
421 atrophy and death in the CA1 and CA4 hippocampal subfields in the months following
422 injury(Maxwell WL et al, 2003). Cellular death following mTBI may also occur with the
423 collective cell loss subsequent to mTBI and aging resulting in a neuropathological
424 manifestation (Omalu BI et al, 2005;Omalu BI et al, 2006).
425 Pathological changes may not be apparent until later in life as young adults with a
426 history of mTBI, like those in this investigation, benefit from cognitive reserve(Katzman
427 R et al, 1988). That is, these individuals likely demonstrated normal functional cognitive
428 performance by recruiting other cortical networks and regions to aid in accomplishing the
429 cognitive task at hand. For example, one investigation found concussed young adults
430 performed normally on functional cognitive evaluations by recruiting additional cortical
431 areas as evidenced by increased blood oxygen level–dependent (BOLD) signals (Jantzen
432 KJ et al, 2004). Cognitive reserve is known to decrease with age (Fratiglioni L and Wang

HX, 2007), but coupled with increased cell death resulting from mTBI, cognitive decline may be exacerbated and ultimately develop into clinical signs and symptoms.

Although significant differences were demonstrated between our concussed and non-concussed groups, the use of participant-report concussion diagnoses limits the strength of the investigation. We find it unlikely that our participants over-reported the number of injuries they sustained as many mTBI go unreported(Langlois JA et al, 2006). In addition, the cross-sectional nature of the study limits our ability to draw conclusions of how these injuries may affect the participants later in life. Lastly, the cross-sectional nature of the study compromises our ability to indicate causation regarding the effect of concussion history on cognition. It is possible, although unlikely, that a secondary factor or set of factors may be responsible for the group differences that were attributed to concussion history. Future investigations should adopt a longitudinal design to better elucidate these effects.

CONCLUSION

In the final analysis, we demonstrated persistent deficits in the neuroelectric system of young adults reporting at least one mTBI over the three years prior to this investigation. Although the changes occurred in absence of functional cognitive declines, these findings support and extend a growing body of literature suggesting that cerebral concussion can no longer be thought of as a transient injury without long term threats to cognitive health. It is not clear if or how these deficits will manifest into clinical pathologies with age, but clearly a conservative approach to mTBI is warranted. At the least, those suspected of sustaining a concussion should be withheld from activity until they perform at or above a pre-morbid level of functioning (Guskiewicz KM et al,

2004;McCrory et al, 2005). Using these guidelines, many athletes will return within one week following injury, but in light of these findings and those presented elsewhere, others have speculated that a longer rest period is necessary(Mayers L, 2008).

Acknowledgements: This project was funded by grants from the Mary Jane Neer Fund for Disability Research and the Research Board at the University of Illinois.

Author Disclosure Statement

No conflicting financial interests exist.

Literature Cited

Offline Analysis of Acquired Data. Compumedics Neuroscan: El Paso.
Ref Type: Book, Whole

Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Johnston K, Kelly J, Lovell M, McCrory P, Meeuwisse W, and Schamasch P (2002). Summary and agreement statement of the first International Conference on Concussion in Sport, Vienna 2001. Br J Sports Med 36**,** 6-7.

Broglio SP, Ferrara MS, Piland SG, and Anderson RB (2006). Concussion history is not a predictor of computerized neurocognitive performance. Br J Sports Med 40**,** 802-805.

Broglio SP and Puetz TW (2008). The effect of sport concussion on neurocognitive function, self-report symptoms, and postural control: A meta-analysis. Sports Med 38**,** 53-67.

Collie A, McCrory P, and Makdissi M (2006). Does history of concussion affect current cognitive status? Br J Sports Med 40**,** 550-551.

Collins MW, Grindel SH, Lovell MR, Dede DE, Moser DJ, Phalin BR, Nogle S, Wasik M, Cordry D, Klotz-Daugherty M, Sears SF, Nicolette G, Indelicato P, and McKeag DB (1999). Relationship between concussion and neuropsychological performance in college football players. JAMA 282**,** 964-970.

Delaney JS, Lacroix VJ, Leclerc S, and Johnston KM (2002). Concussions among university football and soccer players. Clin J Sport Med 12**,** 331-338.

Donchin E (1981). Surprise!...Surprise? Psychophysiology 18**,** 493-513.

Donchin E and Coles MGH (1988). Is the P300 component a manifestation of context updating? Behav Brain Sci 11**,** 357-374.

Donchin E, Karis D, Bashore TR, Coles MGH, and Gratton G (1986). Cognitive psychophysiology: Systems, processes, and applications, in: *Psychophysiology: Systems, processes, and applications*. Coles MGH and Donchin E (eds), The Guilford Press: New York, pps. 309-330.

Duncan-Johnson CC (1981). P3 latency: A new metric of information processing. Psychophysiology 18**,** 207-215.

Dupuis F, Johnston KM, Lavoie M, Lepore F, and Lassonde M (2000). Concussion in athletes produce brain dysfunction as revealed by event-related potentials. Neuroreport 11**,** 4087-4092.

Ellemberg D, Leclerc S, Couture S, and Daigle C (2007). Prolonged neuropsychological impairments following a first concussion in female university soccer athletes. Clin J Sport Med 17**,** 369-374.

Folstein JR and Van Petten C (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology 45**,** 152-170.

Fratiglioni L and Wang HX (2007). Brain reserve hypothesis in dementia. J Alzheimers Dis 12**,** 11-22.

Gaetz M, Goodman D, and Weinberg H (2000). Electrophysiological evidence for the cumulative effects of concussion. Brain Inj 14**,** 1077-1088.

Gosselin N, Theriault M, Leclerc S, Montplaisir J, and Lassonde M (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. Neurosurgery 58**,** 1151-1161.

512 Guskiewicz KM, Bruce SL, Cantu RC, Ferrara MS, Kelly JP, McCrea M, Putukian M,
513 and Valovich-Mcleod T (2004). National Athletic Trainers' Association Position
514 Statement: Management of Sport-Related Concussion. J Athl Train 29**,** 280-297.

515 Guskiewicz KM, Marshall SW, Broglio SP, Cantu RC, and Kirkendall DT (2002). No
516 evidence of impaired neurocognitive performance in collegiate soccer players. Am J
517 Sports Med 30**,** 157-162.

518 Guskiewicz,K.M., Marshall,S.W., Bailes,J., McCrea,M., Cantu,R.C., Randolph,C., and
519 Jordan,B.D. (2005). Association between recurrent concussion and late-life cognitive
520 impairment in retired professional football players. Neurosurgery 57**,** 719-726.

521 Hillman CH, Castelli DM, and Buck SM (2005). Aerobic fitness and neurocognitive
522 function in healthy preadolescent children. Med Sci Sports Exerc 37**,** 1967-1974.

523 Ilan AB and Polich J (1999). P300 and response time from a manual Stroop task. Clin
524 Neurophysiol 110**,** 367-373.

525 Iverson GL, Brooks BL, Collins MW, and Lovell MR (2006a). Tracking
526 neuropsychological recovery following concussion in sport. Brain Inj 20**,** 245-252.

527 Iverson GL, Brooks BL, Lovell MR, and Collins MW (2006b). No cumulative effects for
528 one or two previous concussions. Br J Sports Med 40**,** 72-75.

529 Jantzen KJ, Anderson B, Steinberg FL, and Kelso JA (2004). A prospective functional
530 MR imaging study of mild traumatic brain injury in college football players. Am J
531 Neuroradiol 25**,** 738-745.

532 Jasper HH (1958). The ten-twenty electrode system of the International Federation.
533 Electroencephalogr Clin Neurophysiol 10**,** 371-375.

534 Johnson R (1993). On the neural generators of the P300 component of the event-related
535 potential. Psychophysiology 30**,** 90-97.

536 Katzman R, Terry R, DeTeresa R, brown T, Davies P, Fuld P, Renbing X, and Peck A
537 (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with
538 preserved mental status and numerous neocortical plaques. Ann Neurol 23**,** 138-144.

539 Kaufman AS and Kaufman NL. Kaufman Brief Intelligence Test. 1990. Circle Pines,
540 MN, AGS.

541 Knight RT (1984). Decreased response to novel stimuli after prefrontal lesions in man.
542 Electroencephalogr Clin Neurophysiol 52**,** 9-20.

543 Knight RT (1997). Distributed Cortical Network for Visual Attention. J Cogn Neurosci 9**,**
544 75-91.

545 Kok A (2001). On the utility of P3 amplitude as a measure of processing capacity.
546 Psychophysiology 38**,** 557-577.

547 Kutas M, McCarthy G, and Donchin E (1977). Augmenting mental chronometry: the
548 P300 as a measure of stimulus evaluation time. Science 197**,** 792-795.

549 Langlois JA, Rutland-Brown W, and Wald MM (2006). The epidemiology and impact of
550 traumatic brain injury: A brief overview. J Head Trauma Rehabil 21**,** 375-378.

551 Lovell,M.R., Collins,M.W., Iverson,G.L., Field,M., Maroon,J.C., Cantu,R.C., Podell,K.,
552 Belza,M., and Fu,F.H. (2003). Recovery from mild concussion in high school athletes . J
553 Neurosurg 98**,** 296-301.

554 Magliero A, Bashore TR, Coles MGH, and Donchin E (1984). On the dependence of
555 P300 latency on stimulus evaluation processes. Psychophysiology 21**,** 171-186.

556 Maxwell WL, Dhillon K, Harper L, Espin J, MacIntosh TK, Smith DH, and Graham DI
557 (2003). There is differential loss of pyramidal cells from the human hippocampus with
558 survival after blunt head injury. J Neuropathol Exp Neurol 62**,** 272-279.

559 Mayers L (2008). Return-to-play criteria after athletic concussion: a need for revision.
560 Arch Neurol 65**,** 1158-1161.

561 McClincy MP, Lovell MR, Pardini JE, Collins MW, and Spore MK (2006). Recovery
562 from sports concussion in high school and collegiate athletes. Brain Inj 20**,** 33-39.

563 McCrea,M., Guskiewicz,K.M., Marshall,S.W., Barr,W., Randolph,C., Cantu,R.C.,
564 Onate,J.A., Yang,J., and Kelly,J.P. (2003). Acute effects and recovery time following

565 concussion in collegiate football players: the NCAA Concussion Study. JAMA 290**,**
566 2556-2563.

567 McCrory,P., Johnston,K., Meeuwisse,W., Aubry,M., Cantu,R., Dvorak,J., Graf-
568 Baumann,T., Kelly,J., Lovell,M., and Schamasch,P. (2005). Summary and agreement
569 statement of the second International Conference on Concussion in Sport, Prague 2004.
570 Br J Sports Med 39**,** 196-204.

571 Ohman A, Hamm A, and Hugdahl K (2000). Cognition and the autonomic nervous
572 system. Orienting, anticipation, and conditioning, in: *Handbook of Psychophysiology 2nd*
573 *Edition*. Cacioppo JT, Tassinary LG, and Berntson GG (eds), Cambridge University
574 Press: Cambridge, MA, pps. 533-575.

575 Oldfield RC (1971). The assessment and analysis of handedness: The Edinburgh
576 inventory. Neuropsychologia 9**,** 97-113.

577 Omalu BI, DeKosky ST, Hamilton RL, Minster RL, Kamboh MI, Shakir AM, and Wecht
578 CH (2006). Chronic traumatic encephalopathy in a national football league player: Part
579 II. Neurosurgery 59**,** 1086-1092.

580 Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, and Wecht CH (2005).
581 Chronic traumatic encephalopathy in a National Football League player. Neurosurgery
582 57**,** 128-134.

583 Pellman EJ, Lovell MR, Viano DC, and Casson IR (2006). Concussion in professional
584 football: recovery of NFL and high school athletes assessed by computerized
585 neuropsychological testing-part 12. Neurosurgery 58**,** 263-274.

586 Peters A (2002). Structural changes that occur during normal aging of primate cerebral
587 hemispheres. Neurosci Biobehav Rev 26**,** 733-741.

588 Polich J (1987). Task difficulty, probability and inter-stimulus interval as determinants of
589 P300 from auditory stimuli. Electroencephalogr Clin Neurophysiol 68**,** 311-320.

590 Polich J (1996). Meta-analysis of P3 normative aging studies. Psychophysiology 33**,** 334-
591 353.

592 Polich J (1997). EEG and ERP assessment of normal aging. Electroencephalogr Clin
593 Neurophysiol 104**,** 244-256.

Polich J (2007). Updating P300: An integrative theory of P3a and P3b. Clin Neurophysiol 118**,** 2128-2148.

Polich J and Heine MRD (1996). P3 topography and modality effects from a single-stimulus paradigm. Psychophysiology 33**,** 747-752.

Ridderinkhof KR and van der Stelt O (2000). Attention and selection in the growing child: Views derived from developmental psychophysiology. Biol Psychol 54**,** 55-106.

Squires NK, Squires KC, and Hillyard SA (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 38**,** 387-401.

Tashlykov V, Katz Y, Gazit V, Zohar O, Schreiber S, and Pick CG (2007). Apoptotic changes in the cortex and hippocampus following minimal brain trauma in mice. Brain Res 1130**,** 197-205.

Verleger R (1997). On the utility of P3 latency as an index of mental chronometry. Psychophysiology 34**,** 131-156.

Table and Figure Legends

Table 1: Participant demographics and ImPACT scores (mean (standard deviation)) across concussion history grouping. (*) indicates significantly greater than the no concussion group.

Table 2: Task performance (mean (standard deviation)) across concussion history grouping.

Figure 1: Grand averaged ERP waveforms for each concussion group and task condition

Table 1: Participant demographics and ImPACT scores (mean (standard deviation)) across concussion history grouping. (*) indicates significantly greater than the no concussion group.

	No Concussion History (n=44)	Concussion History (n = 46)
Age (yrs)	19.4(1.3)	20.0 (1.2)*
Body Mass Index	25.9 (3.3)	26.3 (3.9)
K-Bit (IQ)	107.7 (8.0)	105.5 (6.1)
Previous Concussions	0.0 (0.0)	1.7 (1.1)
Concussion with loss of consciousness	---	0.8 (1.0)
Concussion with amnesia	---	0.7 (1.1)
Time from last concussion (yrs)	---	3.4 (3.0)
ImPACT Scores		
Composite Verbal Memory	89.56 (10.29)	90.36 (8.67)
Composite Visual Memory	82.95 (9.45)	82.16. (9.82)
Composite Motor Speed	43.92 (9.76)	44.08 (6.95)
Composite Reaction Time	0.53 (0.07)	0.53 (0.06)
Total Symptom Score	8.08 (8.77)	6.91 (9.79)

Table 2: Task performance (mean (standard deviation)) across concussion history grouping.

	No Concussion History	Concussion History
Non-Target Response Accuracy (%)	99.8 (0.3)	99.8 (0.3)
Novelty Response Accuracy (%)	99.6 (1.2)	99.4 (1.5)
Target Response Accuracy (%)	97.2 (5.2)	95.0 (6.2)
Target Reaction Time (ms)	417.4 (43.1)	418.1 (39.2)

Table 2: Task performance (mean (standard deviation)) across concussion history grouping.

	No Concussion History	Concussion History
Non-Target Response Accuracy (%)	99.8 (0.3)	99.8 (0.3)
Novelty Response Accuracy (%)	99.6 (1.2)	99.4 (1.5)
Target Response Accuracy (%)	97.2 (5.2)	95.0 (6.2)
Target Reaction Time (ms)	417.4 (43.1)	418.1 (39.2)

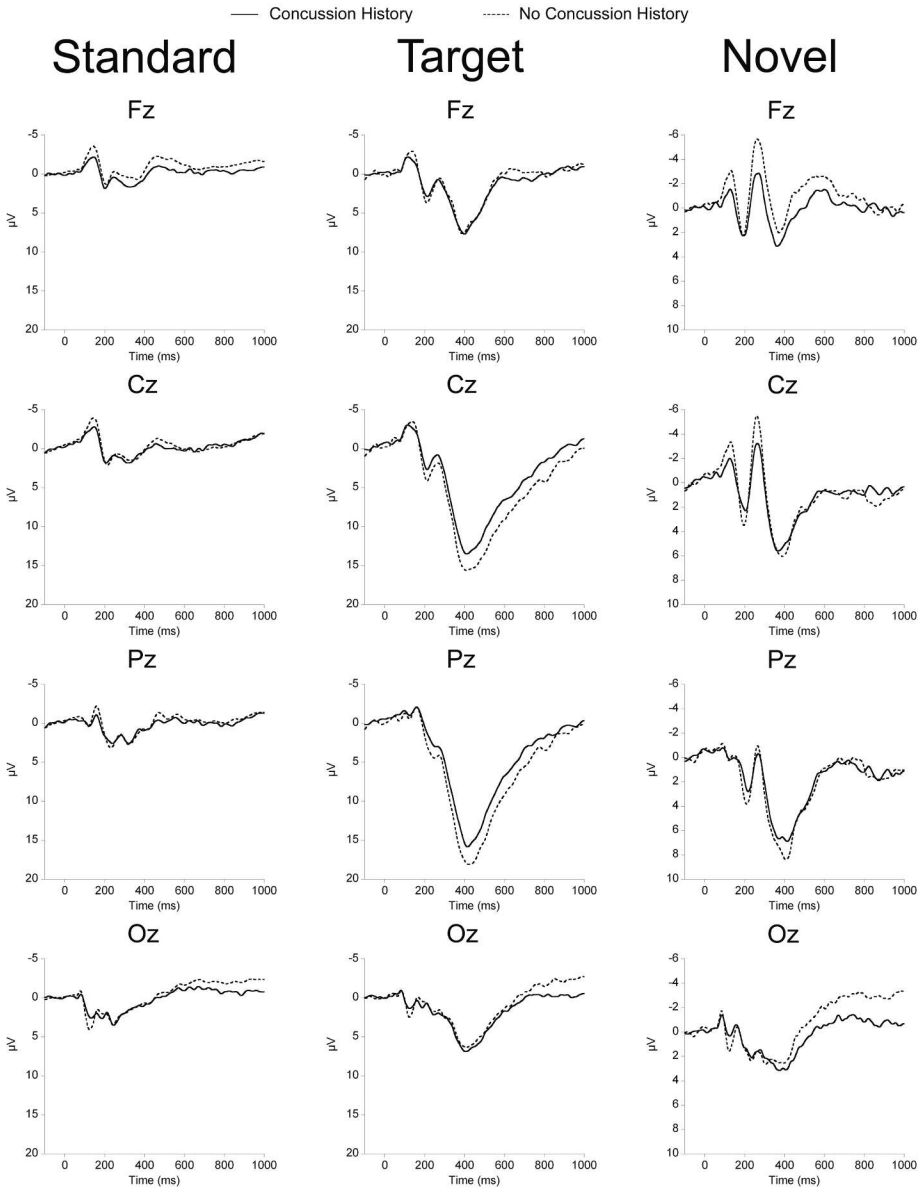

Figure 1: Grand averaged ERP waveforms for each concussion group and task condition
254x317mm (300 x 300 DPI)