Modulation of Feedback-Related Negativity in Individuals with a History of Mild Traumatic Brain Injury

by

Kelly N. Farrell

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Approved: ____
Robert F. Simons, Ph.D.
Professor in charge of thesis on behalf of the Advisory Committee

Approved: ____
Jared Medina, Ph.D.
Committee member from the Department of Psychological and Brain Sciences

Approved: ____
Dayan Knox, Ph.D.
Committee member from the Board of Senior Thesis Readers

Approved: ____
Michelle Provost-Craig, Ph.D.
Chair of the University Committee on Student and Faculty Honors

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ABSTRACT

Recent studies have shown that traumatic brain injury (TBI) can cause disruptions in cognitive processing and emotion regulation for weeks or longer after the initial accident. Most of this work has focused on severe injuries, which are less common but can produce more pronounced post-concussion symptoms. In comparison, very little research has been done on mild TBI (mTBI) – which makes up more than three-fourths of total head injuries – resulting in a clinical profile that is unclear. The current study sought to expand on past research demonstrating disrupted error monitoring in individuals with mTBI in order to determine whether external, as well as internal, feedback processing systems are influenced by mild head injury. A group of participants with a history of one or more mild concussions, as defined by the Department of Defense's concussion severity scale, and a group of healthy control participants were recruited to participate in a 5 Doors task in order to compare mean feedback-related negativity (FRN) amplitudes. Results revealed that participants with a history of mTBI had significantly smaller feedback-related negativity (FRN) amplitudes than did control participants, which indicates that external feedback processing may be altered as a result of even mild head injury. These results can help to explain some of the emotional and behavioral symptoms that are described as a "post-concussive syndrome"; an area with implications for concussion research and rehabilitation.

Chapter 1

Introduction

1.1 Traumatic Brain Injury: Overview

Traumatic brain injuries (TBIs) can have profound effects upon the lives of those who suffer from them. Individuals with a history of TBI (most commonly known as a "concussion") experience several lingering effects of their injury including slower cognitive processing, episodic memory loss, and an increased likelihood of psychiatric disorders (Nuwer et al., 2005). One method of assessing the link between these issues and TBI is through the examination of electrophysiological changes related to executive function. Electroencephalography (EEG) provides a noninvasive means of determining if there is an association between head injury and alterations in information processing and other types of executive functioning, indexed by event-related potentials (ERPs). The present study focuses on the feedback-related negativity (FRN), which has not been studied in relation to mild concussions. Alterations in the FRN among those who have suffered a mild TBI (mTBI) could indicate that the processing of feedback is different for these individuals – a finding with important implications for occupational therapy and rehabilitation.

1.2 **Mild Traumatic Brain Injury: Assessment, Incidence, and Recovery**

Head injury is a common health complaint, with 1.4 million Americans seeking health treatment each year (Langlois et al., 2004). Most TBIs are considered “mild,” a term which typically indicates a closed-head injury with minimal to no loss of consciousness and which does not require hospitalization (Nuwer et al., 2005). The severity of head injury is most often classified in accordance with grading systems that combine measures such as Glasgow Coma Score ratings, the amount of time spent unconscious, the presence and duration of post-trauma amnesia, and the amount of time spent in an altered state of consciousness (which includes symptoms such as confusion and decreased alertness; Rapp et al. 2013). By these grading standards, mTBI is the most commonly diagnosed type of head injury, with 618 instances per 100,000 people (Nuwer et al., 2005; Sosin et al., 1996). Additionally, the most recent congressional report to address head injury, made by the Center for Disease Control’s (CDC) Center for Injury Prevention and Control, stated that mild injuries account for over three-fourths of all head trauma (2003). Due to the high prevalence of mTBI relative to both the population of head injury patients and the general population, it is important to evaluate the presence of post-injury symptoms using behavioral and physiological measures in order to establish a clinical profile of mTBI and better predict long-term patient outcomes.

Though the short- and long-term effects of mild head injuries are underestimated by the general public (Kaut et al., 2003; Mulhern and McMillan, 2006; Weber and Edwards, 2012), research has found that symptoms can occur weeks, months, or even years after the injury itself (Bohen, Jolles, & Twinjnstra, 1992; Emanuelson et al., 2003; Ingebrigtsen et al., 1998). When they occur, post-concussive symptoms include diminished processing speed, mood disturbances including depression and anxiety, chronic pain, and episodic memory loss. The severity of these symptoms varies quite a bit among those suffering from mTBI. Though these individuals frequently require only minimal medical attention and are perceived as experiencing relatively benign symptoms by the general public, symptoms such as dizziness, vertigo, irritability, decreased attentional capacity, and conceptual organization have been found to linger in certain individuals (Rao and Lyketsos, 2000). At least one of these complaints have been found to persist in up to 86% of mTBI patients one year after the incident, and although 73% returned to work or school within this time, it took them an average of 6 months to do so (Naalt et al. 1999). The present study aimed to examine these alterations through EEG, a noninvasive means of relating brain activity to behavior through the study of electrophysiological activity associated with executive function. Because behavioral profiles of post-injury symptoms are not consistent between individuals and can overlap with those of other conditions, EEG data are important in establishing a link between post-concussion symptoms and past head injury that is not reliant upon self-reported behavioral symptoms.

1.3 Electrophysiology and Traumatic Brain Injury

Recently, researchers have sought to investigate alterations in brain activity and lingering post-injury cognitive and behavioral symptoms. One electrophysiological component that has been studied in this context is the error-related negativity (ERN), which occurs immediately following the conscious or subconscious commission of an error. The ERN is associated with error monitoring and is sensitive to the personal salience of an error (Olvet and Hajcak, 2008). As such, individuals with anxiety and obsessive-compulsive disorders tend to have larger ERNs than does the general population (Hajcak, McDonald, and Simons, 2003; Olvet and Hajcak, 2008; Weinberg, Olvet, and Hajcak, 2010). Individuals with a history of mTBI have been shown to have smaller ERN amplitudes relative to healthy controls (Pontifex et al., 2009). This could be due to diminished error monitoring ability in those with a history of mTBI, but this relationship is less certain due to the correlation between head injury and psychiatric conditions such as anxiety which are typically associated with larger ERNs (Pontifex et al., 2009). Despite the unclear nature of the relationship between the ERN and mTBI, disturbances in the error-processing system after mTBI are important to study in order to refine the clinical profile of head injury and better inform treatment and rehabilitation.

Whereas the ERN is associated with error monitoring, the FRN is associated with feedback processing. The FRN is able to assess external feedback as rewarding (i.e., a gain) or nonrewarding (i.e., a loss or a neutral outcome), with larger FRN amplitudes occurring after negative feedback (Hajcak et al., 2006). The FRN is also sensitive to reward prediction and has been shown to be larger in individuals who, after making a choice, found that they had incorrectly predicted a positive outcome (Moser and Simons, 2009). The FRN is therefore considered to be an electrophysiological index of external feedback monitoring, while the ERN occurs in response to internal feedback.

With regard to head injury, Larson and colleagues (2007) found alterations in the FRN of severe TBI patients, with smaller FRN amplitudes as compared to control participants. Additionally, the severe TBI group showed larger FRNs during reward trials relative to non-reward trials, which stands in contrast to control participants whose FRNs are larger during non-reward trials. Very few studies have examined the FRN in individuals with a history of mTBI, however. Because of the high incidence rate of mild head injury and the importance of feedback processing in everyday life, further research on the association between mTBI and the FRN is crucial to understanding disruptions in daily functioning following this type of injury.

1.4 **Hypotheses**

In light of the relative lack of data on the FRN with respect to mild head injury, no specific hypotheses were made regarding the effect of mTBI on this component. If, like the ERN, the FRN is found to be smaller among those who have experienced a mild head injury relative to control participants, findings would indicate that both the internal (ERN) and external (FRN) feedback processing systems must be targeted in treatment in order to fully address post-injury feedback-related symptoms. If there are no differences in FRN amplitude for mTBI and control participants, feedback processing may be unaffected following mild head injury. This would also have clear implications for treatment, as it would indicate that mTBI patients may require direct feedback in order to compensate for disruptions of the internal error processing system. A larger FRN in those with a history of mTBI relative to control participants could indicate that individuals with past head injury are particularly sensitive to external feedback. Results similar to those recorded in the aforementioned study by Larson and colleagues (2007) would indicate that external feedback processing in individuals with a history of mTBI differs fundamentally from that of the general public, which could suggest that these people require different types of feedback in order to learn most effectively. In all cases, further study is required to fully establish a link between mild head injury and the feedback processing system.

Chapter 2

Methods

2.1 Participants

Participants were 26 students enrolled in an introductory psychology course at the University of Delaware. Of these, 12 (5 female) indicated a history of at least one instance of mild head injury (inclusion/exclusion criteria detailed below), while the remaining 14 (7 female) reported no history of head injury. All were undergraduates between the ages of 18 and 23, with 77.8% (21) identifying as Caucasian. Students received both course credit and financial compensation for their participation in the present study.

2.2 Measures

2.2.1 Head injury classification.

Participants were asked to indicate whether or not they had experienced one or more head injuries. The severity of the injury or injuries was assessed through questions adapted from the VA/Department of Defense classification system, which relies on Glasgow Coma Scores (Teasdale and Jennett, 1974) and post-injury episodic memory loss (Department of Defense, 2009). The questions asked about the length of time spent unconscious or in an altered state of consciousness after the injury, as well as the length of time memory loss was experienced. Participants were asked to choose the interval of time in which they experienced each symptom, such as "0 to 30 minutes," "30 minutes to 24 hours," and "greater than 24 hours." A participant was considered to have a history of mTBI if his or her most severe injury caused 30 minutes or less of unconsciousness, 24 hours or less of post-injury amnesia, and 24 hours or less of alterations of consciousness.

2.2.2 Post-concussive symptoms.

Post-concussive symptoms were evaluated using the Rivermead Post-Concussive Symptoms Questionnaire (King et al., 1995). The present study used the 3-group scoring system recommended by Ryan and Warden (2003) in which symptoms are categorized as being somatic, cognitive, or emotional in nature. Participants with a history of mTBI used a 5-point rating system to indicate the extent to which symptoms such as headaches, fatigue, poor concentration, and light sensitivity have caused problems in their lives since their injury. Participants without a history of head injury received a similar questionnaire, with references to injury omitted. Rather, they were asked to compare their current level of (dis)comfort with what they experienced one month prior to the study. For instance, a participant with a past head injury would be asked to indicate the presence and severity of his or her headaches in comparison to the headaches he or she experienced prior to the injury. In contrast, a non-injured participant would be asked to rank the current presence and severity of headaches in comparison to headaches he or she experienced one month prior to the experiment. Because post-injury symptoms are often similar to that of other conditions—such as drug abuse and mood disorders—comparing the general health of both groups is important to determine if overall wellbeing differs significantly between populations with and without a history of concussions (Iverson and McCracken, 1997).

2.2.3 General wellbeing.

All participants were evaluated for physical, emotional, and social health using the 36-Item Short Form Health Survey (SF-36; Ware & Sherbourne, 1992) and Symptom Checklist-90 Revised (SCL-90-R). Some of the questions, such as whether or not physical health problems limited the amount of time spent on work or activities, required require a yes or no answer. Others, including questions about the extent to which physical pain impacted their activity levels, included a rating scale that ranged from “not at all” to “yes, limited a lot.”

2.3 Stimuli and procedures

2.3.1 Experimental Setup

Before completing a consent form, participants were given a brief overview of the experimental task and informed that, in addition to course credit, they would have the opportunity to earn a cash reward based on their performance on the task.

Participants were given a brief orientation to the EEG recording equipment before an experimenter applied the electrocap. They were then placed in a small room and seated in front of a computer. Participants were introduced to the presentation software (Presentation; Neurobehavioral Systems, Inc.) and given task instructions (detailed below).

2.3.2 Five Doors task.

During the Five Doors task, participants were told that they began with $10 in financial credit supplied by the experimenter. They were informed that during each trial they would have the opportunity to gain or lose a portion of this money, but that they would never owe money to the experimenter in the case of a negative sum at the end of the task.

During each trial, five doors, centered horizontally and vertically, appeared on the screen. Participants were instructed to press one of five buttons on a response box in order to select their door of choice, with each door containing a different sum (or loss) of money. After a participant's response selection, a symbol appeared on the screen indicating the amount of money gained or lost on that trial: a green "+ + +" indicated a gain of 25 cents; a green "+" indicated a gain of 5 cents; a white "0" indicated no change in the net sum; a red "-" indicated a loss of 5 cents; and a red "- - -" indicated a loss of 25 cents. Between each trial, a fixation cross appeared on in the center of the screen for 1000 milliseconds. Participants completed 5 practice trials, after which they completed 10 experimental blocks with 30 trials per block for a total of 300 trials.

After completing this task, participants completed the Rivermead Post-Concussion Questionnaire, SF-36, and a demographics survey on a separate computer using Qualtrics software.

2.3.3 Psychophysiological recording and data reduction

An electrocap containing 30 Ag/Cl electrodes was used to collect EEG data, as well as 2 electrooculography (EOG) electrodes placed approximately 1 cm below the eyes. Data were referenced on-line to the right mastoid (M2) and forehead ground

(AFZ), with electrode impedances measured at or below 20 kΩ. All data were digitized at 500 Hz using Snapmaster software (HEM Data Corporation) with James Long Company Isolated Bioelectric Amplifiers. Continuous EEG data were corrected for eye blinks using BESA software, after which the data were band-pass filtered from 0.1 to 30 Hz with a Butterworth digital filter and re-referenced to an average of right and left mastoids. Trials containing artifacts greater than ±75 μV were rejected.

The region of interest (ROI) for the FRN was defined at fontro-central electrodes Fz, Cz, FC1, and FC2, similar to past studies (e.g., Bismark et al. 2012, Cooper et al. 2014, Massar et al. 2012, Smillie et al. 2010) and examined for confirmation. The FRN was quantified as the mean amplitude 200-300 ms post-feedback stimulus at each of the ROI electrodes. Consistent with past work on the FRN and concussive symptoms (Larson et al., 2007), a difference wave was created by subtracting each participant's FRN on nonreward trials (lose a lot, loose a little, no change) from his or her FRN on reward trails (win a lot, win a little). Questionnaire scores and mean component amplitudes were analyzed using SPSS (Version 22).

Chapter 3

Results

3.1 Behavioral Results

A repeated measures analysis of variance (ANOVA) of participant response choices on the Five Doors task revealed no significant interaction between participant status (mTBI vs. control) and the doors chosen for each trial ($F(4,21) = 1.296$, $p = .260$).

3.2 ERP Results

In accordance with past studies that have shown the FRN reflects binary positive and negative outcomes without respect to magnitude (Hajcak et al., 2005, Holroyd et al., 2006, Yeung & Sanfey, 2004), waveforms for “gain” outcomes (win a little, win a lot) and “no gain” outcomes (no change, lose a little, lose a lot) were averaged together. Consistent with past work, the results of a repeated measures analysis of variance (ANOVA) revealed that, across all participants, the FRN was largest in response to no gains than to gains ($F(1, 23) = 38.601$, $p < .001$, partial $\eta^2 = .627$). A difference wave (dFRN) was then created by subtracting mean FRN amplitudes on no gain versus gain trials for each participant. The results of a univariate ANOVA indicated that mean dFRN amplitude was significantly smaller for participants with a history of mTBI than for those without ($F(1, 18) = 8.077$, $p = .011$; partial $\eta^2 = .310$). See Figure 1 for grand average waveforms by condition (mTBI versus control).

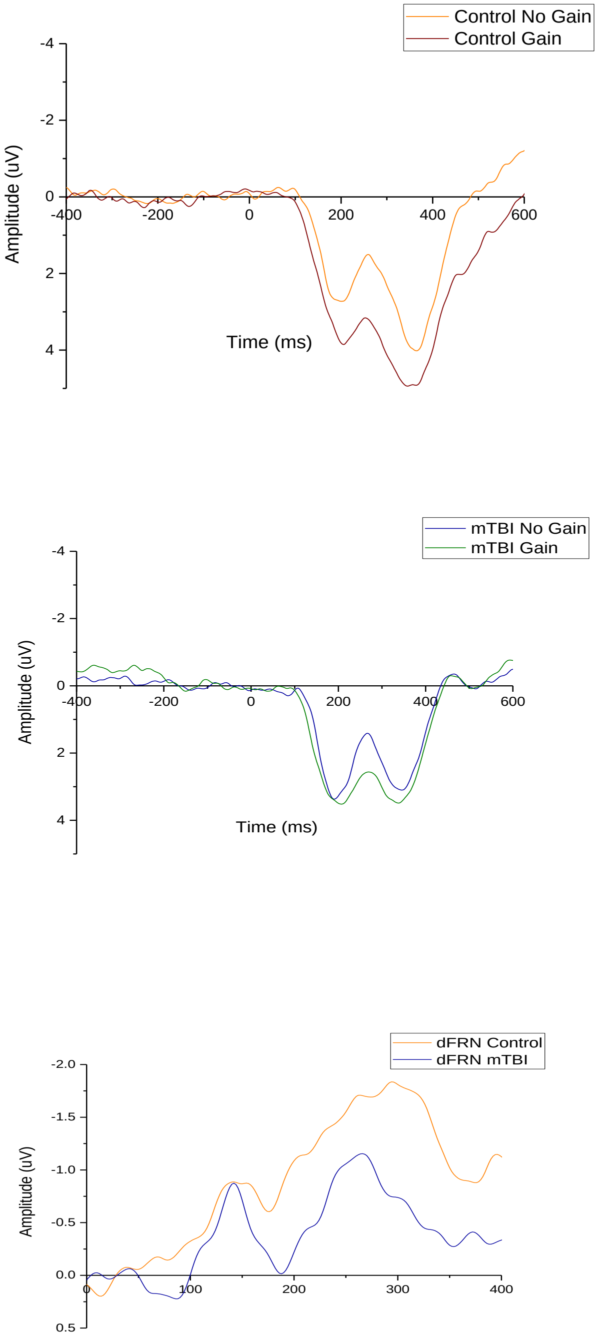

Figure 1. Mean FRN amplitudes in mTBI (top) and control participant groups (middle), as well as dFRN amplitudes (bottom).

3.3 Self-Report Measures

Self-report data from the SCL-90-R, SF36, and the Rivermead Post-Concussion Questionnaire were analyzed in order to assess for differences between participants with and without a history of mTBI. Composite scores across the two groups are presented in Figure 2.

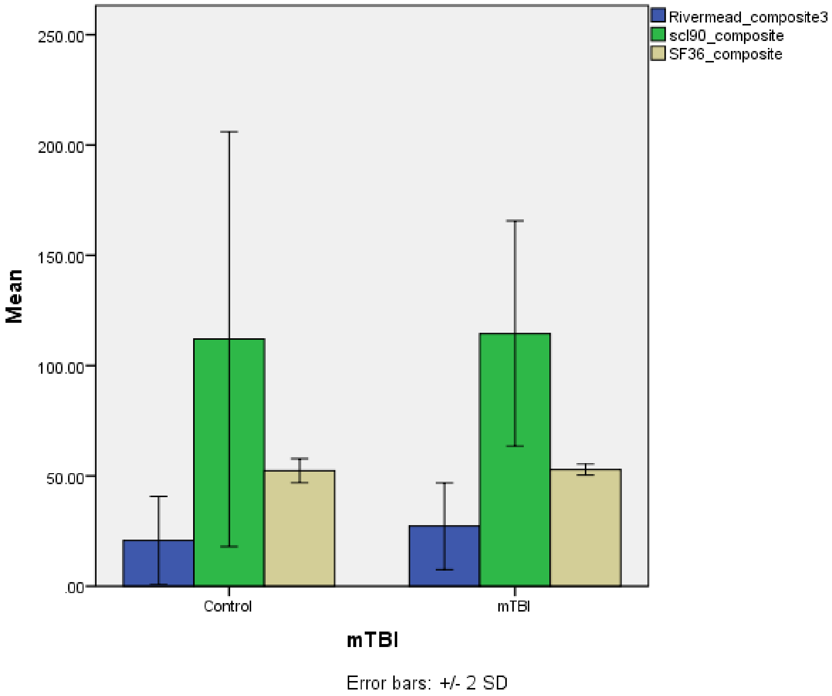

Figure 2. Composite scores on the Rivermead Post-Concussion Questionnaire, SCL-90-R, and SF-36 in control participants and participants with a history of mTBI

Univariate ANOVAs revealed no significant differences between the two experimental groups on SCL-90-R scores (*F*(1, 24) = 0.723, *p* = .404), SF-36 scores (*F*(1, 22) = 0.344, *p* = .563), or experiences of chronic pain (*F*(1, 24) = 0.852, *p* = .365). The Rivermead Post-Concussion Questionnaire was analyzed both in terms of the RPQ3 (*F*(1,24) = 2.756, *p* = .110) and RPQ16 scores (*F*(1,22) = 2.187, *p* = .090) as well as RPQ (Cognitive) (*F*(1,24) = 4.189, *p* = .149, RPQ) (Emotional) (*F*(1, 24) = 2.301, *p* = .087), and RPQ (Somatic) (*F*(1,22) = 2.316, *p* = .142). See Table 1 for a symptom subgroup categories of the RPQ.

Table 1: Categorization of the subgroups used to score the Rivermead Post-Concussion Questionnaire

Rivermead Post-Concussion Questionnaire Subgroup Categories

Subgroup	Symptoms
RPQ3	Headache, dizziness, nausea/vomiting
RPQ13	Noise sensitivity, sleep disturbances, fatigue, irritability, depressed affect, feeling of frustration, blurred vision, light sensitivity, double vision, restlessness, forgetfulness, poor concentration, taking longer to think
RPQ (Cognitive)	Forgetfulness, poor concentration, taking longer to think
RPQ (Emotional)	Irritability, depressed affect, feeling of frustration, restlessness
RPQ (Somatic)	Fatigue, headache, dizziness, nausea/vomiting, sensitivity to noise, sleep disturbances, blurred vision, double vision, light sensitivity

Chapter 4

Discussion

4.1 General Discussion

The results of the present study further the notion that the ERPs of individuals with mTBI differ significantly from those of controls. Specifically, it was demonstrated that the dFRN is attenuated by a history of one or more mild brain injuries. This is in line with findings by Larson and colleagues (2007) which demonstrated that patients with a history of severe TBI have smaller dFRNs relative to a group of control participants. The present study thereby replicated past work demonstrating reduced dFRN amplitudes following TBI, as well as extended the existing literature by demonstrating that such an effect is present even after mild injury.

As the FRN is associated with the processing of external feedback (Heldmann et al., 2008), present results suggest that this system is disrupted by mTBI. Similarly, past results have also implicated mTBI as modulator of the ERN (Pontifex et al. 2009), which is associated with internal performance processing (Gehring et al. 1993, van Veen and Carter 2002, Yeung et al. 2004). Taken together, it appears that there is a general feedback processing deficit present in individuals with a history of any head injury that is not specific to internal or external feedback. This may be attributable in part to damage to limbic structures including the angular cingulate cortex, which is thought to be involved in the production of both the ERN and FRN. Supporting this theory are fMRI data showing atrophy of the cingulate gyrus following traumatic brain injury (Yount et al., 2002), diffusion tension imaging showing a decreased apparent diffusion coefficient in the cingulate bundle following mTBI (Wu et al., 2010), and animal research showing axonal deterioration in the cingulate cortex after mTBI (Dikranian et al., 2008). As most mild brain injuries are diffuse in nature (Alexander et al. 1995), damage could be either to the limbic structures themselves or to the connections between them and their intended cortical targets.

Notably, all measures of general well being (SCL-90-R, SF-36, Rivermead Post-Conssion Questionnaire) were found to be similar across individuals with and without a history of mTBI. This supports the notion that mTBI patients experience deficits even when asymptomatic, and suggests that cognitive processes may be altered in well-functioning individuals who have returned to work and studies after injury.

4.2 Implications

Given the demonstrated disturbances in feedback processing in even high-functioning university students following mTBI, the effects of a mild head injury may be substantial in terms of daily challenges and recovery. Diminished processing of and response to external and internal feedback may be a practical concern within a rehabilitation context, as feedback given to patients may not be interpreted in ways that are most beneficial to their recovery. Occupational or physical therapists may therefore need to change the ways they reward and motivate patients in order to account for altered feedback processing. Additionally, the results of the present study indicate that, while patients may appear capable of returning to work or study within a short amount of time after an accident, even a mild brain injury can result in significant electrophysiological abnormalities relating to specific aspects of cognition such as error monitoring and feedback processing. Patients may need to undergo neuropsychological assessment in the months following their injury to monitor the ways in which these processing systems are disrupted.

4.3 Limitations and future directions

The present study is not without limitation. While global component blunting has been brought forth as a possible explanation for disruptions in ERPs after head injury, there is substantial evidence that electrophysiological abnormalities are not present at every level of processing in participants with TBI. Some early components such as the N2pc (Beaumont et al., 2007, Gosselin et al., 2012) have been shown to be unaffected by TBI. Therefore, the feedback processing deficits highlighted in this and other studies (e.g., Larson et al., 2007), appear to have some specificity.

It may also be noted that, because they were recruited outside of a clinical setting, participants' memories of injury severity may be flawed. However, the vast majority of head injuries are classified as mild, and many individuals do not receive formal care (McCrea et al., 2004). Indeed, the more urgent symptoms associated with moderate to severe TBI would be likely to necessitate evaluation than mild injury. It is therefore unlikely that a substantial number of participants with more severe injuries were included in the present sample.

Additionally, it is of note that there is some controversy surrounding current concussion grading scales (primarily based on Glasgow Coma Scores and relative alertness after injury), specifically as to whether or not classifications of mild, moderate, or severe TBI are predictive of recovery and long-term outcomes for patients. Currently available questionnaires about concussion history do not seem to account for the amount of time since a head injury or the presence of multiple head injuries. In the present study, some participants reportedly experienced difficulty responding to the Rivermead survey because they were uncertain of their relative functional abilities prior to an injury that had occurred years prior, nor does there appear to be consistent criteria to assess the severity of a past concussion outside of a clinical setting. Although the current study utilized guidelines for assessment based on information distributed by the U.S. Department of Defense/Veterans' Affairs and discussed by Rapp and colleagues (2013), many similar scales exist with no clear consensus on how to administer them weeks or months after an accident.

Further study of factors such as the amount of time since head injury, as well as a direct comparison across multiple levels of severity, should be conducted in the context of a larger clinical study in order to better examine and parse apart some of the symptoms associated with head injury. Other variables for future research include comparison between participants who have experienced only one TBI and those who have a history of multiple injuries. Performing the same experimental tasks across multiple groups of individuals who have suffered from mTBI will allow for a more precise clinical profile of symptoms occurring after head injury by incorporating variables such as time since last injury, number of injuries, and cause of injury, and help to establish guidelines for medical practitioners in the assessment and treatment of mild brain injury.

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